



ECRIN ANNUAL REPORT 2017

EUROPEAN
CLINICAL
RESEARCH
INFRASTRUCTURE
NETWORK

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FOREWORD



Whereas ECRIN-ERIC kept gaining momentum and visibility over 2017, the clinical research ecosystem underwent progressive but major changes that will strongly impact how clinical research will be designed, planned and managed in the near future. This represents a series of challenges and opportunities for ECRIN as a facilitator for multinational clinical research in Europe.

This evolving context, and its consequences in terms of national and European science policy, represents for ECRIN a permanent stimulation, and acts as the main driver for the progressive changes in ECRIN's organisation and activities as described in this 2017 annual report.

Jacques Demotes
ECRIN-ERIC Director General

A white handwritten signature of Jacques Demotes on a blue background.

CHALLENGES



PERSONALISED MEDICINE APPROACH

The first challenge is the rise of the personalised medicine approach - this was the topic of the International Clinical Trials day celebrated by ECRIN in May 2016 in Prague. Personalised medicine aims at delivering the best appropriate healthcare strategy to each patient subgroup, and depends on research towards patient stratification. This first requires identification of patient groups based either on the understanding of disease mechanisms (hypothesis-driven approach), or following a mechanism-agnostic clustering (data-driven approach). Although both approaches co-exist, the data driven approach is now made easier because of the availability of large multimodal datasets combining clinical, imaging and multiomics data from broad patient populations, collected either prospectively or retrospectively, in the context of either observational or interventional studies. Such large datasets are exploited by machine-learning algorithms to stratify the patient population.

Whatever the approach used to stratify patients, randomized trials are necessary to compare and validate treatment strategies. Depending on the nature of the biomarker signature underpinning stratification, and on

the understanding of the mechanism of action of drugs, linking a biomarker profile with a treatment option may be a rather easy (for a drug targeting a mutated protein in cancer) or a very difficult task (when the biomarker signature doesn't provide any clue regarding possible therapeutic targets). New designs (basket and umbrella trials) were proposed to validate these treatment options in randomized trials, as well as adaptive 'platform trials' consisting of a clinical trial infrastructure allowing continuous, multi-arm testing of multiple drugs in a given disease condition. Although these approaches were first designed and implemented in the field of cancer, they have now spread rapidly to other disease areas.



OPTIMAL USE OF DATA

The second, and partly related challenge lies in the optimal use of data - this was the topic of the International Clinical Trials day celebrated by ECRIN in May 2017 in Lisbon. As mentioned above, multimodal data management and stratification through machine learning is becoming common practice, and one of the specific challenges for ECRIN is the exploitation of

multinational datasets. Sharing and reuse of clinical research data (from either observational or interventional studies) represents a major opportunity for European clinical research if we are able to build a system enabling easy reuse of multinational data. This raises multiple questions regarding the data standards and interoperability across countries or between observational and interventional studies, and regarding personal data protection in the context of the General Data Protection Regulation and its national implementation.

In addition, reusing data collected in the context of healthcare or health systems would represent a major breakthrough for clinical research, even more if this data would be available for transnational or multinational studies. Pilots already exist, with for instance hospital data warehouses allowing the secure reuse of electronic health records for research purposes, the conduct of a randomized clinical trial based on registry data, or cohorts collecting data from national health databases for participant follow-up. However reuse of multinational health and healthcare data raises additional issues with regards to data security, including the need for a federated infrastructure compliant with national requirements, and a mechanism allowing aggregation of data from multiple national sources.



CLINICAL & TRANSLATIONAL RESEARCH IN PAEDIATRICS

Clinical and translational research in paediatrics was the third major opportunity for ECRIN in 2017. Promoting evidence-based practice in paediatric medicine raises many scientific questions, specific to each age group, that require appropriate research. Pan-European collaboration is the best strategy to address those research questions, as efficient access to paediatric patients and to paediatric research expertise requires multinational collaboration. In addition, addressing these scientific questions also requires adapted instruments and services for translational and clinical research in paediatrics. However it is essential to clarify the respective roles of the stakeholders involved – paediatric research expertise, access to paediatric patients, and scientific services to paediatric research.

In 2017 the PedCRIN infrastructure project, coordinated by ECRIN, started with the objective of developing tools and services needed to support paediatric trials, and of conducting three pilot paediatric and neonatal trials to test the services and the organization. In 2017, ECRIN also participated in the application for a “European Paediatric Translational

Research Infrastructure (EPTRI) design study” (start date 2018) exploring the need and the specification for a research infrastructure supporting preclinical paediatric drug development. ECRIN also participated in the IMI-2 c4c consortium (also starting in 2018) with the objective of establishing a pan-European network of paediatric hospitals to access and investigate paediatric patients in industry-sponsored and investigator-initiated trials. This clustered success of the paediatric research community now requires a careful strategy to avoid duplication and to take the best possible advantage of the existing resources and competences, clearly distributing the roles between partners addressing the research questions, providing access to patients, and offering scientific services. Finding a sustainable solution for paediatrics will help establish, in the future, stable partnerships between research infrastructures and the scientific communities, as promoted by the CORBEL Medical Infrastructures Users Forum (MIUF), and as recently proposed in a H2020 project on the structuring of an investigation network for infectious diseases.

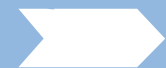


NEW REGULATIONS

New regulations represented the fourth challenge and opportunity for ECRIN in 2017. The Clinical Trial Regulation adopted in 2014, still awaiting implementation, is expected to facilitate the clinical trial authorization process through a coordinated approach, and also includes provisions reducing the administrative burden for the 'low intervention' trials. The Medical Device Regulation adopted in 2017 is certainly an interesting opportunity as it will make clinical trials (renamed 'clinical investigation') necessary for the higher-risk devices to access the European market, and because it will result in a better integrated (although not fully harmonised) regulatory context for medical device trials in Europe. And as mentioned earlier, the General Data Protection Regulation may have a major impact of the optimal reuse of research and healthcare data for secondary research purposes – the critical question will be how broad will the broad consent be? If it doesn't restrict data reuse for medical research purposes, it will be a powerful facilitator for secondary use of data collected in the context of healthcare or research projects; if the 'broad' consent is restricted to a research topic or to a

research institution, or requires a re-consent from the participants, there is a major risk of introducing selection biases in the secondary use of data that may hamper the validity of the studies based on such secondary use.

INTRODUCTION



INTRODUCTION

The major challenge identified in the ECRIN-ERIC 2017 work plan was the scaling-up of ECRIN activities, especially the operational support to multinational clinical studies, which represents the core of ECRIN's mission. This resulted in an upgrade of the organization, with new competences and new resources allocated to the operation unit, in particular with the recruitment of the Medical Expert and the Clinical Operation Manager. Reinforcing the activity of the European Correspondents was also part of the solution through the set-up of a mentoring activity. Structuring projects also require additional resources, and this included the recruitment of a project manager for the pediatric projects and the decision to hire a data scientist.

Quality of ECRIN organisation was also identified as a major challenge, and this resulted in the strategic decision to apply for ISO certification of ECRIN (with an audit planned in 2019). The 'quality as a service' activity includes the ongoing data centre certification programme, now extended to a pilot initiative in Asia, as well as a similar initiative on defining specifications for the qualification of pharmacovigilance centres.

The development of the personalised medicine approach also has a tremendous impact on the activities of ECRIN, which is reflected in the ECRIN support provided to a handful of patient stratification studies outside the field of cancer (ie. in inflammatory

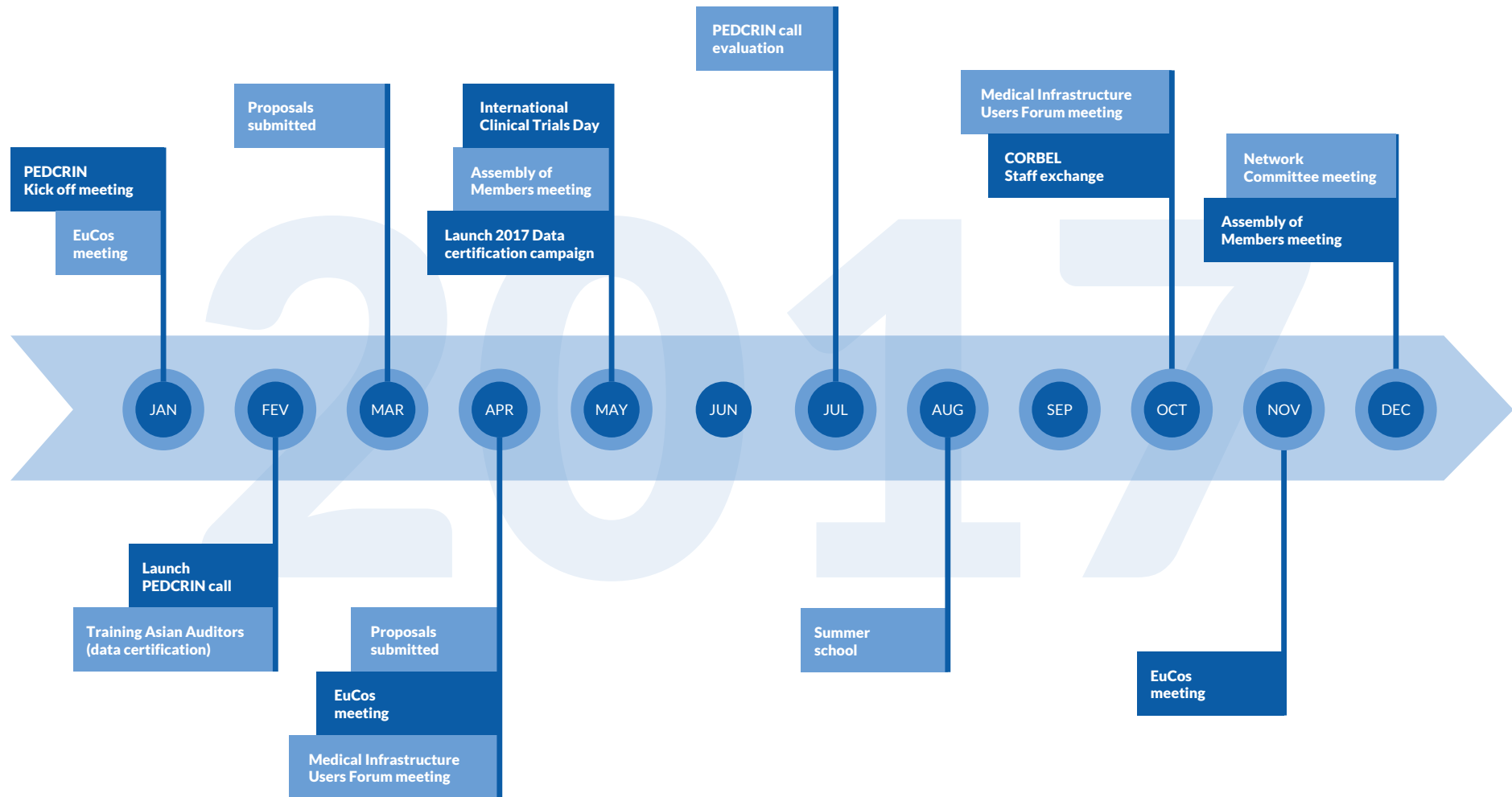
diseases or in psychiatry). As a consequence, ECRIN had to make a series of key decisions, including whether it should also participate in the support to observational studies (as patient stratification studies mostly rely on retrospective or prospective observational data collection). Another issue was to define the ECRIN policy regarding multimodal data management, with the objective to facilitate multimodal data management and analysis for multinational studies (which will be part of future EOSC projects). As a consequence of the EU personalised medicine policy, there are more H2020 calls for patient stratification and biomarker profiling, however this is correlated with a decrease in the funding opportunities for randomised trials, which raises an obstacle to the development of ECRIN activities, and argues in favor of alternative mechanisms to support multinational clinical research (ERA-Net mechanism, foreign sites eligible to national funding schemes, etc).

The European Open Science Cloud (EOSC) initiative offers an outstanding opportunity for ECRIN to work towards optimal use and reuse of data collected either in the context of research projects, or in the context of the healthcare / health system, especially focusing on the use and reuse of these data in transnational / multinational research projects. ECRIN is a participant in the EOSC-pilot project, in charge of working on policy aspects, and in the EOSC-hub project defining

the governance of the EOSC. ECRIN is also participating in the H2020 Extreme Data Cloud (XDC) project to develop a clinical trial metadata repository. In the CORBEL project, ECRIN works on clinical trial data sharing and reuse, and also participates in the development of solutions for multimodal data management. This will be extended in the EOSC-Life application where reuse of observational study data, or reuse of data derived from healthcare and health databases will be addressed at the multinational level.

Interaction with the paediatric community will be a major topic for ECRIN in the next few years, because of the PedCRIN project, of the EPTRI and c4c initiatives, and will act as a demonstrator on how best to ensure sustainability of tools and stable partnerships with investigation networks, while avoiding duplication. These projects will also benefit the rare disease community, as the vast majority of rare disease trials are conducted in paediatric departments.

Key Milestones



CLINICAL TRIAL OPERATIONS /1

OVERVIEW

Clinical Trial Operations represent ECRIN's core activity, which is to support academic investigators in the preparation of grant proposals, the development, set-up, conduct and management of multi-national clinical trials. In addition, ECRIN clinical trials operations is also contributing to the improvement and extension of ECRIN quality assurance system. This section provides an overview on the activity and an update on progress made throughout the year.

SUPPORT TO MULTINATIONAL CLINICAL TRIALS

ECRIN provides support to investigators and sponsors in ECRIN Member and Observer Countries from the preparation of EU funding applications, to the validation of study protocols, and all the way from regulatory approvals, trial set-up and monitoring to scientific publication through its various trial management services.

GRANT APPLICATION SUPPORT

The majority of support was provided for H2020 call proposals, but ECRIN also assisted with applications to other calls, i.e. the E-Rare ERA-Net call for repurposing clinical trials in rare diseases.

The ECRIN-On-Board (EoB) initiative was implemented in 2016 as a means of early support on the protocol and consulting on the logistical/operational aspects of project design, which is provided by ECRIN's European Correspondents (EuCos), ideally as tool for improving a grant application.

ECRIN's EuCos can provide support on a variety of aspects for a proposal: advice on suitable funding calls, work package architecture, evaluation of potential impact of the project; the management, governance, and composition of a consortium; and multinational clinical trial management. Most importantly, the EuCos can provide information on national facilities which have the capacity and services needed to manage the trial. They ensure that the CTUs selected for the study have the necessary expertise and capacity. In the preparation phase EuCos can assess the practicality of the proposed trial in each of the selected countries, and in case of difficulties, provide alternatives to ensure that the trial can be conducted. Finally, ECRIN can provide methodological consulting and an independent peer review of the study protocol. This evaluation is prepared by ECRIN's Scientific Board, which is composed of clinical research and methodology experts.

CLINICAL TRIAL OPERATIONS IN 2017

40+

supported multinational trials in the ECRIN portfolio

7

average number of countries per ECRIN-supported trial

33

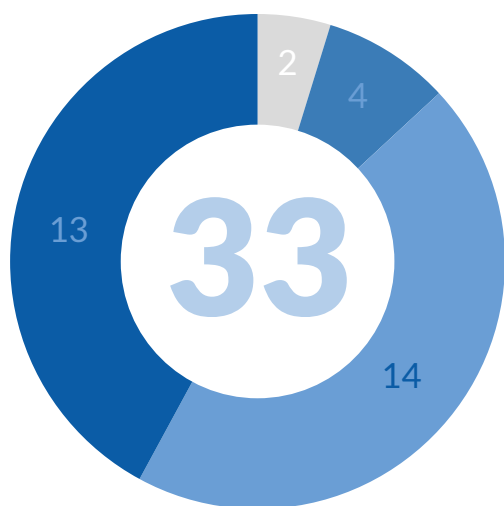
grant applications supported

9

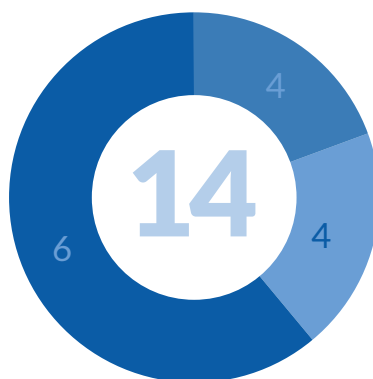
protocols reviewed by Scientific Board

Numbers & topics of the 2017 H2020 applications

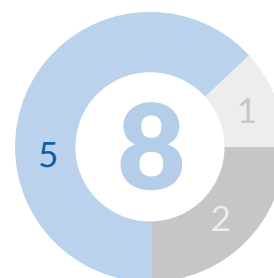
Overall, in 2017 ECRIN Clinical Trial Operation supported 33 H2020 applications submitted for two-stage calls, and 22 full H2020 applications. After review, 3 projects received funding, and 3 proposals were on the reserve list (and 1 was eventually funded).



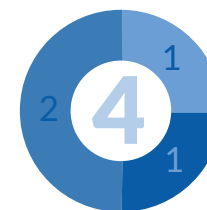
APPLICATIONS TWO-STAGE CALLS



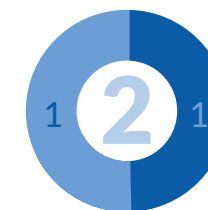
SUBMITTED SECOND STAGE



APPLICATIONS ONE-STAGE CALL



FUNDED



RESERVE LIST

Personalised computer models and in-silico systems for well-being (SC1PM-17)

In-silico trials for developing and assessing biomedical products (SC1-PM16)

New therapies for rare diseases (PM08)

Regenerative medicine (PM11) one-stage call

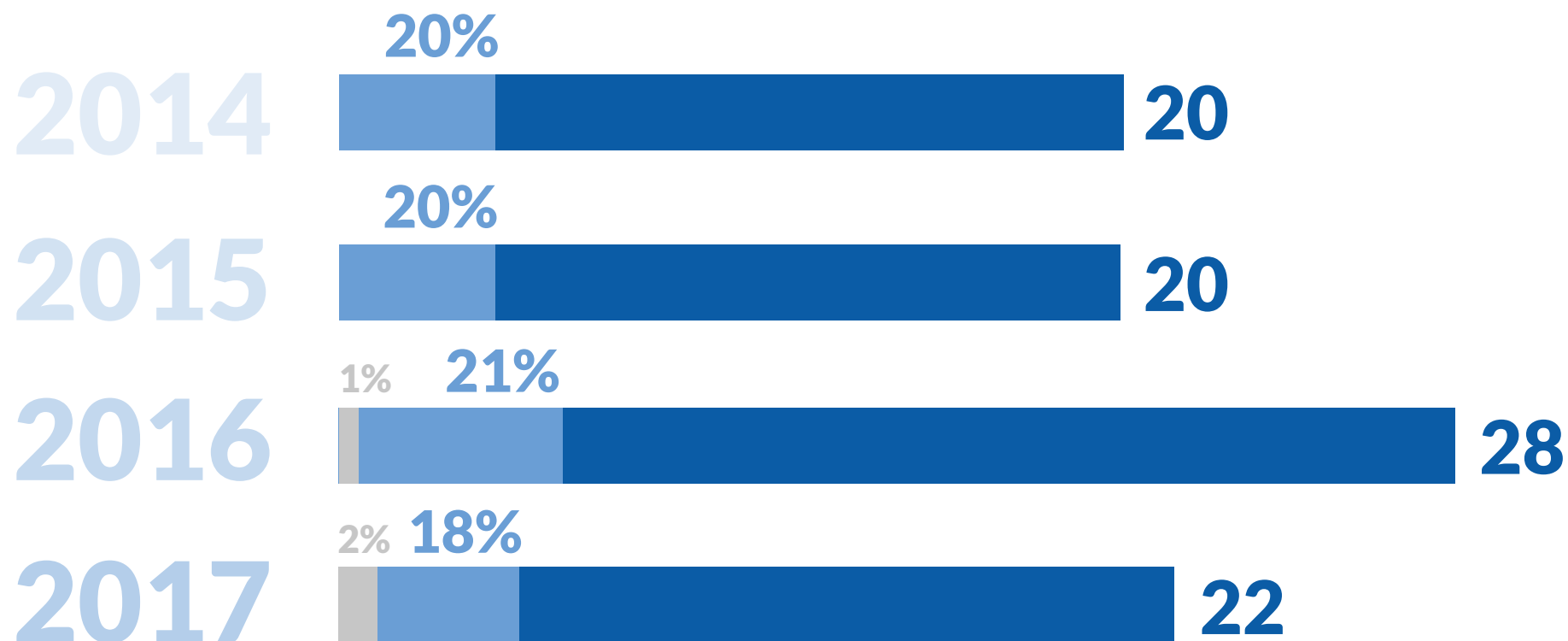
Comparing the effectiveness of existing healthcare interventions in the adult population (PM10)

New concepts in patient stratification (PM02)

Promoting mental health and well-being in the young (PM07)

Trend in H2020 applications 2014 to 2017

This activity and the outcomes are in line with the trend of ECRIN's involvement in H2020 applications, as shown below.



RESERVE LIST FUNDED TOTAL APPLICATIONS

**CLINICAL TRIAL
OPERATIONS IN 2017**

40+

supported multinational trials
in the ECRIN portfolio

7

average number of countries
per ECRIN-supported trial

33

grant applications
supported

9

protocols reviewed by
Scientific Board



CLINICAL TRIAL OPERATIONS /2

SUPPORT TO MULTINATIONAL CLINICAL TRIALS

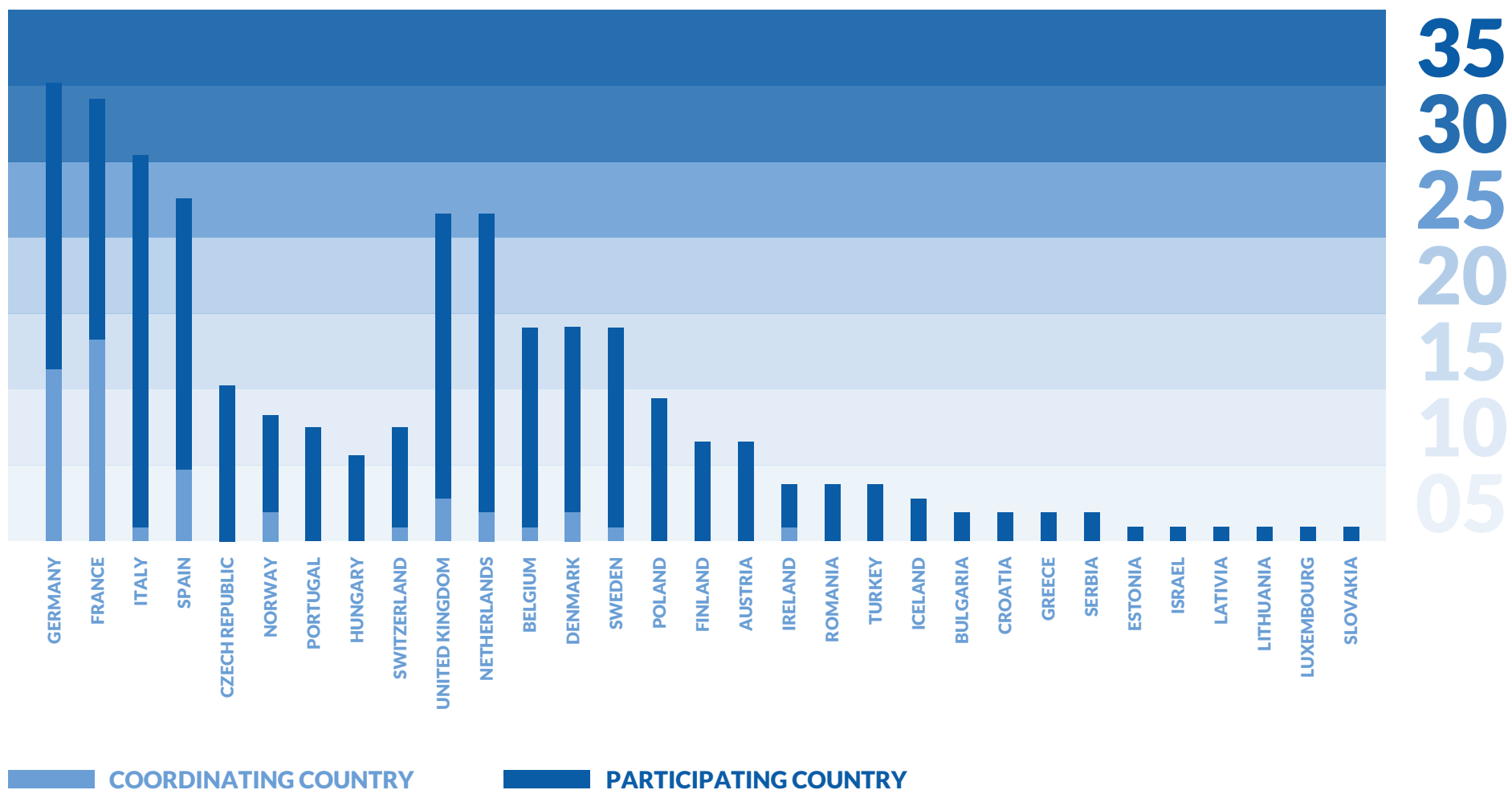
In 2017, 10 new clinical trials (mainly funded by H2020) were started, coordinated by 5 different countries. In total, 18 countries were involved either as coordinating or participating country, providing services for those multinational clinical trials (eligibility to ECRIN support requires the participation of at least 2 ECRIN-ERIC Member or Observer countries, however ECRIN is open to the participation of additional countries).

TRIAL MANAGEMENT SUPPORT

For funded projects, ECRIN offers investigators and project coordinators various trial management services for the set-up and implementation of a trial across several countries. ECRIN, through its national partners (the national networks of CTUs), performs central and national project management. This includes i.e. the submission to competent authorities and ethics committees in participating countries to obtain regulatory and ethics approvals; provision of on-site monitoring in the different countries; and conduct of local pharmacovigilance tasks. Through its partners, ECRIN can also provide central pharmacovigilance services. It can offer multinational data management through its certified data centres. It can also provide support with the requirement of national or multinational trial insurance, and support to drug management and sample handling across countries.

Overview of ECRIN Trials Portfolio

By the end of 2017, there were a total of 43 ongoing trials in the portfolio, conducted each on average in 7 countries.



CLINICAL TRIAL OPERATIONS /3

EARLY SUPPORT TO SPONSORS / INVESTIGATORS

Taking advantage of its expertise in the management of multinational clinical trials, ECRIN provides advice on the clinical study design and planning. As a unique contact point, the European Correspondent in the country of the principal investigator and sponsor coordinates this early support.

CHALLENGES FOR CLINICAL TRIAL OPERATIONS

Supporting the investigators in the planning of clinical research projects is a key activity for ECRIN. This activity, involving both the European Correspondents (EuCos) and the ECRIN core team, represents a major investment from the ECRIN budget. However, this free support helps ECRIN to influence the study design and planning, and also increases the success rate of the applications, for the benefit of the investigators and of the ECRIN Member countries, who maximize their return on investment in H2020. This is the hallmark of the ECRIN economic model, and the number of applications also reflects the attractiveness of ECRIN for the users' communities.

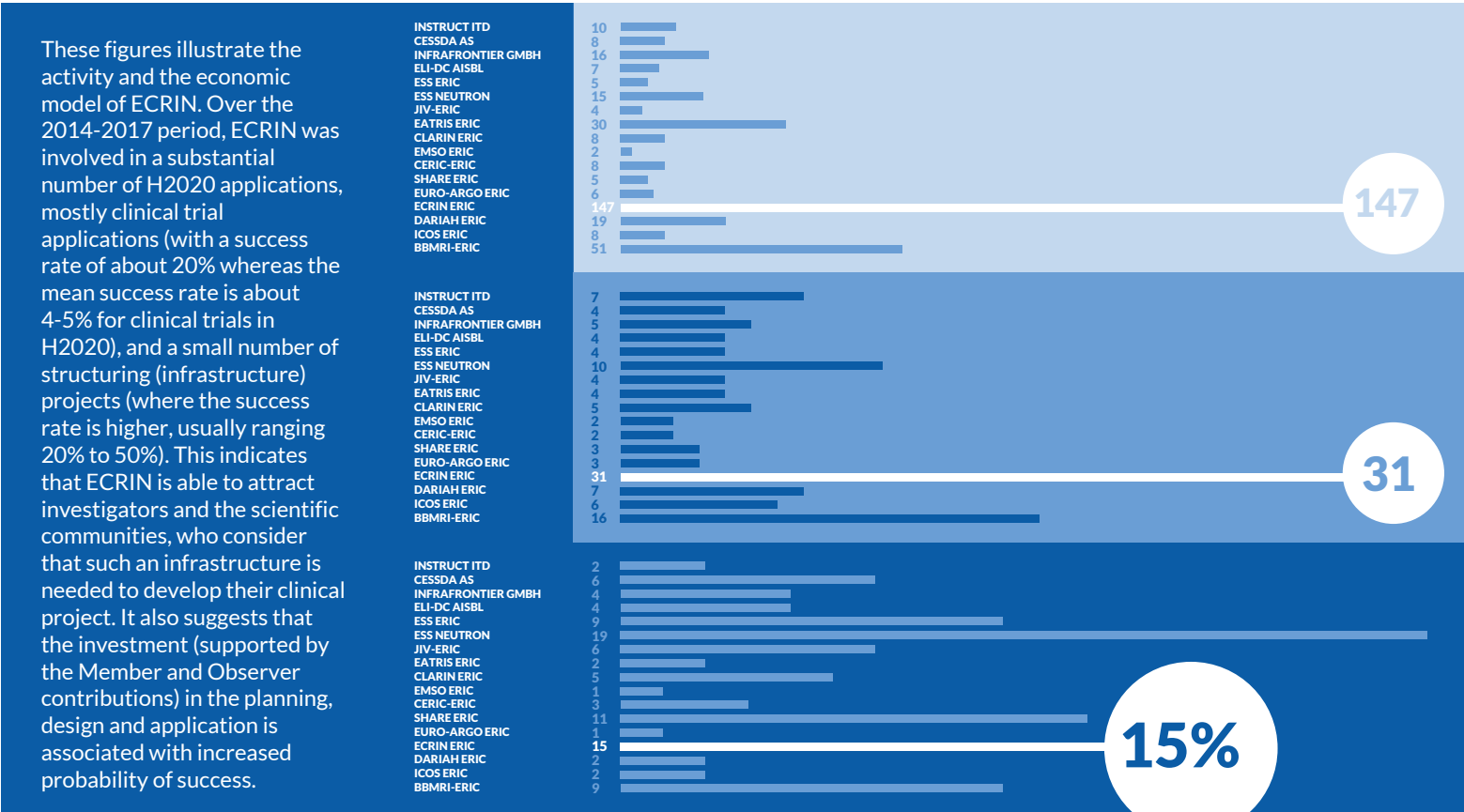
Such early investment in project preparation for trials coordinated by Member and Observer countries requires subsequently a commitment of ECRIN to support the maturation of the project, and its conduct if the funding is granted.

Collaboration requests for projects are received by ECRIN's European Correspondents at different stages: at a very early stage with an initial idea; at a more advanced stage before the submission of the proposal to a funding application; after the project has already been funded, or even once the project is already running for an international extension. The decision to collaborate should be made in a very short period of time, and in particular at an early stage of project development, when ECRIN's support is most beneficial.

As a solution in 2017, an early and multidisciplinary board was proposed as a pilot for the evaluation of the scientific merit, the relevance and feasibility of project and the medical relevance. This board started as a pilot phase towards the end of 2017, and it is planned to evaluate the value and impact after a 6 month pilot period.

H2020 applications, participation 2014 to 2017

Over the 2014-2017 period, ECRIN participated in 147 applications to H2020, of which 31 were funded, securing 15% of the H2020 71M€ budget allocated to the ERICs (resulting in 10.5M€ for the 31 projects with ECRIN participation, with a mean value of 0.35M€ for ECRIN per project, and 2.6M€ per year).



APPLICATIONS
/ 349

PARTICIPATIONS
/ 117

FUNDING (%)
/ 71M
EUROS

Source: EU Commission

QUALITY /1

OVERVIEW

Significant achievements were made by ECRIN in order to upgrade its quality management system (QMS). The objective is to enhance its ability to consistently meet its partner's requirements, and address future needs and expectations when fulfilling its European coordinating mission.

ISO 9001:2015 OBJECTIVE

One ECRIN strategic decision made in early 2017 was to shape its quality initiatives, and structure the ECRIN QMS with the objective to apply for an ISO 9001:2015 certification¹. This quality approach includes a risk-based prioritisation of quality actions, while ensuring an end-to-end process and service quality.

ECRIN QUALITY MANAGEMENT SYSTEM (QMS)

In this perspective, ISO 9001:2015 is adding value towards regulatory compliance as it embeds a common ground with this new regulatory environment, especially for continuous risk assessment and mitigation through Corrective and Preventive Action (CAPA), but also for the change control and information management.

To drive the update and development to be performed for alignment of ECRIN's quality system, an independent ISO 9001:2015 diagnostic audit was conducted in September 2017, as well as a gap analysis of current QMS towards the ICH GCP E6(R2) requirements. The framework of ECRIN QMS was designed according to a Plan Do Check Act model as displayed in the figure below.

NEW REQUIREMENTS

Furthermore, as any actor of clinical research, ECRIN will have to successfully address regulatory challenges and align its activity and quality management system with the new requirements that were recently adopted in Europe, or will be adopted in the upcoming years, in particular:

- European adoption in June 2017 of the GCP renovated ICH E6 (R2)²
- EU Clinical Trial Regulation 536/2014³
- EU General Data Protection Regulation (GDPR) 2016/679⁴

ECRIN Quality Management System

PLAN ✓

- ECRIN ANNUAL WORK PLAN, AND 3 YEAR STRATEGIC PLAN
- QUALITY DOCUMENT ANNUAL DEVELOPMENT PLAN
- QUALITY AUDIT ANNUAL INTERNAL/ EXTERNAL

ACT ✓

- CAPA AND IMPROVEMENT PROCESSES DRIVEN BY KEY PERFORMANCE INDICATORS (KPI)
- AUDIT FOLLOW-UP
- MANAGEMENT REVIEW FEEDBACK



DO ✓

- MAINTAIN A RISK BASED ASSESSMENT OF THE ECRIN SERVICES
- IMPLEMENT ECRIN SERVICES ACCORDING TO QUALITY STANDARDS
- COMPLY WITH ECRIN SERVICES LEGAL ENVIRONMENT

CHECK ✓

- ESCALATED NON CONFORMITIES AND CAPA COMPLETION
- IDENTIFIED IMPROVEMENTS, INTERNAL AND EXTERNAL AUDITS
- QUALITY COUNCIL MANAGEMENT REVIEW

QUALITY /2

DATA CENTRE CERTIFICATION PROGRAMME

Offering high-quality data management services for ECRIN-supported, multinational trials is based on the certification of professional, non-profit clinical trial data management centres. ECRIN certification audits ensure the compliance with a set of 129 criteria transposing into practical processes the ICH-GCP, US-FDA and European guidance and requirements.

Although resource-intensive, this approach avoids competition between ECRIN and its national partners, raises the quality of the national infrastructure, and can be extended to other centrally-deployed services such as pharmacovigilance.

ECRIN QUALITY POLICY

The ECRIN quality policy was set up to define, revisit and clarify ECRIN's quality strategy and objectives, but also ECRIN governance, stakeholders, customers, services and processes.

From this founding quality document, processes applied to support ECRIN key services are progressively being developed using written procedures, and updated where relevant to reflect new regulatory requirements (project, quality document, risk, deviation and non-compliance, CAPA, contracting and information management).

To promote its culture of service quality and to proactively enhance its performance, SMART Key Performance Indicators have been formalised for each process to evaluate how ECRIN⁵ meets its set of operational and strategic goals. A first assessment through an annual quality management review, conducted in November 2017, allowed for risk identification and mitigation as well as for prioritising the next years quality work plan.

Finally, to streamline its customers' support, and also to optimise and secure the ECRIN information management, an analysis of the whole electronic information environment was initiated in 2017 (based on ISO 27001: 2013 recommendations⁶) and will be pursued in 2018.

QUALITY AS A SERVICE (QAAS)

For several years, ECRIN has been a key contributor to overall academic quality improvement, and providing quality as a service at its partners request, through a program certifying CTUs for specific central services (data management, and in the future central pharmacovigilance).

In 2017, this programme gained momentum promoting excellence in data management in Europe and beyond, and contributed to promote quality in academic research⁷.

The certification scheme uses a published set of requirements, or standards, some focusing on IT, other on data management, and other on more generic aspects of trial management. These were originally developed by ECRIN between 2009 and 2011, and have been revised twice since - currently version 3.1⁸. The trial unit is assessed against these standards during an on-site audit, with the audit reports being sent to ECRIN's Independent Certification Board for a final decision on certification.

The requirements are intended to transpose good clinical practice in data and IT management in clinical trials, together with the EU regulations and the FDA requirements. They were developed by senior experts working in non-commercial clinical trials units in Europe, and are designed as a practical guide for staff working in IT and data management in that sector (though the same principles apply to all clinical research environments).

Calls were launched each year, to identify non-commercial trial units in ECRIN Member countries, seeking ECRIN data management certification. The certification scheme was successfully implemented from 2014 to 2017 with a renewal of the program until 2020.

Furthermore, radical changes appeared in recent years in the technical capabilities, in particular the increasing use of a cloud based infrastructure and of SaaS (software as a service) for clinical trial data management systems (CDMS), and in the regulatory requirement for data integrity⁹. This led to a comprehensive revision of the standards, launched in 2017 with a new revised version 4.0 of the standards being ready for publication by 2018.

AUDITS

To date, including the pilot initial scheme, there have been 18 audits of Clinical Trial Units (CTUs), 10 CTUs are currently certified as high-quality data centres, 8 CTUs are under evaluation (initial or re-audit). Three CTUs were awarded certification at the first attempt (17%), whereas 6 units (33%) were certified based on CAPA documentary evidence and 9 units (50%) were judged non-compliant and required a re-audit.

As expressed by one recently audited CTU:

"The Department of Clinical Research Support (CTU) at the Oslo University Hospital indeed considers an ECRIN data management certification to be a valuable target. The communication before and during the audit was clear, and the auditors were very competent in all areas of IT and data management. Their thorough and supportive approach fosters learning during all steps of the audit, and made the process very valuable to us."

Finally, Asian countries – specifically Singapore, Japan, South Korea and Taiwan, expressed interest in the ECRIN Data Management (DM) centre certification programme, resulting in the following collaborative achievements: in 2017 the DM standards (version 3.1) were translated into Japanese, auditor training session took place in February 2017 at ECRIN Paris office, followed by 3 DM audits in Europe, involving Asian auditors as observers.

To continue this collaboration, in 2018, ECRIN will perform a pilot audit programme in 2 Japanese DM centres (Nagoya and Kobe), confirming their interest in the certification model as well as their readiness for audit. This pilot audit programme will be conducted in parallel to the EU ongoing 2018 DM centre audit programme, and will be fully funded by the Asian applicants.



CAPACITY /1

OVERVIEW

In 2017, ECRIN continued to develop the infrastructure through projects, initiatives or collaborations intended to improve the capacity and to update or upgrade tools, to provide the users and scientific community with the most relevant and cutting-edge services.

CAPACITY, SERVICES AND TOOLS

Highlights from 2017 include the strengthening or development of the capacity to manage multinational paediatric trials, the upgrade of the ECRIN regulatory and ethical database, the development of data sharing principles and services, the improvement of clinical trial methodology, as well as training activities.

DEVELOPING THE CAPACITY, SERVICES AND TOOLS

PAEDIATRICS

The development of evidence-based therapeutic solutions adapted to the various paediatric age groups, and their implementation in clinical practice, raise a significant number of scientific questions that require a better structuring of the paediatric scientific community at the pan-European level. However, specific tools and competences are also required to support this scientific activity (and they will also benefit the research on rare diseases).

A new H2020 funded project, PedCRIN, coordinated by ECRIN, started in January 2017, with the objective to strengthen and/or develop the specific competences and infrastructure needed to manage paediatric clinical trials.

Priorities and tools to be developed were identified through a survey that targeted the paediatric community. The most expected services were innovative approaches in the design of paediatric studies, pharmacovigilance tools and sample management.

ECRIN REGULATORY AND ETHICAL DATABASE

The ECRIN regulatory and ethical database is a central resource providing information about clinical trial regulatory and ethical requirements covering 22 European countries and multiple study types such as drug trials, clinical investigations of medical devices, combination of drug-device studies, nutrition studies. The specific regulatory and ethical information related to paediatric clinical research (PedCRIN) and also about vaccine clinical research (TRANSVAC 2) have been collected to upgrade the database.

DATA SHARING

Data sharing and optimal reuse of data is a key issue for the clinical research community.

ECRIN published, in the context of the H2020 CORBEL project, a consensus document on clinical trial data sharing recommendations and principles, with the objective of facilitating and harmonizing practice for multinational studies¹⁹.

Further work will be performed within the CORBEL project to provide training (webinar) and practical solutions to data sharing implementation.

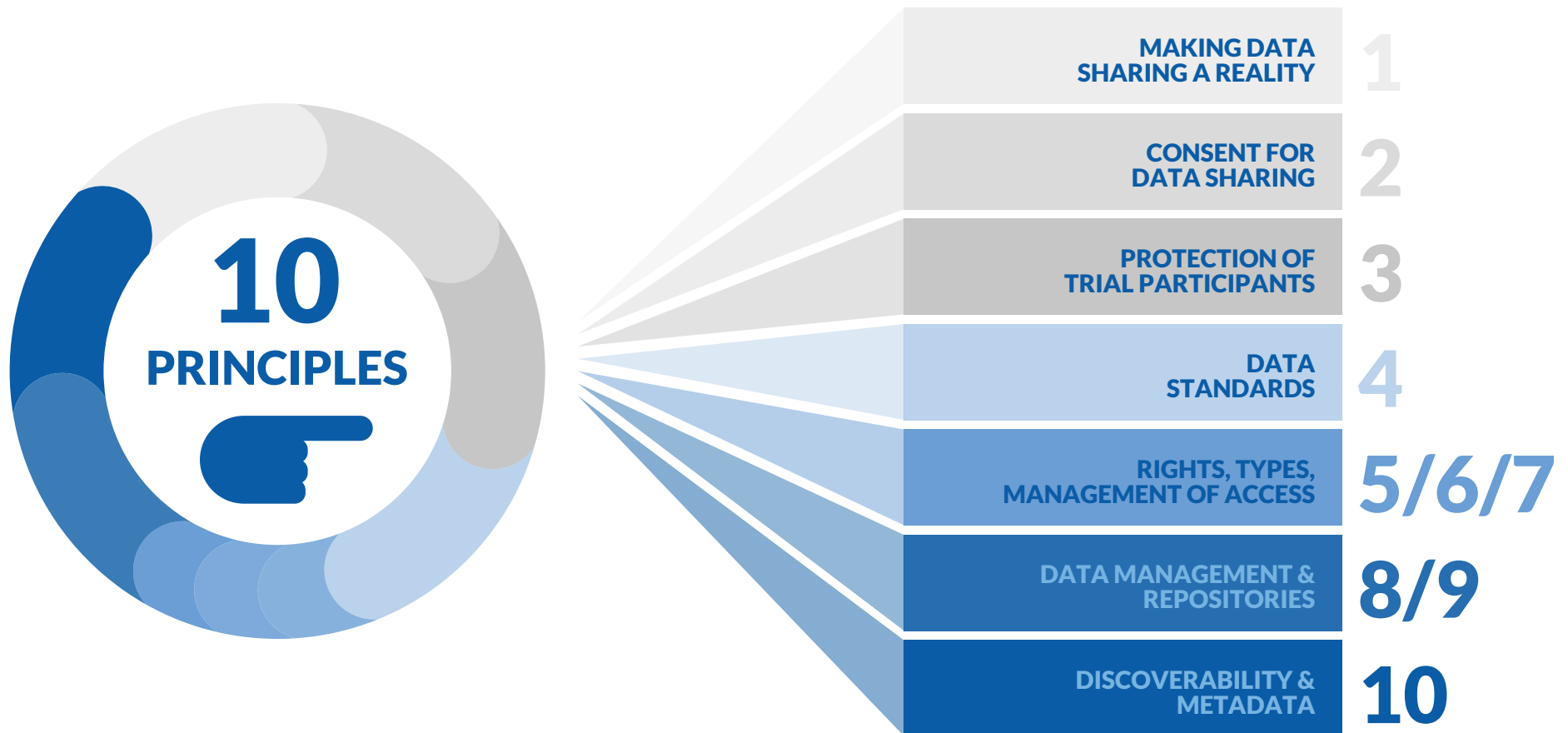
The analysis and re-use of data is also tackled by European Open Science Cloud (EOSC) projects, and in particular this EOSC Pilot, in which ECRIN developed, in collaboration with BBMRI, policy recommendations about ethical issues related to the use and re-use of data.

The access to data and their re-use will impact the next generation of clinical trials and the work will be continued through the current projects, and future EOSC projects.

¹⁹Ohmann C. et al., Sharing and reuse of individual participant data from clinical trials: principles and recommendations. *BMJ Open*. 2017, 7(12):e018647. doi: 10.1136/bmjopen-2017-018647



Clinical Trial Data Sharing



NEW METHODOLOGY AND TECHNOLOGY

ECRIN is also involved in initiatives developing new methodology and technology for clinical trials. In particular, ECRIN is partner in the Marie Curie MiRoR (Methods in Research on Research) project, supporting a cohort of 15 PhD students working on various aspects of trial methodology, with the objective to reduce waste in research. In 2017, ECRIN provided mentoring activities and advice for the development of the projects of 4 students that will later on, in 2018 and 2019, be seconded to ECRIN and will use ECRIN as a practical implementation platform for the tools developed.

TRAINING

ECRIN was involved in developing training activities as participant in two H2020 projects. For CORBEL (Coordinated Research Infrastructures Building Enduring Life-science services), ECRIN has hosted a staff exchange on data sharing and data protection. For RItrain (Research Infrastructure Training Programme), whose objective is to train the managers of the Research Infrastructures, ECRIN has successfully submitted an application to host a staff exchange on project management within a distributed infrastructure.

ECRIN also developed a webinar about clinical development within the C-Comend project coordinated by EATRIS.

Internally, the ECRIN Summer School provides specific training for the ECRIN team and the 2017 edition focused on quality management and in particular the renovation of ICH E6, the changes in the regulatory framework, and their impact on the ECRIN activities.

In addition, a dedicated and personalised support is provided to new staff, or staff starting new activities, with the implementation in 2017 of mentoring activities given by an experienced European Correspondent.

CAPACITY /2

INTERACTION WITH OTHER RESEARCH INFRASTRUCTURES, STAKEHOLDERS AND INTERNATIONAL PARTNERS

Close collaboration with national partners, research communities, other research infrastructures and international partners is needed to capture the needs of the community and ensure the development of the appropriate capacity and services.

PARTNERSHIPS

CORBEL

Medical Research Infrastructures (RIs) play a pivotal role in the advancement of knowledge and technology, and represent a powerful instrument to promote, facilitate and enhance regional, national and transnational collaboration, offering a shared access to facilities.

Close collaboration with research communities is required to ensure appropriate development of tools and services, and to ensure the effective alignment of the RI capabilities and services to the needs of the various medical users' communities in Europe.

The two Medical Infrastructures Users Forum (MIUF) meetings driven by ECRIN and organised in 2017, contributed to capture the needs of the medical research communities, and of the related funding schemes: needs in terms of scientific services, to drive the development of services meeting users' expectations; need to clarify the respective role of the research infrastructures (methodological and technical services) vs the medical research communities (scientific content and access to patients); need to avoid duplication of equipment, tools and services, and to take advantage of this arrangement to promote cross-fertilization of medical specialities through common instruments deployed by the generic research infrastructures. A strategic paper is under development.

RISCAPE

ECRIN acts as representative of the Biomedical Research Infrastructures cluster in the RISCAPE project, whose objective is to map the current landscape of research infrastructure services globally. A first list of major or unique facilities was identified in various world regions, and a common methodology to evaluate those organisations was developed. The collection of information will be performed in the second quarter of 2018, with first results expected by end of the year.

CRIGH

ECRIN also promotes global cooperation in clinical trials, with the objective to facilitate, for European investigators, access to patients and to medical expertise worldwide, which is particularly relevant for rare diseases. As a follow-up of the OECD Council Recommendation on the Governance of Clinical Trials, the Clinical Research Initiative for Global Health (CRIGH, www.crigh.org) was launched in January 2017, as a worldwide partnership of 40 Members and Observers, including the OECD and WHO as partners¹¹. The CRIGH secretariat is shared between the US NIH and ECRIN. CRIGH covers various aspects of international cooperation such as (1) Infrastructure and

¹¹ Demotes-Mainard J, Melien O, Sgard F, Bouësseau MC, Trimble ET: Global health: Boost multinational clinical research. *Nature* 545:289 (2017) doi:10.1038/545289b

funding, (2) Global core competencies, (3) Research ethics, (4) Patient involvement, (5) Comparative effectiveness research, (6) Regulatory awareness.

STRUCTURING NATIONAL PARTNERS

Sharing best practice among national scientific partners is a major added value for the ECRIN infrastructure. This is provided through international expert working groups focusing on various activities such as pharmacovigilance, role of lead CTUs, or through specific discussions initiated by the country.

In 2017, a meeting was organised by the Hungarian government, and some recommendations were provided to develop the national capacity in line with national and ECRIN expectations.

EXPANSION

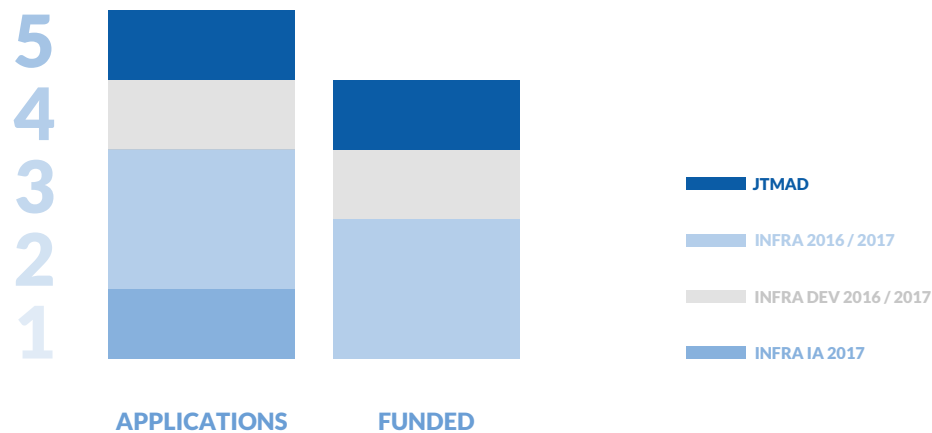
Size matters for the access to patient populations, and ECRIN continues to develop partnerships. No new country joined ECRIN-ERIC in 2017, however several new contacts were established and the partnership process is ongoing in Turkey, Ireland and Slovakia, with expected membership in 2018.

The observer status of Czech Republic ended in 2017 and Czech Republic decided to join as a Member as of 1st January 2018.

NEW PROJECTS

ECRIN participated in 5 infrastructure proposals in 2017, of which 4 were successfully evaluated and funded. One proposal was accepted for the second step and was eventually not funded.

This will allow to further strengthen and advance research about data (XDC and EOSC Hub) and to participate in the structuring of paediatric research (EPTRI and c4c).



ORGANISATION

SIGNIFICANT CHANGES

The ECRIN-ERIC organisation underwent significant changes over the year 2017, as the scaling up of the activity required changes in the spectrum of competences and volume of activity. The ECRIN Team was partly reorganised and some activities redistributed within the new organisation chart. In particular the Operation Department was reinforced by the Clinical Operations Manager and the Medical Expert, whereas one of the experienced European Correspondent now acts as a part-time mentor to support the European Correspondents. In addition a project manager was recruited for the paediatric projects.

CORE TEAM

Jacques Demotes	Director General
Christine Kubiak	Operations Director
Sabine Kläger	Clinical Operations Manager
Gonzalo Calvo	Medical Expert
Alicja Szofer-Araya	Administrative and Finance Manager
Jayne Maddock	Administrative Assistant
Christine Tonéatti	Quality and Risk Manager
Mihaela Matei	Legal and Regulatory Officer
Sabrina Gaber	Communication Officer
Audrey Strader	Clinical Operations Project Manager
Serena Battaglia	Capacity Project Manager
Salma Malik	Paediatric Project Manager

EUROPEAN CORRESPONDENTS

Katerina Nebeska	Czech Republic
Lenka Souckova	Czech Republic
Amélie Michon (part-time mentor)	France
Luc Wasungu	France
Linda Stöhr	Germany
Anke Streng-Hesse	Germany
Zita Tarjanyi	Hungary
Elena Toschi	Italy
Arianna Valerio	Italy
Valentina Cabral-Iversen	Norway
Catarina Madeira	Portugal
Eva Lopez-Guerrero	Spain
Joaquín Saez-Penataro	Spain
Caecilia Schmid	Switzerland

EXPERTS AND CONSULTANTS

Christian Ohmann	Data Management Expert
Vittorio Bertelé	Scientific Board Secretariat
Chiara Gherardi	Scientific Board Secretariat
Steve Canham	Data Management Consultant

National Partners

COUNTRY	NATIONAL HUB	NATIONAL CTU NETWORK	HOST INSTITUTION (LINKED THIRD PARTY)
CZECH REPUBLIC	BRNO	CZECRIN	MASARYK UNIVERSITY
GERMANY	BERLIN	KKSN	KKSN
SPAIN	BARCELONA	SCREN	ISCIII
FRANCE	TOULOUSE	F-CRIN	INSERM
HUNGARY	PECS	HECRIN	HECRIN
ITALY	ROME	ITACRIN	ISS
NORWAY	TRONDHEIM	NORCRIN	ST OLAF'S HOSPITAL
PORTUGAL	LISBON	PTCRIN	NOVA UNIVERSITY
SWITZERLAND	BERNE	SCTO	SCTO

Network Committee and Assembly of Members

NETWORK COMMITTEE

Regina Demlova	Czech Republic	
Olivier Rascol	France	
Heiko Von Der Leyen	Germany	
Gabor Kovacs	Hungary	
Lucia Palmisano	Italy	
Ola Dale	Norway	
Emilia Monterio	Portugal	
Antonio Portoles	Spain	
Fabian Tay	Switzerland	
Annette Magnin	Switzerland	Vice Chair
Christian Ohmann	Germany	Chair

ASSEMBLY OF MEMBERS

Rafael De Andres-Medina	Spain	Chair
Maria Ferrantini	Italy	Vice Chair
Jan Burianek	Czech Republic	
Eric Guittet	France	
Alexander Grundmann	Germany	
Csaba Vadadi-Fulop	Hungary	
Oyvind Melien	Norway	
Daniel Carapau	Portugal	
Annette Magnin	Switzerland	NC Vice Chair
Christian Ohmann	Germany	NC Chair
Jacques Demotes	ECRIN	DG



OUTREACH

OVERVIEW

The clinical research communities remained a central target of our external communication. ECRIN organised and participated in various European and international scientific meetings and conferences.

COMMUNICATION

The main event in 2017 was the celebration of the International Clinical Trials Day (ICTD) and the annual ECRIN meeting. The 2017 edition was hosted by PtCRIN and held in Lisbon on May 19th under the topic of 'Data sharing and reuse: attitudes and practices in multinational clinical research' with the participation of numerous European and Portuguese representatives of various scientific communities.

DISSEMINATION

Dissemination activities included the participation in numerous meetings, congresses and conferences, and the publication of articles in scientific journals, in particular a series of papers on clinical trial design and methodology, articles on data centre certification and data sharing, and papers on international cooperation.

2017 PUBLICATIONS

Ohmann C, Canham S, Demotes J, Chene G, Lauritsen J, Martins H, Mendes RV, Nicolis EB, Svobodnik A, Torres F : Raising standards in clinical research – The impact of the ECRIN data centre certification programme, 2011-2016; *Cont Clin Trials Commun.* 5 (2017) 153-159.

Demotes-Mainard J, Melien O, Sgard F, Bouësseau MC, Trimble ET, Boost multinational clinical research. *Nature* 545:289 (2017)

Djurisic S, Rath A, Gaber S, Garattini S, Bertele V, Ngwabyt SN, Hivert V, Neugebauer EAM, Laville M, Hiesmayr M, Demotes-Mainard J, Kubiak C, Jakobsen JC, Gluud C. Barriers to the conduct of randomised clinical trials within all disease areas. *Trials*, 2017,18(1):360.

Auffray C, Sagner M, Abdelhack S et al. Viva Europa, a land of excellence in research and innovation for health and wellbeing. *Progr Prev Med* 2017, 2:e006.

Laville M, Segrestin B, Alligier M, Ruano-Rodríguez C, Serra-Majem L, Hiesmayr M, Schols A, La Vecchia C, Boirie Y, Rath A, Neugebauer EAM, Garattini S, Bertele V, Kubiak C, Demotes-Mainard J, Jakobsen JC, Djurisic S, Gluud C. Evidence-based practice within nutrition: what are the barriers for improving the evidence and how can they be dealt with? *Trials* 2017,18:425.

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Rath A, Salamon V, Peixoto S, Hivert V, Laville M, Segrestin B, Neugebauer EAM, Eikermann M, Bertele V, Garattini S, Wetterslev J, Banzi R, Jakobsen JC, Djurisic S, Kubiak C, Demotes-Mainard J, Gluud C. A systematic literature review of evidence-based clinical practice for rare diseases: what are the perceived and real barriers for improving the evidence and how can they be overcome? *Trials*. 2017, 18(1):556.

Harman NL, James R, Wilding J, Williamson PR; Battaglia S, Demotes-Mainard J, Gailus-Durner V, Garattini S, Prinsen CAC, Raess M, da Silva-Buttkus P, Terwee CB. SCORE-IT (Selecting Core Outcomes for Randomised Effectiveness trials In Type 2 diabetes): a systematic review of registered trials. *Trials*. 2017 Dec 15;18(1):597.

Ohmann C, Banzi R, Canham S, Battaglia S, Matei M, Ariyo C, Becnel L, Bierer B, Bowers S, Clivio L, Dias M, Druml C, Faure H, Fenner M, Jose Galvez J, Davina Ghersi D, Gluud C, Groves T, Houston P, Karam G, Kalra D, Knowles RL, Krleža-Jerić K, Christine Kubiak C, Kuchinke W, Kush R, Lukkarinen A, Marques PS, Newbigging A, O'Callaghan J, Ravaud P, Schlünder I, Shanahan D, Sitter H, Spalding D, Tudur-Smith C, van Reusel P, Veen EB, Visser GR, Wilson J, Demotes-Mainard J. Sharing and reuse of individual participant data from clinical trials: principles and recommendations. *BMJ Open* (2017) 7:e018647.

2017 SELECTED COMMUNICATIONS

ECRIN support to multinational trials : the clinical trial data management challenge. i~HD hospital network workshop, Brussels February 9th, 2017.

ECRIN standardization by ECRIN Data Center Certification. Towards Standardization and Harmonization Strategy for Global Clinical Trials. First Global ARO Workshop, Tokyo March 2nd, 2017.

The ECRIN initiative. Investigator-initiated global clinical research in foreign countries. Japan Agency for Medical Research and Development; Global Clinical Trial Development Project; First Global Clinical Trial Advanced and Planning Symposium, Tokyo March 4th, 2017.

Will novel medicine and artificial intelligence help humanity and how? (and the unsustainable price of novel medicinal products). The Future of Humanity Through the Lens of Medical Science - Rewriting the Contract, Rome April 4-5th, 2017. Report in *Lancet* 389:1500 (2017)

ECRIN, the pan-European network for clinical research. ECRIN Meeting in Estonia, Tartu, 15th June 2017

The Role and Mission of ECRIN. Establishing and Internationalizing the Thematic Network for Clinical Research in Hungary, Pecs, 13th July 2017

ECRIN, Supporting the management of multinational clinical research in Europe, Personalized medicine and biomarkers, H2020 European Health Brokerage Event, Copenhagen, 11th September 2017

European Clinical Research Infrastructure Network - Supporting multinational clinical research in Europe European Society of Coloproctology, Berlin, 19th September 2017

ECRIN Role in TESA II. TESA II Kick off Meeting (Trials of Excellence in Southern Africa). Maputo (Mozambique) 30th October 2017.

ECRIN Data Center Certification and Consensus Document on Principles of Sharing Individual Patient Data from Clinical Trials. 2nd Global ARO Network Workshop, Accelerate academic innovation to overcome intractable diseases. University of Texas AT&T Conference Center, Austin, 17th November 2017

Implementing the EU Clinical Trial Regulation - An academic perspective. French e-Pharma Day, Paris, 28th November 2017

STRATEGY PLAN

OVERVIEW

The 2016-2019 strategy plan is based on strategic questions requiring appropriate answers before implementation.

In particular, the agenda for 2017 included a review of the scientific board (SB) activity and of the scientific board peer-review mechanism. This resulted in a proposal to slightly change the composition and the role of the SB, with an extension whose mission is to give an early GO / NOGO signal to the projects requesting ECRIN services before the ECRIN team invests in the support to the project planning and design. This was set-up for a pilot phase by end of 2017, which will now be evaluated to further drive the change in the project evaluation process.

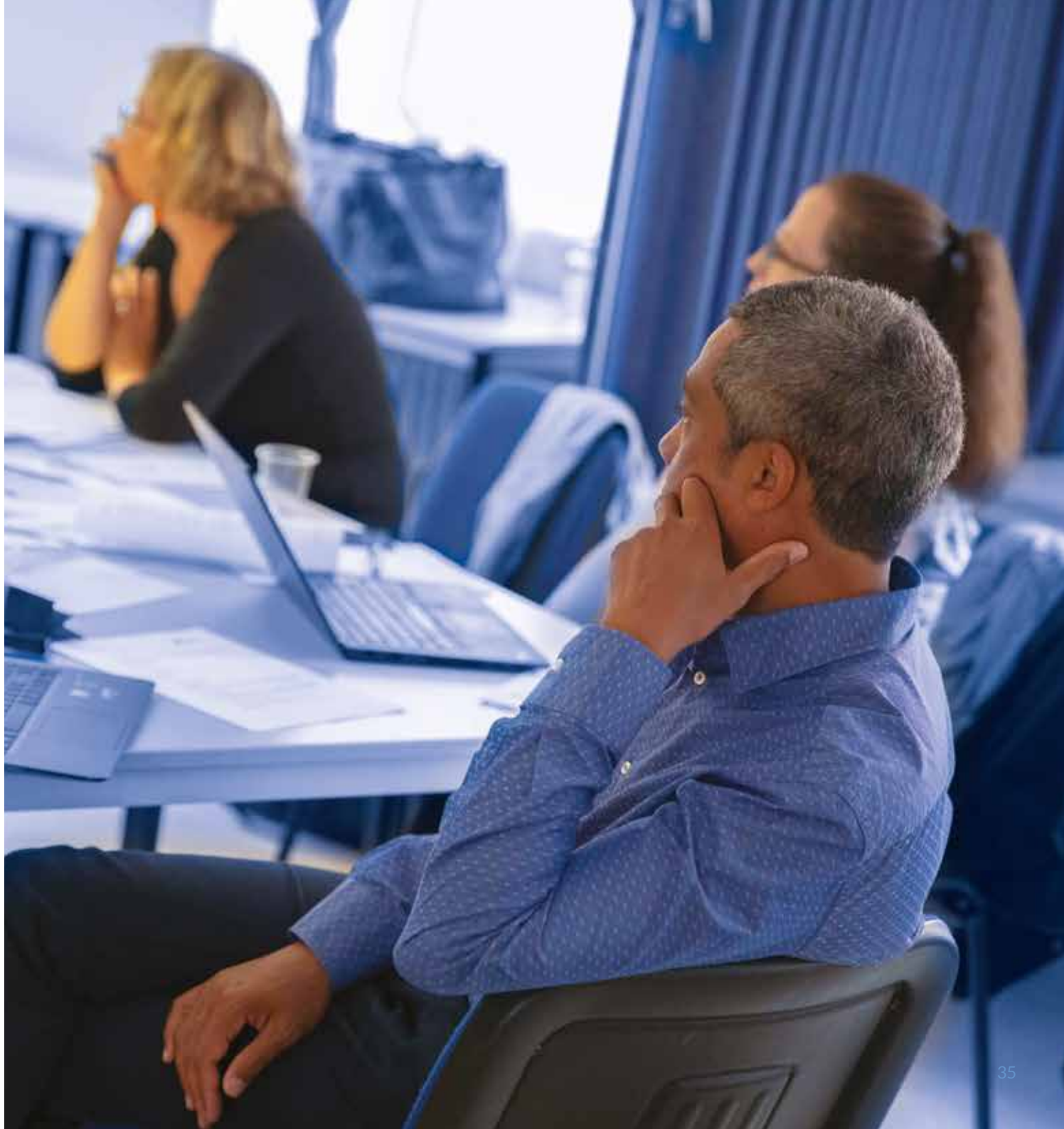
A series of scientific papers published in 2017 addressed the issue of clinical trial design and methodology, making recommendations on trial design in rare diseases, medical device and nutrition. Such effort should be continued in the future, especially for paediatric trials, or for the design of personalised medicine trials. In addition, practical training on trial design and methodology should be developed.

Changing the ECRIN website to become a source of comprehensive information for clinical trialists is an ambitious question that has still to be investigated in terms of content, workload, cost, possible duplication, update and upgrade mechanisms.

As mentioned earlier, the question of whether ECRIN should also support multinational observational studies received a positive answer, in the perspective of the personalized medicine projects, and in the context of improved quality in observational study data, and of dampening borders between healthcare, observational and interventional data.

The paediatric projects, as well as other future partnership projects, represent a framework model for the interaction with medical specialties / investigation networks.

Finally, ECRIN is already involved in a significant number of trials with spin-off or SMEs, using various funding models. In spite of possible difficulties raised by contracting, insurance or intellectual property, the role of ECRIN in such projects appears rather positive whenever the company lacks trial management capacity either locally, or internationally. A discussion with the AoM should however help with defining the criteria for eligibility of such projects: common criteria (2 member or observer countries as participants) ? or specific criteria (SME based in a member or observer country) ?



FINANCIAL SUMMARY

OVERVIEW

Under article 13 of the statutes "Accounts", the financial statement of ECRIN-ERIC shall be presented to the Assembly of Members accompanied by a report on financial management of the last financial year.

ECRIN's statement of activities shows a net result of 274 774 € composed as follows.

INCOME	ACTUAL 2017	PROVISIONAL 2017
MEMBERSHIP CONTRIBUTIONS	€1 320 000	€1 315 360
EU PROJECTS	€866 971	€855 491
OTHER INCOME	€93 083	-
FINANCIAL INCOME	€20 332	€12 000
TOTAL INCOME FOR 2017	€2 300 386	€2 182 851

EXPENDITURES	ACTUAL 2017	PROVISIONAL 2017
SALARIES AND SOCIAL EXPENSES	€898 016	€1 179 380
OTHER OPERATING EXPENSES	€1 115 146	€957 380
FINANCIAL EXPENSES	€7 572	€2 500
INCOME TAX	€4 877	€3 000
TOTAL EXPENDITURE FOR 2017	€2 025 611	€2 142 260

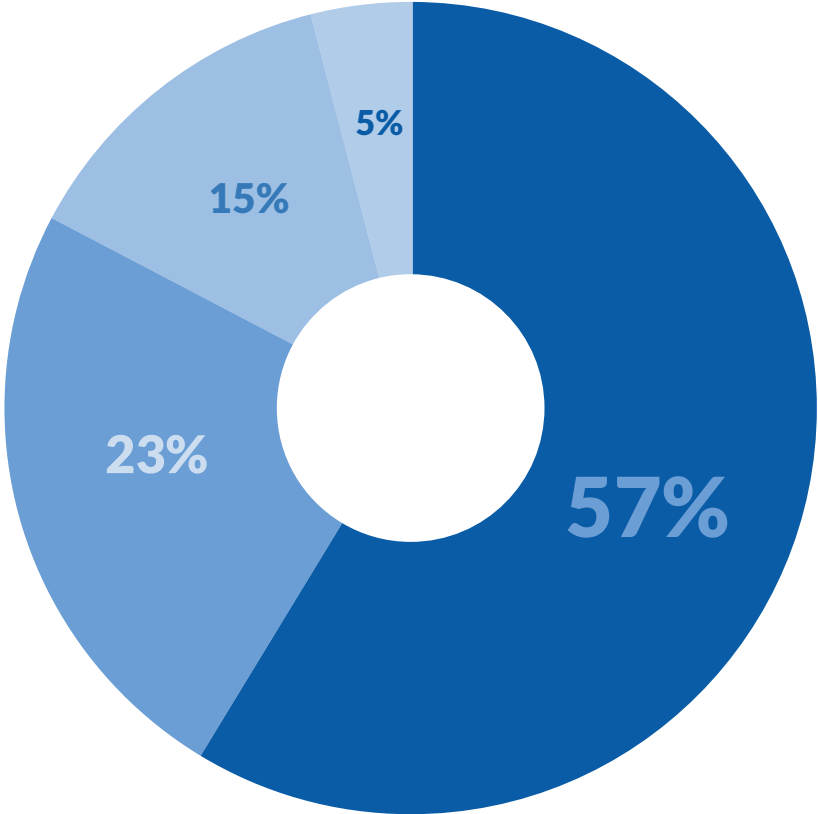
NET RESULT	ACTUAL 2017	PROVISIONAL 2017
NET RESULT FOR 2017	€274 774	€40 591

IN-KIND CONTRIBUTIONS	ACTUAL 2017	PROVISIONAL 2017
LOCAL IN-KIND CONTRIBUTIONS	€650 000	€750 000

INCOME

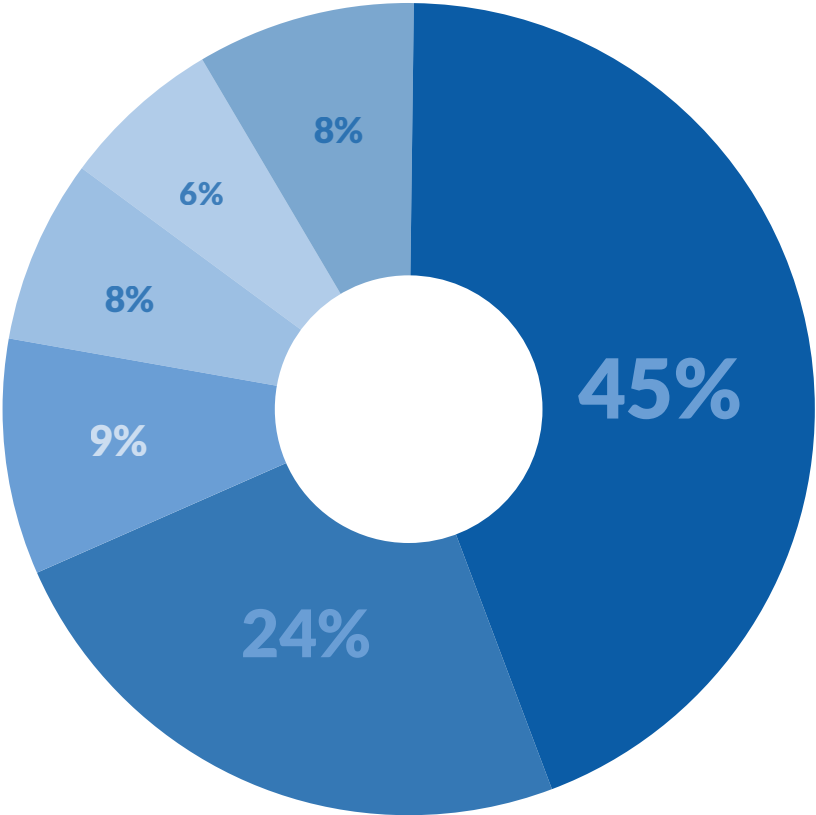
The main sources of ECRIN's income are the financial contributions of ECRIN-ERIC Members and research projects, mostly FP7 and H2020 projects funded by the EC.

MEMBERSHIP CONTRIBUTIONS	€1 320 000	57%
CLINICAL TRIALS	€532 863	23%
STRUCTURING PROJECTS	€334 108	15%
OTHER INCOME	€113 415	5%
TOTAL INCOME FOR 2017	€2 300 386	100%



EXPENSES

SALARIES AND SOCIAL EXPENSES	€898 016	45%
SERVICES (ECRIN PARTNERS)	€489 461	24%
TRAVEL AND MEETINGS	€188 691	9%
RENT AND INSURANCE	€152 103	8%
SCIENTIFIC BOARD	€127 750	6%
OTHER EXPENSES	€169 590	8%
TOTAL EXPENDITURE FOR 2017	€2 025 611	100%



NOTES (capacity projects mentioned in the text)

CORBEL: Coordinated Research Infrastructures Building Enduring Life-science services.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Grant Agreement No H2020 654248

RISCAPE : European Research Infrastructures in the International Landscape.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Grant Agreement No H2020730974

PEDCRIN: Paediatric Clinical Research Infrastructure Network.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Grant Agreement No H2020 731046

XDC: eXtreme DataCloud.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Grant Agreement No H2020 777367

EOSC PILOT: The European Open Science Cloud for Research Pilot Project.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Grant Agreement No H2020 739563

ESOC HUB : Integrating and managing services for the European Open Science Cloud.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Grant Agreement H2020 777536

MiRoR: Methods in Research on Research.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement N° 676207

TRANSVAC 2: European Vaccine Research and Development Infrastructure.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Grant Agreement No H2020 730964

RITRAIN: Reseach Infrastructures Training Programme.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Grant Agreement No H2020 654156

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