Report of the ERA4Health Partnership- WORKSHOP. Analysis of the Bottlenecks and Challenges in Designing and Conducting Multicountry Investigator Initiated Clinical Studies (IICs) Pillar 2B

1. Executive Summary

The application of the CTR (Clinical Trials Regulation) strengthens Europe as an attractive location for clinical research. The new Regulation streamlines the processes for the application and supervision of clinical trials but there is still a lack of harmonization for investigator-initiated clinical studies (IICS), and some types of studies are still under divergent national regulations. An optimal funding scheme for multinational investigator-initiated clinical studies is still lacking and new complex designs are emerging, raising additional challenges.

The ERA4Health Partnership organised a physical workshop in Paris on the 14th and 15th of September 2023, which was hosted by the European Clinical Research Infrastructure Network (ECRIN). Sixty representatives from the different institutions of the ERA4Health consortia and other relevant stakeholders, including sponsors, investigators, EMA/ACT-EU and European Medicines Agency, ethics committees and methodologists, met together to discuss challenges in the planning and designing of IICS. The European Commission (DG-RTD) representative, Grzegorz Owsianik, and the Project Officer from HaDEA, Monica Ensini, attended the event as well.

This summary report provides an overview of the main obstacles reported from all perspectives, from funding and sponsorship through to regulatory and operational aspects. All in all, this feedback will help us guide the investigators and sponsors planning multicountry clinical studies and shape the future multicountry investigator initiated clinical studies calls.

2. Introduction

Investigator-initiated clinical studies face a lot of challenges, and multinational clinical trials even more so. Emerging new trial designs add extra complexity.

Despite the recent application of the 536/2014 Regulation on clinical trials (CTR) and the 745/2017 Regulation on medical devices, many investigator-initiated clinical studies are still not covered by harmonized EU Regulations. This is for example the case of studies testing procedural interventions, which are currently regulated by divergent national regulations. Although the latest EU Regulations generated significant harmonization, ethical review under CTR or different interpretations of data protection regulation (GDPR) still leads to significant differences.

In addition, there is still no optimal funding scheme for multinational investigator-initiated clinical studies, and the multinational design adds an extra layer of complexity when it comes to cross-border contracting or national provisions of insurance or indemnification, for example.

Emerging new trial designs, such as adaptative platform trials, including complex trials used in personalised medicine or targeted therapies (basket and umbrella designs), trials within cohorts (TWiCs), or decentralized trials, provide new opportunities for research but also raise methodological and logistical challenges.

Funded by the European Union under the Horizon Europe Framework Programme. Grant Agreement Nº: 101095426.

In line with ERA4Health's main objectives and the preparation of the 2nd phase of the Partnership, adding multinational calls for Investigator Initiated Clinical Studies (IICS) to the Partnership, an important first step was to collect the main obstacles to the conduct of multinational IICS in Europe from all perspectives. Identifying the challenges raised by the new clinical studies methodologies was also of great importance. This information will drive the guidance to investigators and sponsors in the planning and conduct of multinational IICS and shape the future multicountry IICS calls.

With this in mind, ERA4Health organized this workshop dedicated to identifying the bottlenecks and challenges in designing and conducting multicountry IICS. Representatives of key stakeholder groups (see Annex 2) attended the meeting. Although presentations were limited to the intervention of select stakeholders, all perspectives were considered through the inclusion of interactive sessions.

3. Discussion

The first day kicked off with a presentation of the status of one of ERA4Health´s deliverables, a report on the obstacles and challenges to the planning and conduct of IICSs. Through a systematic literature review, this report will describe what has been published so far on the topic, with main barriers related to funding, personnel training, lack of harmonization in applicable regulation and administrative constraints. The day continued with presentations of different stakeholders' perspectives, including investigators, sponsors, funders and regulators. The session was followed by a lively debate on the difficulties encountered in funding these clinical trials, mostly relying on complex public funding rules, lack of flexibility and inadequate timing. Even with proper project management, anticipation is not always possible (many studies were delayed due to the covid crisis) and unexpected events might require additional funding or funding reallocation. Regulators highlighted the lack of awareness by the scientific community of the tools developed by regulators to support academia (STARS project and national initiatives for regulatory support to academic sponsors and researchers). National Competent Authorities (NCAs) call for early interaction with academic sponsors and investigators to anticipate key bottlenecks and optimize resources.

Funders highlighted the importance of developing a framework to ensure and improve the quality of funded IICSs, through a monitoring procedure. Furthermore, investigators call for improving projects evaluation including assessment of sponsor´s operational capacity.

The second day focused on challenges and opportunities for new trial methodologies: clinical trials with complex design (basket, umbrella and platform trials), trials within cohorts (TWiCs) and decentralized trials. Challenges and opportunities were described through different perspectives (study design, sponsorship, regulation and funding) and audience feedback was collected through an interactive session. The main challenges are linked to the lack of experience in the implementation of some new methodologies (decentralized trials) while others more widely implemented (platform trials) still face difficulties linked to the administrative burden of the current Clinical Trials Regulation (CTR) implementation and site contracting.

It is expected that this work will contribute to one of ERA4Health's main objectives, establishing a framework to support multinational Investigator Initiated Clinical Studies.

4. Consideration and proposed actions

In line with ERA4Health Pillar 2B objectives, some actions to be followed include:

- Further discussion on public funding mechanisms for multinational clinical studies, more tailored to the academic community's needs (timing, flexibility). A follow-up workshop involving key stakeholders will be organized to delve into this topic.
- Implementation of proactive measures to support future applicants of calls funding IICS and to minimize the risk of failure: dedicated training monitoring procedures, harmonization of site agreements, recommendations for academic sponsor and investigators interested in setting up multinational IICS.

Annex 1. Agenda

ERA4Health Partnership

AGENDA

WORKSHOP: Analysis of the Bottlenecks and Challenges in Designing and Conducting Multicounty Investigator Initiated Clinical Studies Pillar 2B

14th of September (day 1)

14H TO 16H30

14H | Opening Words

Investigator-Initiated Clinical Studies, why are they fundamental for research?

Cristina Nieto, PhD, ERA4Health Coordinator ; ***Grzegorz Owsianik,*** PhD, European Commission, DG Research ***& Jacques Demotes,*** MD, PhD, ECRIN General Director.

14H25 | Presentation of ERA4Health Task 14.1 Deliverable

D2B.1.1 - Bottlenecks to the planning and conduct of multicountry investigator-initiated clinical studies

Sigrun M. Hjelle, PhD, ECRIN EuCo Norway ***& Niall Hore***, MSc, ECRIN EuCo Ireland.

14H40 | Interactive Session

15H05 | Round table - Investigator-Initiated Clinical Studies: Challenges & Opportunities *(chaired by Jacques Demotes, MD, PhD - ECRIN)*

15h05 - Investigator's Perspective

Frank Bellivier, MD, PhD Professor of Psychiatry, Head and Chair, Department of Psychiatry and Addiction Medicine - Expert Centres University of Paris, R-Link trial, France

15h15 - Academic Sponsor's Perspective

Sylvie Broussous, PhD, Head of the Promotion-Europe Team, Research and Innovation Unit, Montpellier University Hospital, RESPINE trial, France

15h25 - Regulator's Perspective

Yoana Nuevo, PhD, Responsible of the Innovation Office & National Scientific Advice Unit, AEMPs STARS Project, Spain

15h35 - Funder's Perspective

Oonagh Ward, MSc, Head of Research and Innovation Infrastructures Research Strategy & Funding Directorate, Ireland

15h45 - Discussion with Panelists and audience

16H25 | Wrap-up

Co-funded by the European Union

ERA4Health Partnership

AGENDA

WORKSHOP: Analysis of the Bottlenecks and Challenges in Designing and Conducting Multicounty Investigator Initiated Clinical Studies Pillar 2B

9H TO 13H

15th of September (day 2)

9H | Task 2B.1.2 Challenges for New Trial Methodologies

Clinical trials with complex design, trials within cohorts & decentralized trials.

Joana Batuca, PhD, ECRIN EuCo Portugal ***& Emilia Monteiro,*** MD, PhD, Professor of Pharmacology NOVA University of Lisbon, Portugal

9H45 | Interactive Session

10H30 | Round table - Challenges for New Trial Methodologies *(chaired by Olga Kholmanskikh, MD, PhD - FAMHP)*

10h45 - Related to the study design : Recommendations and QA related clinical trials with complex design
Elke Stahl, *PhD,* German Federal Institute for Drugs and Medicinal Devices (BfArM), Clinical Trials Coordination Group, Germany

11h - Related to study design : Recommendations Decentralized Trials
Bart Lagerwaard, PhD, Julius Center for Health Sciences and Primary Care, UMCU, Trials@Home Project, Netherlands

11h15 - Related to Sponsorship
Inge Olsen, PhD, Oslo University Hospital, SolidAct Platform trial, Norway

11h30 - IRB/ECs Approval Challenges
Maria Alexandra Ribeiro, PhD, President of Portuguese National Ethics Committee for Clinical Research (CEIC), Portugal

11h45 - Multicountry Funding Schemes Challenges
Mario Nuvolone, PhD, MD, Pavia University, REDOX trial (Erare3 JTC2016), Italy

12h - Discussion with Panelists and Audience

12H45 | Wrap-up & Closing Remarks

Co-funded by the European Union

Annex 2. Stakeholders attending the meeting

Funders- National funders, ERA4Health partners and other national funders (NIHR United Kingdom, SNSF Switzerland, KCE Belgium, French Ministry of Health France, ABM Poland), charities (Cures within reach USA)

European Commission – DG RTD

HADEA

EMA- ACT EU

National Competent Authorities (AEMPs-Spain, FAMHP-Belgium, BfArm- Germany)

National Ethics Committees (CEIC Portugal)

CTCG (Clinical Trials Coordination Group)

Academic sponsor (Montpellier University Hospital, Oslo University Hospital, EORTC)

Investigators (Paris University, Pavia University)

Clinical site networks (EUHA- European University Hospital Alliance)

Methodologists (Oslo University Hospital)

European Research Infrastructures (ECRIN, EORTC)

National Research Infrastructures & Academic Clinical Trial Units (F-CRIN-France, SCReN-Spain, CZECRIN- Czech Republic, PtCRIN- Portugal, ItaCRIN- Italy, NCTO- Ireland, NorCRIN- Norway, MUCU- Netherlands)

Other projects/partnerships supporting IICs (STARS, EJP-RD, Trials@Home, REMEDi4All)