



D19.3 Report describing recommendations for activities to increase the attractiveness of Europe for performing clinical trials

WP19



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#1	Marta del Álamo Sabrina Lémeret	ECRIN	02/10/2025
##	Author 2	Partner short name	DD Month 20YY

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¹ PU = Public
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GLOSSARY / LIST OF ACRONYMS

ACT-EU ACCELERATING CLINICAL TRIALS IN THE EUROPEAN UNION

ATTRACT ACCELERATE TOGETHER RARE CANCER TREATMENT

C4C CONNECT FOR CHILDREN

CDISC CLINICAL DATA INTERCHANGE STANDARDS CONSORTIUM

CEPI COALITION FOR EPIDEMIC PREPAREDNESS INNOVATIONS

CTA CLINICAL TRIAL APPLICATION

CTAG CLINICAL TRIALS COORDINATION AND ADVISORY GROUP

CTCG CLINICAL TRIALS COORDINATION GROUP

CTIS CLINICAL TRIAL INFORMATION SYSTEM

CTR CLINICAL TRIAL REGULATION

ECRAID EUROPEAN CLINICAL RESEARCH ALLIANCE ON INFECTIOUS DISEASES

ECRIN EUROPEAN CLINICAL RESEARCH INFRASTRUCTURE NETWORK

EDCTP EUROPEAN AND DEVELOPING COUNTRIES CLINICAL TRIALS PARTNERSHIP

EMA EUROPEAN MEDICINES AGENCY

ERDERA EUROPEAN RARE DISEASES RESEARCH ALLIANCE

EU EUROPEAN UNION

EUPATI EUROPEAN PATIENTS' ACADEMY ON THERAPEUTIC INNOVATION

EUREC EUROPEAN NETWORK OF RESEARCH ETHICS COMMITTEE

EHDS EUROPEAN HEALTH DATA SPACE

EURORDIS EUROPEAN ORGANISATION FOR RARE DISEASES

HDABS HEALTH DATA ACCESS BODIES

HERA HEALTH EMERGENCY PREPAREDNESS AND RESPONSE

HMA HEADS OF MEDICINES AGENCY

HTA HEALTH TECHNOLOGY ASSESSMENT

IICS/IICT INVESTIGATOR-INITIATED CLINICAL STUDY/TRIAL

IMI INNOVATIVE MEDICINES INITIATIVE (NOW IHI INNOVATIVE HEALTH INITIATIVE)

IVDR IN VITRO DIAGNOSTIC MEDICAL DEVICE REGULATION

JTC JOINT TRANSNATIONAL CALL

MDR MEDICAL DEVICE REGULATION

MRECS MEDICAL RESEARCH ETHICS COMMITTEES

MWP METHODOLOGY WORKING PARTY

RFI REQUEST FOR INFORMATION

SCTO SWISS CLINICAL TRIAL ORGANISATION

UK UNITED KINGDOM

EXECUTIVE SUMMARY

Enhancing Europe’s attractiveness as a destination for clinical trials is vital to sustaining its global competitiveness in medical research, improving patient access to innovative therapies, strengthening global healthcare systems and fostering economic growth. Despite Europe’s scientific excellence, fragmented regulations, administrative burdens, and inconsistent national practices continue to hinder the efficiency and appeal of conducting trials across Member States. Addressing these challenges requires a coordinated, strategic approach at both EU and national levels.

In line with ERA4health’s strategic objectives:

- Supporting relevant medical research including clinical fields and intervention areas (prevention, diagnosis, treatment)
- Building capacity, in particular in conducting IICS at EU scale,

the purpose of this report is describing potential activities (recommendations) to be undertaken both at general level and during the ERA4Health partnership, based on hurdles identified as part of D14.1 “Report on Bottlenecks to multicountry IICS”.

Key priorities include promoting well-designed and adequately funded multinational trial calls, streamlining national and European Commission procedures, and investing in modern trial methodologies such as adaptive, platform, and decentralized designs. Strengthening digital health capabilities—through toolkits for remote monitoring, eConsent, and interoperability between hospital systems and trial platforms—will increase efficiency and patient participation. Greater patient involvement in research development, supported by EU-level advisory boards and harmonized ethics review processes, will ensure that trials are feasible, inclusive, and aligned with patient needs.

Europe must also build capacity through trial readiness certifications, harmonized site feasibility platforms, and standardized trial agreements. Financial and regulatory support—such as mechanisms for access to investigational products, tax incentives, and model insurance frameworks—can further empower non-commercial and investigator-initiated trials. Finally, establishing an EU-wide standard for clinical trial data sharing, linked to the Clinical Trials Information System (CTIS) or the European Health Data Space (EHDS), will enhance legal certainty, reduce compliance burdens, and encourage participation in multicenter, data-driven research.

Together, these measures will create a more integrated, agile, and patient-centered clinical research ecosystem across Europe.

1. PURPOSE AND OBJECTIVES

BACKGROUND

Clinical trials are the cornerstone of medical innovation, driving the development of new therapies, improving patient outcomes, and strengthening global healthcare systems. However, in recent years, Europe has faced a decline in its share of global clinical research activity, with many sponsors and companies choosing to conduct trials in regions perceived as more efficient, cost-effective, or regulatory-friendly. This trend poses significant challenges to Europe's competitiveness in the global biopharmaceutical landscape and to the timely access of European patients to cutting-edge treatments.

Recent European level and member state policy initiatives have attempted to increase the capabilities and attractiveness of the clinical trial ecosystem. For example, EU Clinical Trials Regulation (CTR)/CTIS aimed to harmonize clinical trial capabilities across Europe, and make multi-country applications more streamlined, with the goal of boosting Europe's competitiveness in attracting clinical trials. This goal has not yet been met. At best, Europe has held but not improved its position. The EFPIA/IQVIA report, *Assessing the Clinical Trial Ecosystem in Europe*¹ suggests that whilst Europe is a strong performer in commercial multi-country clinical trials, it is losing global share, particularly to Asia and other regions (falling from 25% in 2013, to 19% in 2023). According to the report, the major primary drivers of declining attractiveness are the regulatory fragmentation and complexity and the slower trial set up. The main reasons outlined in the report are:

- Regulatory complexity and uneven implementation of EU regulation (CTR)
- Operational complexity and slow start-up/recruitment timelines
- Competition with other regions with more favorable environments (notably China and US)
- Operational and legal bottlenecks at national level (contracting, data protection, ethics)
- Regulatory/technical spillovers from other EU regulation (MDR, IVDR)
- Capacity and infrastructure constraints (sites, staffing, readiness)
- Funding/investment environment

While the EFPIA report does not explicitly separate out academic trials in its data or conclusions, the systemic barriers it identifies—regulation fragmentation, slow ethics review, lack of harmonized infrastructure—apply equally to academic research. The proposed solutions (streamlined CTR implementation, CTIS modernization, harmonized ethics review, cross-border participation) would therefore also significantly enhance the environment for academic-led clinical trials across Europe.

According to EMA's ACT EU data²:

- From 1,806 trials authorized between January 2022 and December 2023, approximately 58% were commercially sponsored, while a notable 42% were non-commercially (academic) sponsored

This indicates a significantly higher proportion of academic trial activity under the new CTR system compared to historical estimates (20–40%).

Data highlights stark contrast in multinational trial authorization: As of late 2023, only 21 multinational trials were academically sponsored versus 209 commercially sponsored.

This underscores that cross-border academic trials remain rare, even in the CTR era.

The CTR appears to have increased academic sponsorship share of authorized trials, though this may reflect changes in reporting, transition of ongoing studies, or a higher volume of simpler or transitional trials.

Despite this higher share, academic multinational trial activity remains limited—confirmed by the low number of cross-border/multinational academic trials approved under CTIS.

PURPOSE AND OBJECTIVES

In line with ERA4Health's strategic objectives:

- Supporting relevant medical research including clinical fields and intervention areas (prevention, diagnosis, treatment)
- Building capacity, in particular in conducting IICS at EU scale,

a reflection is thus undertaken to find activities to increase Europe's attractiveness for performing multinational investigator-initiated clinical trials (IICT).

The purpose of this report is describing potential activities (recommendations) to be undertaken both at general level and during the course of the ERA4Health partnership, based on hurdles identified as part of D14.1 *"Report on Bottlenecks to multicountry IICS"*.

Of note, translational research will not be addressed in this report since this was part of another deliverable (D19.2-*Overcoming barriers activity report*).

2. METHODOLOGY

Scope-Multinational clinical trials in Europe, with special focus on academic trials.

Approach-Bottlenecks reported in *D14.1-Report on Bottlenecks to multi-country IICS* ³, were used as a starting point to identify how they can affect attractiveness for performing multi-country IICT in Europe and reflect on initiatives working on addressing these issues. After this scoping analysis, other potential activities- both at general and partnership level- are described.

The report summarizes scoping analysis and recommendations following this scheme:

Bottleneck	Impact on attractiveness	Current initiatives addressing this issue	Current/future activities in ERA4Health	Recommendations

3. RESULTS

The following aspects were identified as obstacles for planning and conducting multi-country IICS in Europe ³:

Funding and funding mechanisms

- Lack of provision of adequate resources and infrastructure, including administrative support
- Absence of cross-border initiatives. Focus on national funding project
- Limited funding and grant duration
- Lack of scheme for small/medium multicountry clinical trials

How does it affect attractiveness?

- Risk of financial loss for sponsor and investigator
- Increased complexity/workload for sponsor financial department

Which initiatives are addressing this challenge at general level?

The EC finances multi-country IICS, implementing regular calls for funding through multiannual funding programmes ⁴:

Horizon Europe programme (Regular Calls, Public- public partnerships, Innovation Health Initiative, EDCTP)

HERA (Health Emergency Preparedness and Response)

EC's grants allow cross-border funding, and the amount and duration are variable. Nevertheless, administrative burden for grant applicants and beneficiaries challenges trial's development. The EC is working on simplifying financial reporting for grant holders through the implementation of "lump sum" grants.

Some funding organizations have developed funding mechanisms adapted to multinational trials. For example, the NordForsk Community Research funds clinical studies, including clinical trials, pooling national funding from different Nordic Countries to create a real common pot that allows supporting cross-cutting/cross-border activities.

ATTRACT brought together 5 European charities funding multinational clinical research on cancer through a virtual common pot. Although the virtual common pot scheme does not allow cross-border funding, ATTRACT's financial model supports clinical studies up to 10 years. Supporting this initiative, the EC has recently funded the CSA (Coordination and Support Action) FORCE, involving ATTRACT charities. FORCE will propose foundational pillars for EU strategic support to a European cancer charities network dedicated to organising, implementing and monitoring sustainable and ambitious support for cancer pragmatic clinical trials.

ERDERA, rare diseases partnership co-funded by the European Commission (EC) and EU member states will fund phase I/II multinational trials using the EC contribution as real common pot, facilitating cross-border funding.

Regarding supporting infrastructure, ECRIN is the European Research Infrastructure that supports the planning and conduct of academic multinational clinical trials in Europe. ECRIN works with national networks of clinical trial units (CTUs), and with numerous European and international stakeholders involved in clinical research to support academic sponsors/investigators.

Which ERA4Health activities can address this issue?

- Optimizing current funding mechanisms. ERA4Health Pillar 2B WP16 has worked on adapting the ERA-Net/Partnership's Joint Transnational Call (JTC) mechanism to the particularities of funding academic multinational clinical trials. The adapted funding mechanism is being piloted through the first ERA4Health call for IICS- EfficTrial, launched in November 2024. A new task to keep on reflecting and improving this funding mechanism is proposed for the partnership's phase 2 (Task 22.5).
- Identifying funding sources for multinational IICS. ERA4Health Deliverable D15.1⁵ has mapped national and international funders of IICS in Europe. During ERA4Health Phase 1, WP 5 (Task 5.3) and WP16 (Task 16.3) have contacted/identified potential funders to expand the number of organizations supporting IICS in Phase 2. As a result, 2 new organisations joined ERA4Health to

support the first ERA4Health IICS call EffecTrial and 9 new organizations have joined ERA4Health to support IICS calls in Phase 2.

- Identifying supporting infrastructure for multinational IICS. ERA4Health Deliverable D15.2⁶ has mapped organisations supporting the planning, design and conduct of multicountry Investigator Initiated Clinical Studies (IICS) at national and European level.
- Incentivizing the use of supporting infrastructures (ECRIN). ERA4Health first call for funding IICS-EffecTrial- proposes additional funding to cover trial cross-cutting activities through collaboration with ECRIN.

Protocol design

- Lack of consideration to cultural, language, national and institutional differences
- Adaptive trials designs increase complexity of the protocol leading to higher error rates
- Current regulatory guidelines not adapted to complex trial designs

How this affects attractiveness?

- Delays to get authorizations due to inappropriate protocol adaptations
- Increased complexity/workload for overall project management

Which initiatives are addressing this challenge at general level?

EMA offers regulatory and scientific support to help academics develop medicines⁷. In addition, national regulators have developed scientific and regulatory advice activities. Indeed, there are multiple avenues for seeking scientific advice in the EU with partially overlapping scope which creates room for divergence and contradictions⁸. ACT-EU Priority Action on consolidated advice has mapped⁹ information on current voluntary procedures available from EU regulators on Medicines for Human use and collated this information in the form of questions and answers.

Regarding specific guidance for complex trials, in the frame of the EU RESPONSE and ECRAID Prime projects, ECRIN has developed the “Adaptive Platform Trial Toolbox”¹⁰, to collect the accumulated knowledge, experience, and resources from multiple projects and trials into a practical and guided toolbox to facilitate planning and conduct of future Adaptive Platform Trials (APTs) in any therapeutic area.

Which ERA4Health activities can address this issue?

ERA4Health Deliverable D14.2-*Recommendation booklet for investigators and sponsors in multicountry investigator initiated clinical studies*^{11 12} aims to offer insights into challenges and solutions encountered in trials employing innovative methodologies, including trials within cohorts (TwICs), umbrella trials, basket trials, adaptive platform trials, and decentralized clinical trials (DCTs).

Public/Patient involvement

- Patient involvement in clinical trials and projects is under-prioritised
- Patient involvement is not funded or underfunded
- Timing of initial contact patient-investigator not aligned with funding calls/project planning

How this affects attractiveness?

- Longer patient recruitment windows
- Delays to get authorizations due to inappropriate protocol adaptations
- Poor retention

Without early input from patients and patient organisations, trial protocols can include burdensome procedures, unrealistic visit schedules or insufficiently compelling endpoints—factors that all slow down enrollment. In its recent assessment of the European clinical trial ecosystem, EFPIA notes that “patient recruitment times in Europe may be impacting the attractiveness of Europe as a trial location,” partly because sponsors struggle to find and retain participants in niche populations without the benefit of patient-led recruitment strategies

Which initiatives are addressing this challenge at general level?

The Clinical Trials Coordination Group (CTCG) is a Head of Medicines Agencies (HMA) working group of experts from national regulatory agencies working on the classification, assessment and oversight of clinical trials. In its 2024–2025 workplan¹³, the group launched a dedicated “Patient/Trial participant centricity and inclusivity” action, with concrete activities to:

- Promote patient participation in protocol design and in the preparation of lay summaries of results (status “started”)
- Develop a guidance document for sponsors on how to involve patients meaningfully (status “started”)
- Produce a best practice template for assessors to evaluate patient involvement in clinical trial applications and to update assessment reports accordingly (status “started”)
- Map fair inclusion strategies for underrepresented populations (this action was deemed outside the CTCG’s direct scope)
- Strengthen the connection with patients, sponsors, investigators and assessors.

To our knowledge, results of these actions have not been published yet.

Coordinated by the ACT-EU initiative, the ACT-EU Multi-stake Platform (ACT EU MSP) is a vehicle for facilitating dialogue and collaboration between regulators and clinical trials stakeholders to further improve the clinical research environment in the EU¹⁴. A patient’s organization representative is part of

the MSP Advisory Group. 2024 MSP Meeting's theme, "*A Brighter Future for Clinical Trials in the EU: Continuing the Journey*," put emphasis on the shared commitment to reshaping the clinical trial landscape for greater inclusivity, efficiency, and patient-centered approaches.

Several patients' organizations have developed tools facilitating patient's engagement in clinical trials. EUPATIconnect¹⁵ is a matchmaking platform developed by the European Patients' Academy on Therapeutic Innovation (EUPATI) to facilitate collaboration between trained patient experts and researchers. Its primary goal is to enhance patient involvement in the research and development (R&D) of medicines by connecting EUPATI Patient Experts with researchers seeking patient input on various projects. With a stronger focus on rare diseases, EURORDIS Community Advisory Boards¹⁶ (CABs) are patient-led groups established to facilitate collaboration between individuals affected by rare diseases and stakeholders involved in medical research, such as pharmaceutical companies and academic institutions. These boards aim to ensure that the perspectives and experiences of patients are integrated into the research and development process for new therapies.

The IMI PARADIGM (Patients Active in Research and Dialogues for an Improved Generation of Medicines) project, active from March 2018 to August 2020, aimed to enhance patient engagement in the development of medicines. It focused on three critical decision-making points: research priority setting, clinical trial design, and early dialogues with regulators and health technology assessment (HTA) bodies. A key outcome of this project was the *Patient Engagement Toolbox*¹⁷: A comprehensive, publicly accessible collection of co-created tools and resources designed to facilitate meaningful patient engagement. Most PARADIGM outcomes, together with tools generated by other projects/initiatives are compiled in the *Patient Engagement Resource Center (PERC)*¹⁸, a repository of publicly available guidance, training and practical tools that support researchers with every stage of their patient engagement activity: planning, conducting and evaluating.

Which ERA4Health activities can address this issue?

The first ERA4Health IICS call- EffecTrial- makes patient and public involvement not optional—but compulsory. It expects active participation of patient representatives in trial design and ongoing governance, requires meaningful consideration of patient-valued outcomes, and embeds inclusiveness and RRI (Responsible Research and Innovation) into every stage. In particular, the call aims for:

- i. Early and ongoing engagement of patients and end users
 - Consortia are *mandated* to involve patient and/or care provider representatives in the co-creation and implementation of trial tasks—from design through execution. This includes involving patient organisations as partners, collaborators, or advisory board members to ensure legitimacy and relevance.
- ii. Integration of patient valued outcomes and acceptability

- Proposals must include patient valued outcomes in trial design, improving relevance and impact of research findings in real-world healthcare decision making
- Involving end users early helps ensure the intervention meets real-life needs and is acceptable to patients and providers from the outset.

iii. Responsible Research & Innovation (RRI) principles

- Applicants must explicitly describe how they will approach social, equity, political, cultural, and environmental dimensions of RRI, which encompasses patient involvement and public values. This includes ethical reflection, inclusiveness, and alignment with societal concerns. The partnership has developed RRI guidelines for applicants.

iv. Diverse and inclusive recruitment strategies

- Proposals must address gender equality, diversity and inclusiveness in recruitment of participants, including under-represented or vulnerable groups. This ensures that patient engagement reflects a broad spectrum of populations potentially affected by the interventions.

v. Ethics and public/citizen benefit

- Applications are required to fill an ethical grid and describe how ethical standards (at institutional, national, EU levels) will be met—further reinforcing accountability toward patients and society.

Consortia must demonstrate the benefit to end users/patients/citizens, highlighting a clear implementation potential. A dedicated Patient Advocacy Panel is involved in the full proposals evaluation phase. To further reinforce patient's inclusion in ERA4Health funded projects, ERA4Health WP20 has developed the on-line training "*Management of multinational clinical studies*", which includes a section on Patient Engagement.

During the Phase 2, ERA4Health will continue working on patient engagement through the following planned activities on WP27:

Task 27.4 aims to reflect on potential central financial support for patient engagement activities for ERA4Health calls, with special focus on financial models supporting patient involvement at the proposal stage. Examples from already existing support actions will be sought. Implementation possibilities in ERA4Health and beyond will be reflected on and recommendations will be described in Deliverable D27.3.

Governance / Regulatory barriers

- Lack of harmonization in international regulation
- Lengthy authorisation times
- Outdated and slowly evolving regulatory frameworks

How this affects attractiveness

- Delays in approval timelines
- Administrative burden

Which initiatives are addressing this challenge at general level?

For clinical studies on the scope of the CTR, the CTIS aims to bring high level of harmonisation, increase and improve coordination between relevant regulation bodies at national and international levels, including national ethics committees and competent authorities, and ease the coordination between partners in Europe.

The Clinical Trials Coordination Group (CTCG), part of the Heads of Medicines Agencies (HMA) network, plays a central role in improving the efficiency, coordination, and attractiveness of Europe as a place to conduct clinical trials. It is a coordination body set up to support the implementation of the CTR and to promote a harmonized and efficient assessment process for multinational clinical trials across EU member states. The CTCG's work plan includes explicit elements aimed at improving the EU's attractiveness for clinical research, especially by supporting academic sponsors, harmonizing regulatory practice, enhancing training and system usability, and involving stakeholders in shaping a better trial environment.

MedEthicsEU is a group of national representatives of medical research ethics committees (MRECs) that was created in February 2024 to provide a forum for discussion and mutual learning between EU/EEA Member States Ethics Committees. This allows enhanced cooperation between Member States' Ethics Committees and further supports harmonisation in the ethics review of clinical trials in Europe. MedEthicsEU aims to making Europe a more attractive clinical trial environment by aligning ethical review across countries, clarifying expectations and processes, and coordinating with regulatory bodies to reduce duplication and delays. Its role strengthens the overall predictability, transparency, and efficiency of the ethics part of clinical trial applications—key factors that sponsors consider when choosing trial locations.

The COMBINE programme, launched by the European Commission in June 2023, plays a strategic role in enhancing Europe's attractiveness for combined clinical studies/trials that involve both a medicinal product and a medical device (MD) or in vitro diagnostic device (IVD). It simplifies a traditionally complex and fragmented regulatory landscape by addressing key inefficiencies at the interface of multiple EU regulations: CTR (medicine), MDR (medical devices), and IVDR (IVDs). The COMBINE programme contributes significantly to improving Europe's attractiveness for clinical research by reorganising the way combined studies are evaluated: introducing cross-sector and cross-border coordination, harmonising procedures, improving stakeholder engagement, and enabling digital system integration.

To overcome the regulatory knowledge gaps in academia, the STARS ("Strengthening Training of Academia in Regulatory Science" project (Horizon 2020 CSA 825881, January 2019 – June 2022)) consortium developed a curriculum ¹⁹ to strengthen the awareness of regulatory science in academia, on

the basis of survey data and the outcomes of interactive multi-stakeholder workshops. These curricula were intended as guiding frameworks for EU universities to adopt or adapt—not mandatory replacements of existing programmes.

One of the core objectives of ACT EU is to reduce regulatory hurdles that have historically made the EU less attractive for conducting clinical trials compared to other regions. The programme intends to establish an action plan with clear measures in place to support non-commercial sponsors across the European Union / European Economic Area by creating and maintaining a network of regulatory helpdesks, building on national activities, including extra support for questions on the CTR and CTIS

RED (Regulatory & Ethics Database) is a centralized online resource developed by ECRIN to provide comprehensive, up-to-date information on regulatory and ethical requirements for conducting clinical trials across European countries.

Which ERA4Health activities can address this issue?

With special focus on IICS, as part of WP15, ERA4Health Deliverable D15.2 describes:

- Organizations able to support IICS at national and international level
- Organizations' support capacity and services offered

For organizations providing services on “clinical operations”, the Deliverable describes which organizations can support sponsors for “Regulatory submission” and “Regulatory affairs”.

ERA4Health website signposts free training (tab *IICS recommended training*) for sponsors and investigators, including a specific training category “Clinical Trial Regulations and Ethics”. This catalog has been developed by ERA4Health Task 20. 4.

Deliverable D14.2 – *Recommendation booklet for investigators and sponsors in multicountry IICS*¹² offers insights into challenges and solutions encountered in trials employing innovative methodologies, including trials within cohorts (TwICs), umbrella trials, basket trials, adaptive platform trials, and decentralized clinical trials (DCTs), including recommendations on regulatory and ethical hurdles.

Clinical Site selection

- Inadequate feasibility planning
- Lack of protocols defining infrastructural elements

How this affects attractiveness

- Delays in trial start up
- Missing recruitment milestones

- High site dropout rates

Which initiatives are addressing this challenge at general level?

Some disease-specific investigation networks are being established at national level through public or charity funding. EU funding from the Health programme or the IMI/IHI partnership act as an incentive to structure, in specific areas, the investigation communities at pan-European level. For instance, the IMI funded c4c project created a central clinical sites database (CFS) capturing capabilities, patient pools, infrastructure, and resources across sites for paediatric medicine development. In the infectious diseases field, ECRAID (European Clinical Research Alliance on Infectious Diseases) is a non-profit European research organization focused on strengthening Europe's capacity to conduct high-quality, multinational clinical research on infectious diseases that builds on multi-setting expertise to support infectious diseases research in primary care, hospitals, pediatric settings, long-term care facilities, and labs.

Which ERA4Health activities can address this issue?

ERA4Health Phase 2 WP27, Task 27.6. will map existing clinical trial site networks in ERA4Health areas of interest. For instance, ESOTA (European Stroke Organization Trials Alliance) is a Network of Networks supporting the conduct of randomised clinical trials leading to improved therapies for patients to prevent and treat acute stroke and the longer-term consequences of stroke. By signposting existing clinical site networks, the partnership intends to support coordinating investigators identifying suitable recruiting partners.

Contracting and budgeting

- Underestimation of work effort and costs in start-up
- Legal costs / lack of legal expertise
- Vendor contract delays
- Lack of harmonization in site standards, costs, and site agreement templates
- Templates tailored to industry-sponsored trials, not aligned with Consortium/Grant agreements linked to publicly funded studies
- Country-specific terminology and interpretation of legal responsibilities, intellectual/industrial property, GDPR
- Reference to national legal and regulatory framework (liability and insurance)
- Translations

How this affects attractiveness

- Delays on trial start up

- Legal cost

Which initiatives are addressing this challenge at general level?

Hurdles on the management of clinical site agreements (CSA) have been already reported both in peer reviewed publications ^{20, 21, 22} and relevant European stakeholders meetings ²³.

ACT EU's latest workplan²⁴ includes a workshop on contractual agreements, planned for the third quarter of 2025.

Which ERA4Health activities can address this issue?

As part of WP16, ERA4Health has developed a Clinical Site Agreement template (Deliverable D16.4-*approved*). Several countries have developed templates for Clinical site agreements but, to the best of our knowledge, none of them are tailored specifically for EU multinational Clinical trials.

D16.4 describes the methodology behind the development of the template, aiming at addressing challenges such as legal compliance, negotiation complexities, and national variations. The document should improve efficiency, reduce administrative burden, and ensure compliance with applicable EU regulations. Ultimately, this template will foster better collaboration across member states for Clinical trials.

ERA4Health Phase 2 WP27, Task 27.3, aims at developing actions to promote implementation, enforcement, and endorsement of the above-mentioned site agreement contract. To do so, a workshop will be organized with relevant stakeholders (sponsors and national clinical networks) to discuss strategies promoting implementation, considering country specificities identified in Task 16.5. Among others, a potential way to foster implementation could be through ERA4Health JTC IICS. At minimum, the funded IICS consortia will be informed about the existence of the template of CTA. Finally, the feedback of the institutions using the trial site agreement will be collected and considered for improvement (D27.2).

Study management

- Lack of systematic approach to project management for clinical research
- Lack of experienced administrative support and resources for management team

How this affects attractiveness

- Delays in study start up
- Inconsistent quality and compliance
- Low site performance and recruitment failures
- Duplication of effort and wasted resources

Which initiatives are addressing this challenge at general level?

ICH-GCP E6(R3) both acknowledges and partially addresses the historical lack of a systematic approach to project management in clinical research — but it does not fully resolve it, especially in the European context where structural and institutional fragmentation persists.

Which ERA4Health activities can address this issue?

As part of WP20-Task 20.3 ERA4Health has developed a training on “Management of multinational clinical studies” designed to familiarise investigators, personnel from clinical trial units and sites (principal Investigators, sub-investigators, study coordinators and project managers) with the challenges of initiating and managing multinational studies. Its module on “project management” highlights the importance of project management and adequate tasks split between investigator and sponsor.

ERA4Health website signposts free training (tab *IICS recommended training*) for sponsors and investigators, including a specific training category “Clinical Trial Management”.

Drug procurement and distribution

- Varying access to investigational drug
- Import/export regulations
- Placebo access

In some cases, academic sponsors cannot freely access investigational medicinal products (IMPs)—either due to regulatory restrictions, complex procurement rules, or lack of funding. This makes it difficult or impossible to run head-to-head, repurposing or de-escalation trials that are not aligned with commercial priorities.

How this affects attractiveness

- Fewer investigator-initiated trials
- High-cost burden on academic sponsors

Which initiatives are addressing this challenge at general level?

The European CTR exempts certain investigator-initiated trials using authorized medicines from full GMP and labeling requirements, specifically:

- If the investigational medicinal product (IMP) is already authorized in the EU, and
- The use in the trial aligns with its authorized indication, and
- The drug is not being repackaged or relabeled for the study

→ Then simplified rules apply, especially around drug labeling and release. This reduces cost and administrative burden for IICS using standard-of-care drugs.

Which ERA4Health activities can address this issue?

None of the ERA4Health passed or future activities are directly addressing this issue. Nevertheless, ERA4Health delivers policy-relevant surveys, workshops, and calls (e.g., EffectTrial) that can lead to proposals for solutions.

Liability/insurance

- Lack of common system for liability insurance

Europe's clinical trial insurance landscape is highly fragmented, each EU Member State sets its own rules for: insurance coverage levels, who must be insured (sponsor, investigator, both), whether state indemnity applies, acceptable insurance providers.

How this affects attractiveness

- Increased cost and complexity
- Delays in trial start-up

Which initiatives are addressing this challenge at general level?

During drafting of the EU CTR, policymakers evaluated possible schemes for harmonised insurance:

- Member States establish a national indemnification mechanism—free or nominal fee—for non-commercial trials, reducing the reliance on expensive private insurance
- Simplified rules for authorized IMPs, offering both reduced regulatory requirements and cost-effective indemnification for low-risk/non-commercial trials

While these options were discussed and included in amendments to the Regulation proposal, they were not fully realised in the final CTR text. A clause allowed sponsors in a single country to use one insurance policy across multiple trials, but an EU wide system was not mandated.

Which ERA4Health activities can address this issue?

ERA4Health addresses challenges in infrastructure and funding for academic trials across borders. Its initiatives include efforts to identify operational bottlenecks—which include insurance fragmentation—and to build shared frameworks or pilot solutions. ERA4Health delivers policy-relevant surveys, workshops, and calls (e.g. EffectTrial) that can lead to proposals for national or EU-level indemnity solutions.

Trial Personnel

- Burden of responsibility and tasks
- Lack of relevant experience and training
- Lack of acknowledgement/accreditation impacting physician involvement
- Lack of standardized training for personnel

How this affects attractiveness

- Lower trial performance and sponsor confidence
- Regulatory and audit risk

Which initiatives are addressing this challenge at general level?

The CONSCIOUS and CONSCIOUS II projects aimed at improving the quality and efficiency of clinical trials by enhancing the training and competence of clinical trialists, particularly in academia. Both CONSCIOUS and CONSCIOUS II focused on professionalizing academic clinical research in Europe by:

- Defining and standardizing required competencies
- Identifying and addressing training needs
- Creating structured, role-based training programs
- Supporting certification and career progression

ACT EU has collected, categorized and analysed clinical trials training needs of academia and SMEs (Micro, small and medium-sized enterprise). Its output will inform the next steps in supporting the academic sector and SMEs in the clinical trials environment: Ongoing training initiatives will also be leveraged so better targeted and easily accessible clinical trials training can be made available to researchers in the academic sector.

Which ERA4Health activities can address this issue?

ERA4Health WP20 is entirely dedicated to Capacity Building Activities and Task 20.3. aimed at analyzing existing curricula/targeted trainings to propose a training programme that will contribute to enhancing the methodological and operational quality of the proposals applying to the multicountry IICS calls, with a special focus on clinical trials. Thus, Deliverable D20.9 (sensitive) includes:

- A description of existing training and education programmes/curricula. Several European funded projects have developed curricula/syllabus to train trialists/research teams on clinical research/clinical trials management. The audience and scope of the topics covered is variable.
- An IICS training programme that would support the methodological and operational implementation of publicly funded clinical trials

- A catalogue of free-of-charge training, on the following topics: Proposal writing, clinical trial methodology, Ethical and legal aspects, Good clinical practice, Trial management, Patient engagement

As a result of this work, a list of selected trainings is signposted in the ERA4Health website (<https://era4health.eu/training/iicsretraininglist.php>). Training can be browsed for the following categories: Proposal writing, GCP, Clinical Trial methodology, Clinical Trial management, Clinical Trial Regulation and Ethics and Patient Engagement.

ERA4health Deliverable D20.9 (sensitive) has been shared with ACT-EU to contribute to their efforts regarding identification of training needs.

Patient recruitment and retention

- Challenges in retaining patients
- Outdated manual screening processes/lack of adaptive screening processes
- Protocol burden for patients leading to withdrawal

How this affects attractiveness

- Delays and increased costs
- Increased risk of study failure

Which initiatives are addressing this challenge at general level?

To our knowledge, there is no public initiative explicitly/exclusively working on patient recruitment/retention strategies, but:

- Trials@Home (IMI-grant agreement n° 831458) explores decentralized strategies, including patient recruitment and remote participation to reduce patient burden
- READI (IHI-grant agreement No 101166227) focuses on recruitment/retention of underserved populations
- REALISED (IHI- grant agreement No 101165912) tackles rare-disease trial design and patient reach
- FACILITATE (IHI- grant agreement No t101034366), focused on creating a GDPR-compliant, patient-centered model for returning clinical trial data to participants, strengthening transparency, trust, and long-term engagement in studies

Which ERA4Health activities can address this issue?

As part of WP20-Task 20.3 ERA4Health has developed a training on “Management of multinational clinical studies” designed to familiarise investigators, personnel from clinical trial units and sites (principal Investigators, sub-investigators, study coordinators and project managers) with the challenges of

initiating and managing multinational studies. Its patient engagement module describes, among others, how patient engagement at the trial planning stage can facilitate patient recruitment and retention.

Monitoring

- Lack of knowledge of general accepted methods for risk-based monitoring

How this affects attractiveness

- Increased perception of operational risk

Which initiatives are addressing this challenge at general level?

Monitoring is considered costly and thus underprioritized in academic trials. Risk-Based Monitoring (RBM) is a modern approach endorsed by ICH GCP E6(R2) and EMA that shifts the focus from routine site visits and 100% source data verification (SDV) to targeted, data-driven oversight. It emphasizes:

- Risk assessment at protocol and system levels
- Centralized and remote monitoring
- Focus on critical data and processes
- Proactive identification of issues

Without RBM, trials default to traditional monitoring models, which are:

- More expensive (e.g., heavy on-site SDV)
- Slower to identify issues
- Harder to scale

Global sponsors, for instance large pharma companies, might therefore prefer countries that apply RBM consistently to reduce cost and timelines. For academic sponsors, lack of RBM monitoring might lead to costly and therefore unaffordable trials.

ICH GCP E6(R3)- the latest revision of the Good Clinical Practice guideline — reinforces Risk-Based Monitoring (RBM) by embedding it into the core principles of trial oversight, quality management, and data integrity. It builds on the foundations set by E6(R2) but goes further by making RBM a default expectation, not just an option.

Which ERA4Health activities can address this issue?

With special focus on IICS, as part of WP15, ERA4Health Deliverable D15.2 describes:

- Organizations able to support IICS at national and international level
- Organizations' support capacity and services offered

For organizations providing services on “clinical operations”, the Deliverable describes which can support sponsors for Quality Management, including monitoring and auditing.

Data management and sharing

- Lack of binding international guidelines/principles
- Poor availability of skilled staff members such as statisticians and data managers

How this affects attractiveness

Without harmonized, EU-wide guidelines for how, when, and with whom clinical trial data can be shared, sponsors must navigate country-by-country legal interpretations, especially under the GDPR.

This leads to:

- Delays in trial setup due to legal reviews
- Duplicate efforts in negotiating data sharing agreements
- Higher compliance risks, especially in multi-country trials

Which initiatives are addressing this challenge at general level?

Major global efforts (e.g. TransCelerate, Clinical Data Interchange Standards Consortium - CDISC, or ICH E19) promote harmonized, open, and structured clinical data sharing.

The European Health Data Space (EHDS) is designed to directly address many of the data sharing challenges that currently undermine Europe’s attractiveness for clinical trials — particularly those related to the lack of harmonized guidelines for secondary use of health and clinical trial data. EHDS introduces the concept of Health Data Access Bodies (HDABs) in each Member State to:

- Review requests for secondary data use
- Issue data permits under common EU criteria

This makes it legally and operationally easier for researchers and companies to:

- Access anonymized or pseudonymized trial data
- Use it across borders
- Combine it with real-world data or registries

By reducing administrative burden and unlocking trusted, GDPR-compliant access to high-quality data, EHDS will attract global sponsors and innovators, enable cross-border trials and collaborations, boosting Europe’s profile in digital health and AI (Artificial Intelligence) in medicine

Which ERA4Health activities can address this issue?

ERA4Health Task 16.6 has developed Deliverable D16.5 “*Guidelines for data sharing of investigator-initiated clinical studies*”. These guidelines should be of relevance to stakeholders (funders, grant applicants, co-investigators, research staff, patients’ groups, researchers, academia, professional groups, industry, reviewers, and regulatory authorities and ethics committees) involved in clinical studies with special focus on non-commercial/investigator-initiated trials in Europe. This guideline has been signposted by the first ERA4Health call for IICS, EffectTrial.

Based on all the above-mentioned results, Table 1 summarizes recommendations for activities- in addition to than those described above- to increase the attractiveness of Europe for performing clinical trials.

3.2. Recommendations to increase Europe’s attractiveness for performing clinical trials

Obstacle	Impact	Initiatives	Recommendations
Funding	<p>Risk of financial loss for sponsor and investigator</p> <p>Increased complexity/workload for sponsor financial department</p>	<p>EC calls (Horizon Europe, Partnerships)</p> <p>National funding calls supporting multinational trials</p>	<p>Promoting well designed and funded calls for multinational clinical trials</p> <p>Streamlining national and EC calls</p>
Protocol design	<p>Delays to get authorizations due to inappropriate protocol adaptations</p> <p>Increased complexity/workload for overall project management</p>	<p>EMA and National Competent Authorities Scientific Advice</p>	<p>Support guidance and infrastructure for adaptive trial designs, platform trials, and decentralized clinical trials (DCTs).</p> <p>Create toolkits and best practices for implementing digital health technologies (e.g., remote monitoring, eConsent) in line with GCP.</p> <p>Promote the use of methodology consortia (e.g., Horizon Europe, successor initiatives) to disseminate</p>

			knowledge on efficient trial methodologies.
Public/patient involvement	<p>Longer patient recruitment windows</p> <p>Delays to get authorizations due to inappropriate protocol adaptations</p> <p>Poor retention</p>	<p>Clinical Trials Coordination Group, ACT-EU and patient organizations (EURORDIS, EUPATI) actions</p> <p>Patient Engagement Resource Center</p>	<p>Mandate or encourage patient involvement in protocol development across EU-funded trials.</p> <p>Support patient advisory boards at the EU level to evaluate trial feasibility and burden.</p>
Governance/regulatory barriers	<p>Delays in approval timelines</p> <p>Administrative burden</p>	<p>Clinical Trials Coordination Group, ACT-EU and MedEthicsEU actions</p> <p>CTIS improvement</p> <p>COMBINE programme</p> <p>ECRIN Regulatory and Ethics Database</p>	<p>Offer technical support to Member States to amend or clarify national laws that hinder trial governance.</p> <p>Fund EU-wide workshops, harmonized review templates, and shared training for ethics bodies.</p>
Clinical site selection	<p>Delays in trial start up</p> <p>Missing recruitment milestones</p> <p>High site dropout rates</p>	<p>EC funded capacity building projects supporting clinical research networks (C4C, ECRAID)</p>	<p>Create a pan-European feasibility platform integrating investigator/site capabilities, recruitment potential, and past trial performance.</p> <p>Establish trial readiness certifications for clinical sites based on capability to conduct simplified or complex trials.</p>
Contracting and budgeting	<p>Delays on trial start up</p> <p>Legal cost</p>		<p>Encourage endorsement of a harmonized clinical trial agreement by the European Commission and Member States, possibly via the European Medicines Agency</p>

			(EMA) or Clinical Trials Coordination Group (CTCG)
Study management	<p>Delays in study start up</p> <p>Inconsistent quality and compliance</p> <p>Low site performance and recruitment failures</p> <p>Duplication of effort and wasted resources</p>	ICH-GCP E6 (R3)	<p>Tools or templates for trial budgeting, scheduling, and resource allocation</p> <p>Guidance on vendor management, team coordination, or cross-functional governance</p> <p>Requirements for project performance indicators (e.g. KPIs, timelines, milestone tracking)</p>
Drug access	<p>Fewer investigator-initiated trials</p> <p>High-cost burden on academic sponsors</p>	Clinical Trial Regulation simplified rules on drug handling for some investigator-initiated trials	<p>Pan-European mechanisms for drug donation or discounted access for non-commercial sponsors.</p> <p>National funding schemes that cover drug acquisition costs for academic sponsors.</p> <p>Incentives for industry to support investigator-initiated trials (e.g., tax relief, recognition)</p>
Liability and insurance	<p>Increased cost and complexity</p> <p>Delays in trial start-up</p>		<p>Create a model EU insurance policy or minimum standard recognized across Member States for clinical trials under CTR</p> <p>Define core coverage elements (e.g. scope, limits, claims process) to eliminate national inconsistencies.</p> <p>Allow Member States to opt into mutual recognition of compliant sponsor insurance policies.</p>
Trial personnel	<p>Lower trial performance and sponsor confidence</p>	Training (CONCIOUS, other	Establish an accredited EU training and certification system for trial personnel,

	Regulatory and audit risk	ERA4Health IICS recommended training)	aligned with Good Clinical Practice (GCP) and EU Clinical Trials Regulation (CTR).
Patient recruitment and retention	<p>Delays and increased costs</p> <p>Increased risk of study failure</p>	<p>EC funded capacity projects:</p> <p>Trials@Home, READI, REALISE D, FACILITATE</p>	<p>Support the development and validation of digital recruitment tools (e.g., social media campaigns, mobile apps, geotargeted outreach).</p> <p>Promote interoperability between hospital EHR systems and trial platforms to enable automated eligibility screening.</p> <p>Promote inclusion of patient-reported experience measures (PREMs) to monitor satisfaction and retention risks during trials.</p>
Monitoring	Increased perception of operational risk	ICH-GCP E6 (R2, R3)	Invest in training, harmonized guidance, and infrastructure that promotes risk-based approaches in line with global expectations
Data management	<p>Delays in trial setup due to legal reviews</p> <p>Duplicate efforts in negotiating data sharing agreements</p> <p>Higher compliance risks, especially in multi-country trials</p>	<p>TransCelerate, Clinical Data Interchange Standards- CDISC, ICH E19</p> <p>European Health Data Space (EHDS)</p>	<p>An EU-wide standard for clinical trial data sharing (possibly linked to EMA's Clinical Trials Information System – CTIS or EU Health Data Space) would:</p> <ul style="list-style-type: none"> • Increase legal certainty • Enable trusted secondary use of trial data • Reduce compliance burden • Boost participation in data-driven, multicenter trials

Table 1. Recommendations to increase Europe's attractiveness for performing clinical trials

4. CONCLUSIONS

To strengthen Europe's position as a global leader in clinical research, it is essential to enhance the region's attractiveness for conducting clinical trials. This requires coordinated action across funding, regulation, infrastructure, and patient engagement. Key priorities include promoting well-funded, multinational trial calls and harmonizing national and EU processes to reduce administrative burden. Europe should invest in infrastructure and guidance for adaptive, platform, and decentralized trials, while advancing digital tools such as eConsent and remote monitoring. Greater patient involvement in protocol design and ethical review, alongside harmonized training, review templates, and trial readiness certification, will improve quality and trust. Streamlined governance, standardized clinical trial agreements, and consistent insurance frameworks across Member States can further reduce complexity. Financial incentives and shared mechanisms for drug access should support non-commercial and investigator-led trials. Finally, developing an EU-wide data-sharing standard and enhancing interoperability of digital health systems will enable efficient, data-driven research, ensuring Europe remains competitive, innovative, and patient-centered in the evolving global trial landscape.

Increasing the attractiveness of Europe as a destination for clinical trials is essential. Streamlining regulatory processes, enhancing digital infrastructure, promoting collaboration between public and private sectors, and ensuring access to diverse patient populations can make Europe a more competitive and innovative environment for clinical research. Strengthening Europe's position in this field not only supports scientific excellence and economic growth but also ensures that European citizens benefit directly from advancements in medical science.

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