ECRIN Support for EU Funding Applications & Trial Management

ECRIN
EUROPEAN CLINICAL RESEARCH INFRASTRUCTURE NETWORK

ECRIN Support for EU Funding Applications & Trial Management

ECRIN: A NETWORK TO SUPPORT MULTINATIONAL CLINICAL TRIALS IN EUROPE

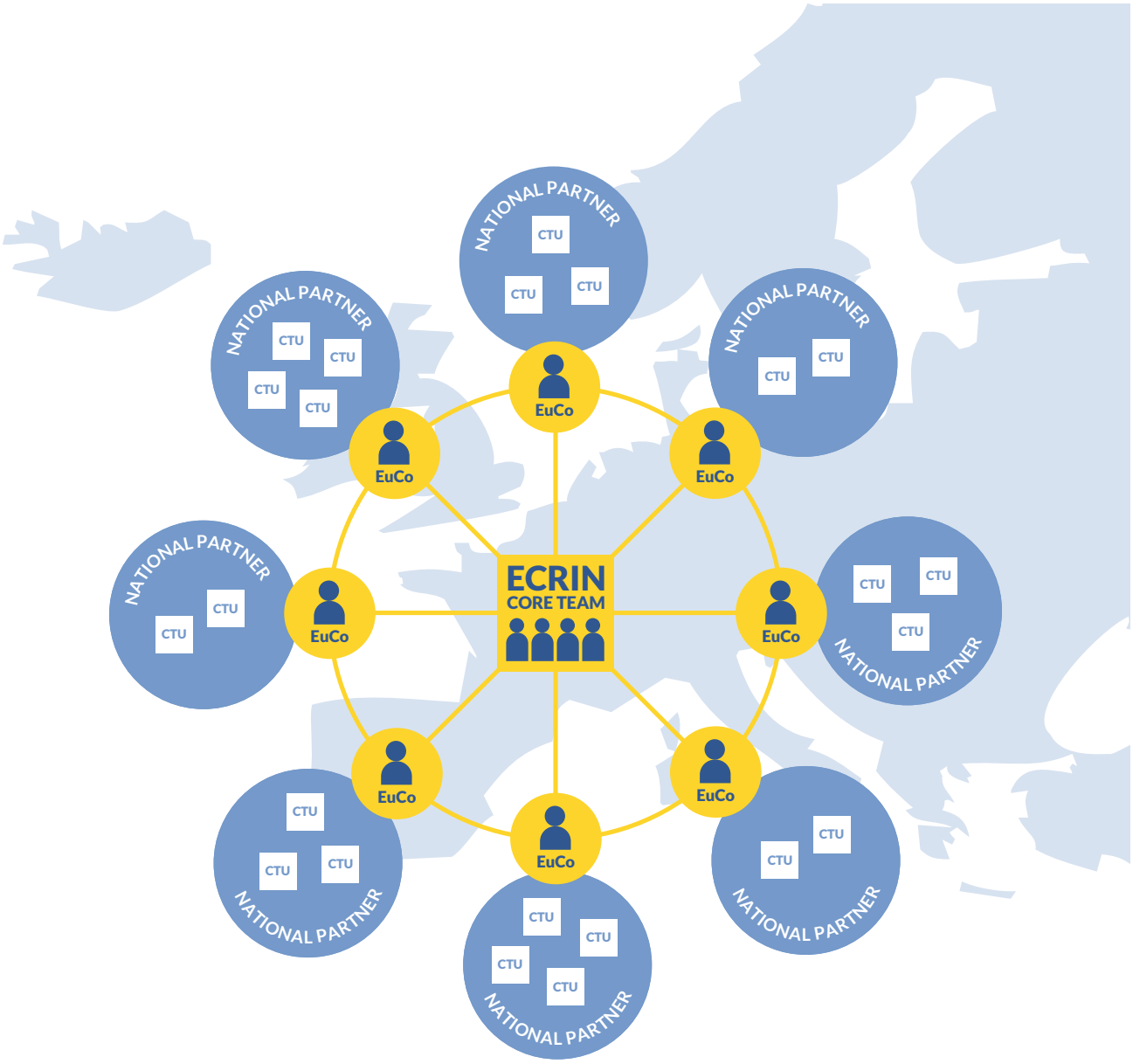
The European Clinical Research Infrastructure Network (ECRIN) is a non-profit, intergovernmental organisation that supports multinational clinical trials in Europe. Multi-country trials provide increased access to patients, resources, and expertise, and, in turn, potentially more robust trial results and greater public health impact.

With a focus on investigator-led, academic studies, ECRIN provides diverse services and tools for trial preparation (e.g., advice on funding applications and trial design, from site selection to logistics and insurance issues), protocol review (scientific and logistical advice), and trial management (regulatory and ethical authorisation, adverse event reporting, monitoring, data management, statistics and project management).

European Correspondents: Your Partner for ECRIN Support

ECRIN's support is largely coordinated by its European Correspondents (EuCos). These clinical research and methodological experts work directly in each of ECRIN's Member and Observer Countries (see "More About ECRIN"), and are at the heart of the organisation's unique ability to successfully work across borders.

Here we present how ECRIN can support investigators/sponsors in the preparation of European Union (EU) funding applications including Horizon 2020 calls. We also detail the services that ECRIN can provide during project implementation, if associated as a project partner. Finally, we describe the tasks that are provided by ECRIN's national scientific partners (networks of clinical trial units, CTUs) during both preparation and implementation.



EuCo European Correspondent | **CTU** Clinical Trial Unit

ECRIN Organisation

ECRIN currently has seven Member Countries (France, Germany, Hungary, Italy, Norway, Portugal and Spain) and two Observer Countries (Czech Republic and Switzerland). Each country has a EuCo who manages the clinical trial portfolio and coordinates with the national scientific partner (i.e., network of clinical trial units, or CTUs), with support from the Paris-based Core Team.

In non-Member/Observer Countries, we have local contacts through our collaborative projects. These individuals can be mobilised to advise on and identify appropriate resources in-country.

ECRIN SUPPORT: PREPARATION OF EU FUNDING APPLICATIONS

ECRIN Role: Advice and Information for Investigators and Sponsors

ECRIN can help investigators and sponsors in ECRIN Member and Observer Countries to prepare EU funding proposals, regardless of their level of experience with such applications.

The scope of ECRIN's involvement in proposal preparation will depend on its role. While information may be freely provided to all, ECRIN can also be involved in designing and completing certain sections of the proposal if associated as a project partner/provider of trial management services (see below).

Support from Call Identification to Proposal Submission

ECRIN can provide general information on the types of available European funding and how to go about applying (strategy, timelines, etc.), if needed. Once the investigator/sponsor has identified an appropriate funding opportunity for the proposed trial, ECRIN can provide advice and information on:

- The facilities that have the capacity and services needed to manage the trial, as well as relevant investigator sites and networks in participating countries (especially those that are ECRIN Members or Observers)
- Additional proposal/trial design elements including multinational clinical trial management, regulatory, ethical and insurance requirements, appropriate trial methodology, cost of ECRIN trial management services, logistical feasibility of proposed plans, work package architecture, potential impact, management, governance, consortium composition, and more.
- The most suitable task distribution and work organisation for the completion of the proposal, based on application deadlines (see Figure 1)

Timeline for Support

The timeline for ECRIN support varies depending on the length of time between the call issue and the deadline, the stage at which the investigator/sponsor contacts ECRIN, and the maturity of the project when ECRIN is contacted (see Figure 1). It is recommended to contact ECRIN as soon as possible for maximum impact.

Figure 1: Proposal Development: Ideal Timeline for ECRIN Support. Example: H2020

STAGE	INITIAL IDEA	INITIAL DESIGN	DETAILED DESIGN	ANNEXES: INITIAL DEVELOPMENT	ANNEXES: FINALISATION	FINALISATION
INVESTIGATOR TASKS (with support from the lead CTU)	Define the intervention and type of clinical study	Draft the outline of the protocol Begin to build the consortium Start the distribution of Work Packages (WPs)	Finalise consortium composition Distribute WPs	Complete the clinical trial annex Start drafting technical annexes 3-5	Revise the clinical trial annex in agreement with all partners Develop the pre-final version of technical annexes 3-5	Finalise the application and submit
ECRIN SUPPORT	Advice	Advice	Advice and scientific consultancy as needed	Advice	Advice	Advice
		ECRIN-On-Board (see box)				
DATES	FUNDING CALL LAUNCHED	→				CALL DEADLINE
	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6

▲ **Recommended: Contact ECRIN at this stage**

ECRIN Role: A Partner in Your Project

ECRIN can provide more extensive support during proposal development when it is involved as a project partner (i.e., consortium member, work package participant or leader, and/or trial management service provider). In particular, ECRIN can:

- Provide a calculation of the cost of its trial management services (see next section) in participating countries
- Write or contribute to the writing of relevant work packages, and provide advice on other work packages
- Provide additional methodological consultancy, and, if relevant, an independent review of the study protocol by ECRIN's Scientific Board of clinical research methodology experts. This external and independent review, conducted as part of "ECRIN-On-Board" (see box) aims to ensure that the protocol is ethically, medically and scientifically sound.

In the application, ECRIN can appear as a participant with a Participant Identification Code (PIC) number. The national ECRIN scientific partners can be designated as project participants, linked third parties (provided that they have signed a framework agreement with ECRIN) or third parties making resources available.

ECRIN-On-Board: A Complement to Traditional ECRIN Proposal Support

As part of its support for trial preparation, ECRIN offers a unique service called ECRIN-On-Board (EoB). The goal is to improve the quality of multinational clinical trials being submitted for EU funding. This is achieved through early support on the protocol and the logistical/operational aspects of project design.

How It Works

The principal investigator (PI) submits a short study synopsis to the ECRIN European Correspondent (EuCo) in his/her country.
ECRIN's Scientific Board provides independent methodological consulting on the protocol, while ECRIN's EuCos advise on issues such as work package organisation.

Timeline

Synopses should be prepared three to six months before the funding application deadline. Support is generally given with a few weeks based on pre-defined deadlines.

Eligibility

EoB is a service reserved for ECRIN Member Countries and can only be used for multi-country projects involving at least two Member or Observer Countries.

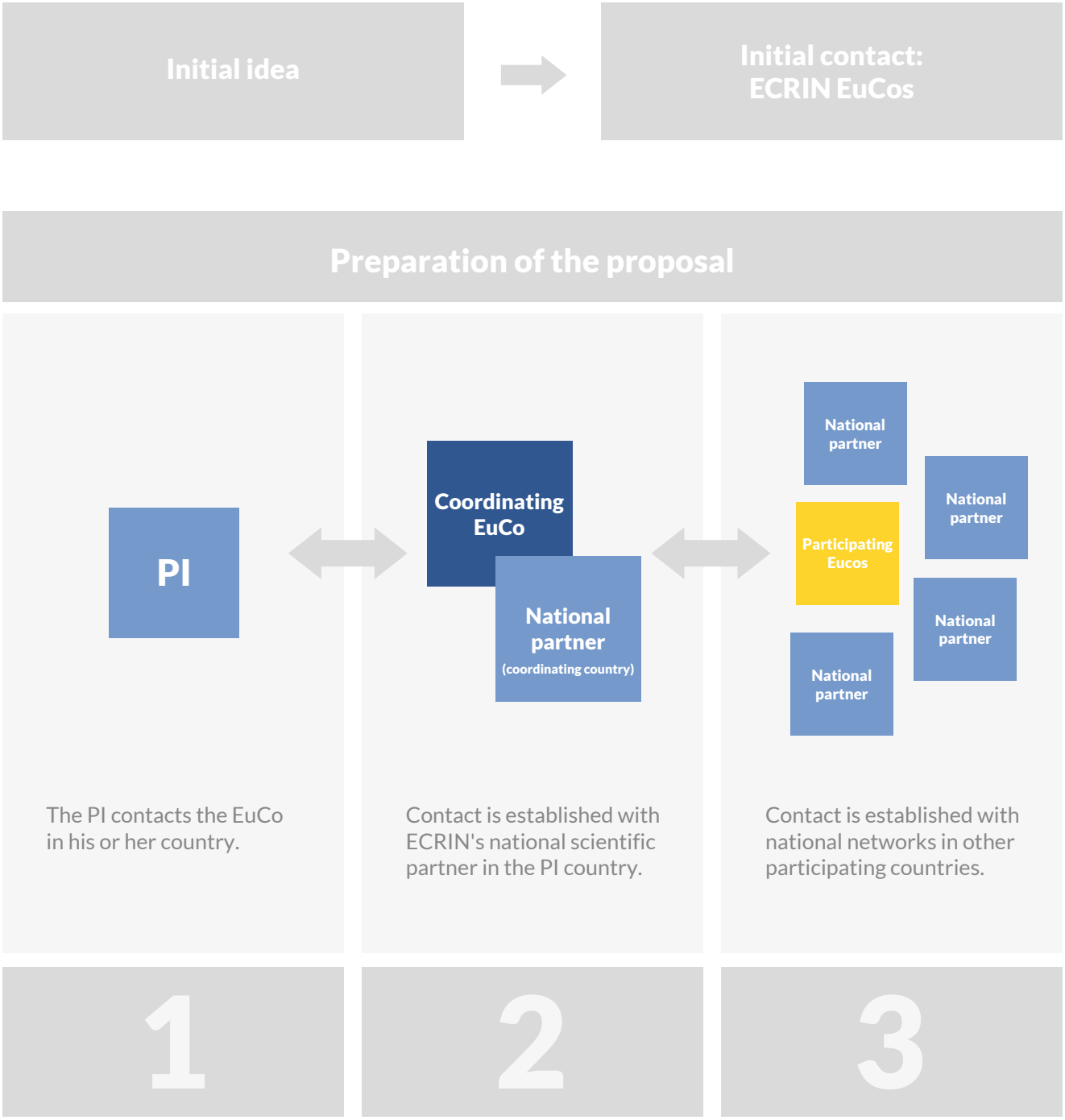
How to apply

Send a study synopsis several weeks before the application deadline to your local EuCo (www.ecrin.org/contact/eu-co) and EoB focal point (ecrinonboard@ecrin.org).
Learn more: www.ecrin.org/activities/ecrin-on-board

Coordination between Actors

ECRIN's EuCos act as the intermediary between the sponsor and service providers (i.e., national networks and CTUs) in different countries, ensuring smooth coordination, communication, organisation and support throughout the funding application process and beyond. How exactly do EuCos interact with the principal investigator (PI) and national networks?
Initially, the PI/sponsor contacts the ECRIN EuCo in the study coordinating country. In most cases, this will be the 'coordinating EuCo', and this person will be the PI's or sponsor's unique point of contact throughout the project.
The coordinating EuCo liaises with the EuCos from the other participating countries. All EuCos coordinate with the national scientific partner in their respective countries.

Figure 2: Proposal Development: Coordination between the PI, Coordinating EuCo and Participating EuCos / National Networks



ECRIN SUPPORT: IMPLEMENTATION OF MULTINATIONAL CLINICAL TRIALS

ECRIN Role: Provision of Services to Ensure Smooth Management

During project implementation, ECRIN offers various trial management services, accompanying investigators and project coordinators all the way from protocol finalisation to patient recruitment and scientific publication. ECRIN coordinates these services, some of which are performed directly by CTUs in ECRIN's Member and Observer Countries; these CTUs are part of the national network and are ECRIN partners. (For more information, see the next section.)

ECRIN trial management services include:

- **Submissions to competent authorities and ethics committees:** ECRIN can manage submissions to regulatory and ethics authorities (and, if applicable, other authorities) in participating countries, ensuring that timelines are respected to avoid delays
- **Monitoring:** All tasks related to monitoring such as training, on-site visits, reporting and remote monitoring can be handled by ECRIN across country sites
- **Pharmacovigilance / Adverse event reporting:** ECRIN can support local reporting according to national requirements
- **Data management:** ECRIN-certified data centres, which are compliant with standards of the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA), are available for data management in multinational trials
- **Global coordination and management**

Distribution of Trial Management Services

ECRIN provides both centralised and local services during trial implementation. Centralised services are performed by ECRIN´s national scientific partner who coordinates the project (usually the country of the PI). Local services are performed by individual CTUs or similar organisations in all participating countries. The selection and distribution of individual CTUs is done by each national scientific partner (based on location, expertise, resources, etc.).

Table 1: Centralised vs. Distributed Services and Role Allocation

WHAT?	CENTRALISED SERVICES	LOCAL DISTRIBUTED SERVICES
WHO?	ECRIN's national scientific partner coordinating the project	Individual CTUs within the ECRIN national partner's network
DESCRIPTION OF SERVICES	Lead monitoring and project management	Local monitoring and local project management
	Global pharmacovigilance	Local pharmacovigilance (submission of report to authorities)
	Methodological and scientific support	Regulatory and ethical submission
	Data management	
	Statistics	

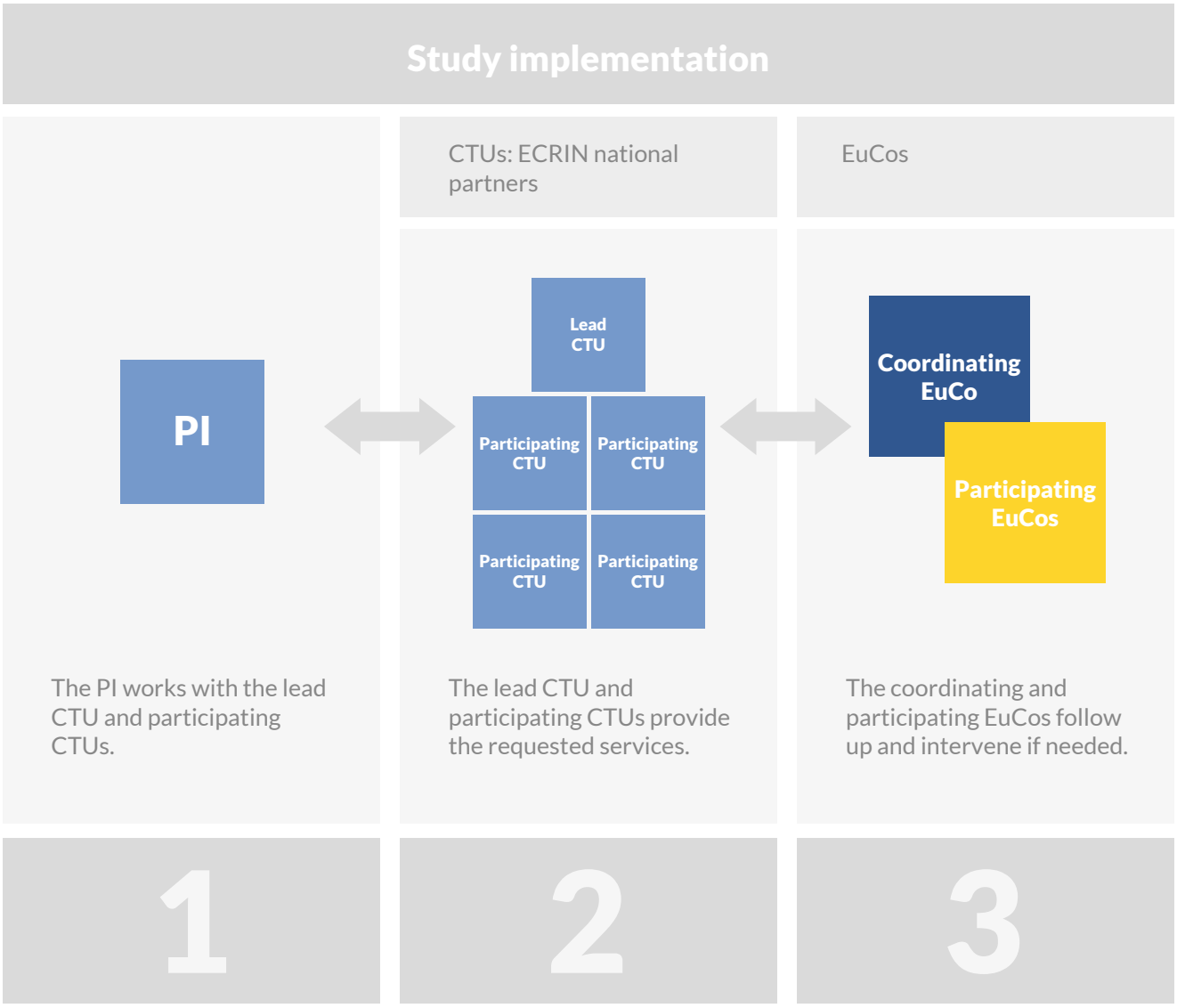
Coordination between Actors

During trial implementation, CTUs typically assume overall coordination and provide services. EuCos, in close collaboration with the Paris-based Core Team, ensure proper organisation and follow-up until trial completion (this will depend on the scope of ECRIN's services). They play an active role in reassuring stakeholders that all the necessary steps are being taken to successfully implement the trial. In particular, EuCos:

- Act as the link between ECRIN and the sponsor's team
- Assist with issues relevant to the sponsor/CTUs

The allocation of roles between CTUs (as part of ECRIN scientific partners), EuCos and the PI is illustrated in Figure 3. More details on the distribution of trial management services between CTUs can be found in the next section.

Figure 3: Trial Implementation: Service Provision by ECRIN National Scientific Partners and Continuous Supervision by EuCos



CTU TASKS: PREPARATION & IMPLEMENTATION OF MULTINATIONAL CLINICAL TRIALS

CTU Role: ECRIN Partners for Trial Preparation and Implementation

In ECRIN-supported clinical trials, CTUs in ECRIN Member and Observer Countries – as well as all other participating countries – play a key role in study preparation and implementation.

CTUs in ECRIN Member/Observer Countries are part of ECRIN's national scientific partner; as such, they are ECRIN partners. These CTUs are selected for a given study based on their resources and areas of expertise.

During the study, the lead CTU coordinates with participating CTUs (in both ECRIN Member/Observer and all other participating countries) to ensure the timely and efficient execution of tasks.

ECRIN's EuCos can provide follow-up and support as needed and as feasible for certain activities.
Below is a list of the typical support tasks that the lead CTU and all local CTUs can perform during preparation and especially implementation.

The following description is a general allocation of tasks. However, the distribution of services within CTUs may vary according to the rules and specific procedures for each of ECRIN's national scientific partners.

Regulatory Submission

Lead CTU:

- Development of core documents for clinical trial submission: protocol, informed consent form (ICF), investigational medicinal product dossier (IMPD), investigator's brochure (IB), recruitment material, procedures, etc.

Local CTUs:

- Adaptation and translation of relevant documents (ICF, questionnaires, etc.) for regulatory and ethical submission; request/proposal of additional documents needed for national submission from the sponsor

All CTUs:

- Regulatory submission to competent authorities and ethics committees in each country
- Submission of amendments, if any
- Regulatory follow-up until the end of the study
- End-of-trial notification (to competent authorities and ethics committees)

Project Management

Lead CTU:

- Global project management[1]:
  - Global coordination of resources
  - Centre feasibility (completion of form with input from CTUs)
  - Preparation and maintenance of sponsor's trial master file
  - Organisation of pathways for central laboratory/biobank with instructions for single sites
  - Elaboration of the monitoring manual
  - Central clinical research associate (CRA) training (web-based and/or on-site)
  - Online, web-based central monitoring
  - Review of monitoring reports of all monitors; if relevant, reporting of measures to the sponsor
  - Organisation of pathway for central distribution of medication from sponsor to sites
  - Communication with local project managers, sponsor, etc.
  - Query resolution and database locking
  - Writing of the final report in International Council for Harmonisation (ICH) format

Local CTUs:

- Local project management :
  - Support in the evaluation of local feasibility
  - Coordination of resources
  - Support to the sponsor for contracting with sites; help in contracting and budget negotiation
  - Management of patient travel costs
  - Local accountability:
    - Assurance that biological samples are transferred as required to the central lab and biobank
    - Assurance that medication is received at the local pharmacy
    - Monitoring of the accountability of monitoring visit logs
    - Support to the sponsor with medication handling at the end of the clinical trial

[1] Local project management may not be needed when the number of participating sites within a country is small.

Monitoring

All CTUs:

- Local monitoring:
  - Assurance that the protocol and monitoring manual are understood and respected, and that the electronic case report form (eCRF) is used appropriately
  - Participation in training, webinars, etc.
  - Communication with lead CTU
  - Preparation, conduct and reporting of initiation visit(s)
  - Preparation, conduct and reporting of pharmacy initiation visit(s)
  - Preparation and maintenance of investigator's site file throughout the study
  - Online, web-based monitoring (support to central, web-based monitoring performed by the lead CTU)
  - Preparation, conduct and reporting of regular monitoring visits
  - Preparation, conduct and reporting of close-out monitoring visit
  - Query resolution and database locking (support to central activity performed by the lead CTU)
  - Pharmacy close-out visit(s) (accountability log and sample track)

Pharmacovigilance

Lead CTU:

- Global pharmacovigilance
  - Writing of the pharmacovigilance section in the protocol
  - Writing of the pharmacovigilance plan
  - Preparation of the pharmacovigilance master file
  - Registration of the study in Eudravigilance
  - Reception, validation, registry and causality evaluation
  - Annual update and report on safety information during the conduct of the study (update on upcoming safety information on the product under evaluation from other clinical studies, which may be relevant for the conduct of the clinical trial)
  - Adverse event (AE) management, including serious adverse events (SAEs) and serious unexpected serious adverse reactions (SUSARs), on an annual basis. Notification to the sponsor, regulatory bodies and ethics committees.
- Periodic reconciliation of adverse events, including SAEs and SUSARs
- Preparation of meeting reports for the Data and Safety Monitoring Board (DSMB)
- Elaboration and submission of annual development safety update reports (DSURs) and other periodic reports if applicable
- Elaboration and submission of final safety report

Local CTUs:

- Local pharmacovigilance[2]:
  - Provision of information about national requirements for reporting to the lead CTU
  - AE management, including SAEs and SUSARs, from national sites
  - Notification of SAEs/SUSARs from the national sites to the lead CTU, and competent and regulatory authorities

[2] For this task, periodic reports and other relevant documents will be provided by the sponsor or lead CTU in English.

Data Management

- Electronic case report form (eCRF) definition
- Elaboration of data management plan (DMP) and data validation plan (specified checks)
- Elaboration and maintenance of validated eCRD
- Performance of quality controls
- Data codification (AEs, medication, diseases)
- Importation of laboratory data, ECG data and/or imaging data
- Support to pharmacovigilance activities (SAE reconciliation)
- Training for investigators and monitors
- Blind Data Review (BDR)
- Data transfer to statistical data

Statistics

- Writing of the statistical section of the protocol
- Preparation of randomisation codes
- Elaboration of the statistical analysis plan (SAP)
- Elaboration of statistical analysis:
  - Interim analyses
  - Final analysis
  - Reports for DSMB meetings
- Special analyses: statistical pharmacokinetic (PK) analysis and results
- Writing of the draft and final statistical report (introduction, methods, results)

More about ECRIN

ECRIN in Numbers

2004	year ECRIN was created
2013	year ECRIN was awarded the status of European Research Infrastructure Consortium (ERIC)
≈ 40	number of multinational trials in the ECRIN portfolio (current/past projects)
7	Average number of countries per ECRIN-supported trial
7	Member Countries (France, Germany, Hungary, Italy, Norway, Portugal and Spain)
2	Observer Countries (Czech Republic and Switzerland)

Website: www.ecrin.org
Twitter: @ECRIN_ERIC

ECRIN Management Office | 5 rue Watt, 75013 Paris, France www.ecrin.org
SIRET: 801 933 235 00021 - APE: 7219Z - TVA Intracom: FR91 801 933 235