Report of the ERA4Health Partnership- WORKSHOP. *Funding mechanisms for Investigator-Initiated Clinical Studies. Pillar 2B, WP 16*

1. Executive Summary

Multinational Investigator-Initiated Clinical Studies (IICS) address issues that are usually neglected by industry despite their high societal value, as explained further in detail. However, an optimal funding scheme for these studies is still lacking (1), (2), (3), (4).

To discuss a possible funding mechanism through Joint Transnational Calls for multinational IICS, the ERA4Health partnership organized a physical workshop in Brussels on February 8th and 9th 2024. The workshop was hosted by the European Clinical Research Infrastructure Network (ECRIN) and brought together ERA4Health current and potential new funders, representatives of the European Commission (DG-RTC) and HaDEA, EMA (ACT EU) and representatives of different initiatives currently funding bilateral/multinational clinical studies.

This summary report provides an overview of the existing initiatives tackling the issue of funding multinational IICS through transnational models and of the discussion among the ERA4Health partnership to start defining a funding mechanism for multinational IICS, adapting the current Joint Transnational Call model implemented by ERA4Health, as well as eligibility and selection criteria for the IICS calls.

The first day kicked off with a presentation of the current funding model for Joint Transnational calls for funding research projects in ERA4Health and was followed by presentations of different initiatives that currently fund, or are working on a funding scheme for, multinational IICS. The second day was restricted to current and potential future ERA4health partners and dedicated to discussing the potential funding mechanisms, eligibility and selection criteria, for multinational IICS calls in ERA4Health. It started with a summary of the key messages from the previous day.

2. Introduction

Clinical research involves testing new discoveries by carrying out carefully controlled investigations on patients known as clinical studies. This includes testing not only new or repurposed drugs, but also comparing various treatment regimens (combination of drugs, different treatment dosage or schedules), medical devices, therapies without medicinal products (e.g. radiation or procedural interventions), diagnostic procedures, prevention measures as well as optimizing the use of existing ones. Many of these studies and trials are non-commercial, initiated by investigators and therefore referred to as investigator-initiated clinical studies (IICS) where the investigator conceives the research and develops the protocol. Among IICS, Randomised Clinical Trials (RCTs) are essential when evaluating the efficacy and safety of all interventions, exploring new indications for authorised drugs (repurposing), and comparing the efficacy and safety of approved healthcare strategies. IICS that are usually neglected by industry

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despite their high social importance include: a) academic innovation, b) drug repurposing, c) comparative effectiveness studies.

Even though they represent almost half of the clinical research activity in Europe, RCT are mostly conducted in one single country. Taking advantage of Europe's half-billion population size, of its medical expertise, of its high-quality healthcare systems, and of its scientific potential, enhanced multinational cooperation in clinical studies would boost clinical research in Europe. It would foster rapid patient recruitment and spread best practice, thus enhancing Europe competitiveness and equity for the benefit of patients and of healthcare systems. However, an optimal funding scheme for multinational IICS, especially for RCT, is still lacking.

In line with ERA4Health's objectives, the planned launch of a pilot multinational IICS call by the end of 2024 and that of subsequent regular IICS calls in the following years, an important step is to discuss with funders a possible funding mechanism for multinational IICS. To do so, we build on the information collected during the previous workshop in Paris in September 2023, the work done in other ERA4Health work packages, a scoping paper generated for the purpose of this workshop, and the feedback provided by a few initiatives that currently fund bilateral/multinational IICS through transnational schemes.

With this purpose, ERA4Health organized this workshop dedicated to discuss the adaptation of the ERA4health Joint Transnational Call for multinational IICS regarding: a) funding mechanism, b) definition of the eligibility/selection criteria and c) evaluation procedure.

3. Outcomes of the Workshop

The first day started with a presentation on the Joint Transnational Call (JTC) funding model currently implemented in ERA4Health for research projects and why this model should be adapted for IICS calls.

A. Joint Transnational Calls

To fund preclinical studies through a Joint Transnational Call (JTC) funders commit voluntarily a certain amount of money in a virtual common pot. This means that the money stays within the country of the funder that commits it. When the JTC is co-funded, the EC adds additional funding, the so called- EC Co-fund, which is used notably for gap filling. Gap filling occurs when a project cannot be funded despite being ranked sufficiently high because one of the funders involved already spent all the money that was committed to the call. When this happens, the first step is to ask the funder if they can increase their contribution, and if not, the EC Co-fund can be used to finance the partner of the project for which the corresponding national funder is out of money. This mechanism is carefully regulated in ERA4health.

This JTC model, previously implemented by ERA-NETs to fund research projects, is not well suited to fund multinational IICS, especially trials. Indeed, previous publications (5) have already pointed out that funding line (both amount and timing) and funding rules are main obstacles hindering the conduct of academic-sponsored trials.

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B. Identified bottlenecks/challenges linked to the funding mechanism

Main barriers to the conduct of multinational trials, related to the current approach of Joint Transnational Call rules include:

- Limitations of budget and duration of the eligibility of costs.
- Lack of flexibility linked to the "virtual common pot" model; money cannot cross the borders.
- Administrative burden
    - Funding application procedure. Applicants must comply with both call-specific rules and national/regional rules required by the funders
    - Tendering requirements for public institutions
    - Reporting requirements both at the national/regional and initiative levels.
- Restrictions linked to national rules (on top of general Joint Call rules).
- Coverage of crosscutting activities.

To discuss this challenge and propose possible solutions, other initiatives currently funding multinational clinical studies through transnational models were invited to the meeting.

C. Clinical research funding models. Is there an adequate transnational funding model for multinational IICS?

GloPID-R: Global Research Collaboration for Infectious Disease Preparedness

Since 2013, the EC funded project GloPID-R brings together funders investing in research related to new or re-emerging infectious diseases. The project is currently working on funding options, with main interest on adapting the Joint Call model to the worldwide scope.

ATTRACT: International call for research proposals on rare cancer drug development

ATTRACT brings together 5 European charities (Belgium, France, Spain, Netherlands) to fund multinational clinical research to develop better treatments for rare cancers. This initiative relays in the "virtual common pot" model but introducing flexible features as:

- Possibility to open recruiting sites out of the funding countries (cross-border funding, possible due to their private status).
- Funding line up to 10 years.

CEPI: New vaccines for a safer world

CEPI (Coalition for Epidemic Preparedness Innovations) is an innovative global partnership launched in 2017 to develop vaccines to stop future epidemics. CEPI is composed of international governments, the European Commission and private foundation. CEPI's mission is to accelerate the development of vaccines and other biologic countermeasures against epidemic and pandemic threats. CEPI funds clinical trials networks and clinical trials themselves via calls building on what is already existing. Funds from government and non-government sources are provided as a real common pot and managed by CEPI, hence they are not tied and can cross borders.

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KCE/ZonMw: BeNeFIT calls for comparative effectiveness

Created in 2006, KCE trials is a department of the Belgian Health Care Knowledge Centre (KCE), an independent research centre that provides scientific advice on topics related to health care. KCE trials selects and fund non-commercial large multi-centre pragmatic RCT. Since 2017, KCE and ZonMw (Netherlands) collaborate through the BeNeFIT program funding non-commercial comparative-effectiveness trials. Both organisations had to work outside of their usual procedures for the success of the programme. Although the programme does not allow cross-border funding, the BeNeFIT model relies on a strong feasibility evaluation and follow up of selected projects.

ERDERA (Rare Diseases Partnership) Joint Transnational Calls for IICS on Rare Diseases

ERDERA (public-private partnership) on Rare Diseases will fund Phase I/II multinational trials, using part of the EC contribution as a "real common pot". This "central budget" will be managed by a private foundation (Italian Telethon). The involvement of a private foundation facilitates the circulation of funds across the borders, increases the flexibility through the management by the third parties (Telethon) and allows the gain of time on the implementation of trial as no public procurement is necessary for subcontracting another entity. The partnership is currently exploring the possibility of adding funding from other funding sources outside ERDERA.

EDCTP

EDCTP is a European/African research partnership on infectious diseases that funds clinical trials and clinical studies, which always include capacity development or networking, through a pooled funding. It is a joint undertaking between the EC and the EDCTP association, with financial contribution of the EC, participating states and third parties. EDCTP3 combines three main sources of funding:

-that of the participating states, which is used to fund transnational calls on research and development (with or without EU cofunding), fellowships, national calls, support to (multi)national EDCTP3 projects.

-that of third parties, which is used for joint calls on research and development and cofunding through strategic activities on thematic topics of interest.

-that of the European Union, which is used to fund centrally managed activities such as research and innovation actions (RIAs), coordination and support actions (CSAs), training and mobility actions (TMAs) and other programme activities.

Nordforsk community research

Founded by the Nordic council of Ministers, Nordforsk funds clinical studies, including clinical trials, following both the "virtual and real common pot" models or mixed models combining both.

Funding models (virtual vs real common pot), sources of funding (government, nongovernment, EC cofund, private entities, etc.), payment scheme (milestone- or activity-based, etc.), type of

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funded studies and topics, eligibility and selection procedures, were discussed. Presenters highlighted the need for a real common pot or the use of EC co-fund to allow money to cross borders in order to provide further budget flexibility to the funded clinical studies, the importance of a dedicated project management, the advantage of milestone-base payment, and the value of a feasibility assessment during the selection process.

D. Potential funding mechanisms of ERA4Health Joint Transnational Call for IICS

The second day, restricted to ERA4Health current or future funders, started with a short summary of the previous day. Then the reasons why the current JTC funding mechanisms should be adapted for a multinational IICS call, as well as the potential funding mechanisms adaptations were presented, highlighting the advantages and disadvantages of each possibility.

Possible adaptations were discussed, including some of the features implemented by funding initiatives presented the previous day:

- Use of EC co-fund as a real common pot to cover crosscutting activities (ERDERA model).
- Involving a "private foundation/charity" to manage the common funding (ERDERA model).
- Evaluating the possibility of cross-border funding for countries/funders allowing this scheme (ATTRACT and Nordforsk models).
- Simplifying the financial model at national level, by allocating the whole of the eligible national funds to a "coordinating" organization (ATTRACT model).
- Facilitating flexible funding to allow the sponsor opening/closing recruiting sites as per the project needs (ATTRACT and Nordforsk model).
- In addition, the importance of the coordination of funds from the different funders.

E. Scope, eligibility criteria and evaluation procedure

As preparatory work for the meeting, a scoping paper was drafted and circulated among funders. The document aimed to provide relevant contextual information to help ERA4Health partners defining eligibility criteria for supported multi-country IICS, scoping the first planned call for funding (First/Pilot Call) in terms of:

- Objectives of the clinical studies.
- Topics.
- Other criteria.

The document (*Scoping paper "Eligibility criteria for supported Investigator-initiated Clinical Studies (IICS) through the ERA4Health Partnership (Pilot Call)"*) suggests possible specifications for the Pilot call and discusses other possibilities.

Scope for the Pilot call on IICS proposed by the scoping paper:

- Comparative effectiveness studies (combination/optimization), pragmatic interventional studies on diagnosis, prevention and treatment.
- Exclusion of topics already funded through other partnerships/initiatives.

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- Trend for a subject on non-communicable diseases, including determined priority research areas covered by the ERA4Health SRIA.

It was generally accepted by the break-out sessions´ working groups but final specifications need to be agreed among ERA4Health Management Board members.

Eligibility criteria:

It was discussed that the consortium of a funded IICS should be composed of at least three eligible legal entities in different countries.

Evaluation procedure:

- 2-steps calls.
- Performing feasibility assessments for pre-selected proposals (BeNeFIT model).
- Performing interviews to both the coordinating investigator and the sponsor of projects for pre-selected proposals (at the second step).

Monitoring procedure:

It was discussed the feasibility to incorporate a milestone-based monitoring procedure of the funded IICS to allow funders making a proper follow up of the project. The procedure would allow funders taking informed decisions about the continuation of the financial support.

4. Consideration and proposed actions

In line with ERA4Health Pillar 2B objectives, the following actions will be implemented:

- Presentation of the conclusions of the workshop discussions and the deemed most promising funding mechanism for multinational IICS at the partnership management level for discussion and approval.
- Implementation of the approved measures.
- Collection of the financial commitments of the funders and preparation of the corresponding call documents for the upcoming multinational IICS pilot call in ERA4Health.

5. Bibliography

1. Djurisic S, Rath A, Gaber S, Garattini S, Bertele V, Ngwabyt SN, et al. Barriers to the conduct of randomised clinical trials within all disease areas. Trials. 2017 Dec;18(1):360.

2. Duley L, Antman K, Arena J, Avezum A, Blumenthal M, Bosch J, et al. Specific barriers to the conduct of randomized trials. Clinical Trials. 2008 Feb;5(1):40–8.

3. Alemayehu C, Mitchell G, Nikles J. Barriers for conducting clinical trials in developing countries- a systematic review. Int J Equity Health. 2018 Dec;17(1):37.

4. Del Álamo M, Bührer C, Fisher D, Griese M, Lingor P, Palladini G, et al. Identifying obstacles hindering the conduct of academic-sponsored trials for drug repurposing on rare-diseases: an analysis of six use cases. Trials. 20220915th ed. 2022 Sep 15;23(1):783.

5. OECD Global Science Forum. Facilitating International Cooperation in non-commercial clinical trials. October 2011. https://www.oecd.org/sti/inno/49344626.pdf

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Annex 1. Agenda

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AGENDA

WORKSHOP: Funding mechanisms for Investigator-Initiated Clinical Studies

8th of February (day 1) — 14H TO 17H

14H30 | Opening Words

Welcome and introduction

Cristina Nieto, PhD, ERA4Health Coordinator ; ***Grzegorz Owsianik,*** PhD, European Commission, DG Research

14H35 | Existing funding mechanisms through Joint Transnational Calls (JTC)

ERA4Health JTCs. Funding Overview

Martine Batoux, PhD, ANR Scientific Coordinator

14H45 | Identified bottlenecks /challenges linked to funding mechanism

Marta Del Alamo, PhD, MSc, ECRIN Head of Capacity Projects

14H50 | Clinical research funding models. Is there an adequate transnational funding model for multinational IICs? *(Keynote by Hans-Eckhardt Hagen, Glopid-R Scientific Advocacy Director)*

15h00 - ATTRACT: International call for research proposals on rare cancer drug development
Delphine Ferrier, Head of Transnational Research and Innovation (Fondation pour la recherche sur le cancer)

15h10 - CEPI: New Vaccines For A Safer World
Saul Walker, CEPI Director Public Partnership

15h20 - KCE/ZonMw: BeNeFIT Calls for Comparative Effectiveness
France Vrijens, Head of KCE Trials Programme

15h30 - ERDERA (Rare Diseases Partnership) Joint Translational Calls for IICs on Rare Diseases
Ralph Schuster, Scientific Officer, DLR & ***Carmen Fotino***, Scientific Officer, Fondazione Telethon

15h40 - EDCTP
Lara Pandya**,** Sr. Strategic Partnership Officer at EDCTP

15h50 - Nordforsk community research
Maria Nilsson, Nordforsk Special Adviser

16H20 | General Discussion & questions

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AGENDA

WORKSHOP: Funding mechanisms for Investigator-Initiated Clinical Studies

VENUE: COMET LOUISE - Pl. Stéphanie 20, 1050 Brussels
Room 4.4. "Tatacoa Escape"

9H TO 13H

9th of February (day 2)

9H | Summary of day 1

9H10 | Potential solutions applicable to ERA4Health JTC/Phase II

Plenary

10H10 | JTC call on IICs. Eligibility criteria and selection procedure

Plenary and break out sessions

10h10 Scoping paper overview. Plenary

10h15 Break-out sessions

10h40 Wrap up break out sessions and general discussion. Plenary

11H10 | Coffee break

11H30 | JTC call on IICs. Selection procedure.

Plenary

12H30 | Wrap-up & Closing Remarks

13H | Take away lunch

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Annex 2. Initiatives and funders attending the meeting

Funders- National ERA4Health partners, and other national funders (NIHR United Kingdom, SNSF Switzerland, KCE Belgium, French Ministry of Health France, ABM Poland, Czech Health Research Council, Departament de Salut Generalitat de Catalunya, Swedish Research Council),

European Commission – DG RTD

HADEA

EMA- ACT EU

Other projects/partnerships supporting IICs (ATTRACT, CEPI, BENEFIT (joint KCE-ZonMw program), ERDERA, EDCTP, NORDFORSK, GloPID-R)

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