



Scientific Workshop “Multinational Clinical Trials”

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ERA-NET NEURON



Contents

Summary	1
Introduction to the ERA-Net NEURON.....	2
I. Investigator-driven multinational clinical trials: Rationale, definition and needs	3
<i>Prof. Christian Ohmann (ECRIN, Heinrich Heine University, Düsseldorf, Germany)</i>	
Clinical research - a challenge in innovation transfer.....	3
Definition of clinical trials	4
The need for investigator-driven clinical research in Europe.....	5
Recommendations for encouraging and improving multinational investigator-driven clinical research in Europe	6
II. Need for support and for funding to multinational investigator-driven clinical trials: the role of ECRIN.....	8
<i>Prof. Jacques Demotes (ECRIN and Ministry of Higher Education and Research, France)</i>	
ECRIN – the European Clinical Research Infrastructures Network.....	8
Core activity: Services to multinational clinical research.....	9
ECRIN: Impact and added value	10
Critical issues for funding multinational clinical trials via an ERA-Net call	10
ECRIN recommendations for setting up a multinational clinical trial.....	11
III. A psychiatrist’s perspective on multinational clinical trials.....	12
<i>Prof. Rene Kahn (University Medical Center Utrecht, The Netherlands)</i>	
EUFEST: The study in a nutshell.....	12
Hurdles to overcome when conducting a multinational clinical trial	13
IV. A neurologist’s perspective on multinational clinical trials	15
<i>Prof. Wolfgang Oertel (University of Marburg, Germany)</i>	
The need for investigator-initiated clinical trials in neurology	15
Experiences from the German Parkinson Study	16
Recommendations for a funding scheme in the ERA-Net	17
V. Multinational Clinical Trials in the context of the ERA-Net E-Rare	18
<i>Dr. Sophie Koutouzov (Coordinator of the ERA-Net E-Rare, GIS – Institute of Rare Diseases, France)</i>	
The ERA-Net E-Rare	18
The position of ERA-Net E-Rare towards clinical trials funding.....	19
VI. Conclusions of the Round Table Discussion	21
Status Quo: Funding of clinical research by the ERA-Net NEURON	21
Needs of the scientific community in the field of disease-related neuroscience.....	21
Methodological requirements for multinational clinical trials	22
Funding multinational clinical trials and the ERA-Net scheme.....	22
Annex: List of Participants.....	23

The workshop was opened with greetings from PD Dr. Marlies Dorlöchter, NEURON Coordinator who presented the ERA-Net NEURON scheme and the scope of the workshop.

This workshop is part of Work Package 2 STRATEGIC PREPARATION OF PROGRAMME COORDINATION AND PROGRAMME OPENING ACTIVITIES lead by FNR.

Published in December 2011

Summary

Many exciting results in neuroscience research accumulated in the past years. However, in many cases, findings on basic disease-related mechanisms do not translate into applications for patients. Clinical research, with clinical trials in particular, is strongly needed to overcome this alarming gap.

The NEURON consortium organized the workshop “Multinational Clinical Trials” to analyze the current situation in the field of disease-related neuroscience in the European Research Area. Fifteen representatives from 13 funding organisations and ministries participating in the NEURON consortium attended the workshop. Five expert speakers addressed the participants of the workshop:

- **Professor Christian Ohmann** (Heinrich Heine University Düsseldorf) provided background knowledge on multinational clinical trials, covering definitions, the need for such trials, and their current status in Europe.
- **Professor Jacques Demotes** (European Clinical Research Infrastructures Network, ECRIN) introduced the ECRIN network, an initiative sponsored by the European Commission to support researchers conducting multinational clinical trials in Europe.
- **Professor René Kahn** (University Medical Centre, Utrecht) and **Professor Wolfgang Oertel** (Philipps-University, Marburg) presented a view on “real life” hurdles and potentials of multinational clinical trials in the fields of psychiatry and neurology.
- **Dr. Sophie Koutouzov**, coordinator of the ERA-Net E-Rare, highlighted how the E-Rare consortium approaches the question of funding multinational clinical trials.

The workshop ended with a Round Table discussion, with active participation of the expert speakers and the NEURON consortium partners. The conclusion was that there is a real need for joint funding of multinational clinical trials, but, to date, this clearly faces obstacles.

The workshop was held on May 3rd, 2011 at the Villa Vigoni, Loven di Menaggio, Italy.



Introduction to the ERA-Net NEURON

The ERA-Net NEURON (= Network of European Funding for Neuroscience Research) is a pan-European project funded for 5 years by the European Commission (2007-2011). The aim of the NEURON is to coordinate and promote research funding activities on disease-related neuroscience in the European Research Area (ERA).

To this end, 18 funding organisations and ministries from 13 EU member states, Israel and Canada are closely collaborating¹.

In the ERA-Net, NEURON partner organisations exchanged information on funding activities in neuroscience, worked out common strategic needs, connected programme managers and researchers, and, most importantly, launched four annual joint transnational calls (JTC) for proposals. The calls covered broad topics of high scientific and societal importance. The themes of the JTCs were: (1) neurodegeneration, (2) advancement of methods and technologies in neuroscience, (3) mental disorders and (4) cerebrovascular diseases. To date, the NEURON partners fund about 180 research groups all over Europe, Israel and Canada with a budget of about 40 million €.

Due to the many achievements of the ERA-Net NEURON, funding of the European Commission was prolonged for a second 4 years period (2012-2015). In the ERA-Net NEURON II, the network has expanded to 21 partner organisations.

More information on NEURON online: <http://www.neuron-eranet.eu>



¹ Partners in the ERA-Net NEURON:

- Austria: Austrian Science Fund (FWF)
- Canada: Canadian Institutes of Health Research (CIHR) and Fonds de recherche du Québec-Santé (FRQS)
- Finland: Academy of Finland (AKA)
- France: National Research Agency (ANR), French National Centre for Scientific Research (CNRS), and National Institute for Health and Medical Research (INSERM)
- Germany: Project Management Agency in the German Aerospace Centre (PT-DLR) for the Federal Ministry of Education and Research (BMBF)
- Israel: Chief Scientist Office-Ministry of Health (CSO-MOH)
- Italy: Ministry of Health (MOH)
- Luxembourg: National Research Fund (FNR)
- Poland: National Centre for Research and Development (NCBiR)
- Romania: Ministry of Education and Research (MedR) and National Centre for Programme Management (NCPM)
- Spain: Institute of Health Carlos III (ISCIII) and Ministry of Education and Science (MICINN)
- Sweden: Swedish Research Council (SRC)
- United Kingdom: Medical Research Council (MRC)

I. Investigator-Driven Multinational Clinical Trials: Rationale, Definition and Needs

Prof. Dr. Christian Ohmann, Germany

Christian Ohmann, PhD, is Professor at the Heinrich-Heine-University in Düsseldorf, Germany, and has a graduation in mathematics. Christian Ohmann is head of the “Coordination Centre for Clinical Trials” at the Medical Faculty of the Heinrich-Heine-University. Since 1999, he is board member of the Network of German Coordination Centres for Clinical Trials (KKS Network). He is the German representative for ECRIN and Chairman of the ECRIN Network Committee.



Abstract

Investigator-driven clinical research in Europe is strongly needed. To date, innovative medicinal products appear on the market too rarely, with a gap between the development of drugs and patients' interests. Available research, in turn, is dominated by pharmaceutical interventions.

The main areas to be covered by future investigator-driven clinical research are

- to establish comparative effectiveness of treatments and therapeutic strategies,
- to evaluate drugs for rare diseases,
- to extend variability of treatment to fragile populations and
- to optimize available treatments.

In order to implement investigator-driven multinational clinical trials, appropriate infrastructures at the national, European and global level are needed as well as funding sources to support the multinational and independent assessment of health care strategies. Furthermore, there are needs for a risk-adapted legislative framework and to reinforce transparency for clinical trial data. The role of the European Commission in funding multinational clinical research should be strengthened.

Multinational clinical trials have a great potential. They could provide an adequate number of patients more easily, shorten the time required for conducting clinical trials and improve the generalisability of study results as compared to national clinical trials. Moreover, innovative trial designs may bring together specific resources and expertise.

Clinical research - a challenge in innovation transfer

Clinical research is crucial for advancing knowledge on diseases and their treatment. However, the transfer of innovative ideas into applications is often long and stony. Many different kinds of scientific evidence are required before a novel medicinal product or a novel treatment strategy may finally be approved to become available in medical care.

As a first step, basic bodily mechanisms have to be uncovered and understood, often starting from *in vitro* or animal models (=basic research). In a next step, researchers must be able to show that such mechanisms are indeed relevant for pathological processes of a defined disease (disease-oriented research). If so, research must shift to studies in patients and prove relevant for improving defined disease-related parameters (patient-oriented research). Then, a medicinal innovation should prove useful and cost-effective (health service research studies). Only when these steps are successfully completed and comprehensive evidence is provided, a novel treatment idea may finally be frequently used in medical health care (see fig.1).

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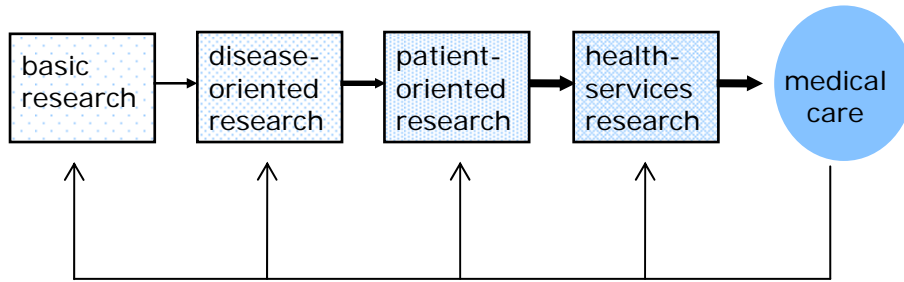


Figure 1: Steps in innovation transfer

These steps form in fact a highly selective funnel: A recent analysis shows that out of 101 promising novel therapeutic/preventive approaches, only about one fourth make its way into patient-oriented research. Out of these, again only about one in five novel technologies eventually gets licensed – ultimately leading to just one novel technology extensively applied in medical care.

Definitions of clinical trials

The International Clinical Trials Registration Platform (ICTRP) provides a rather broad definition of a “Clinical Trial”:

„ [...] a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Clinical trials may also be referred to as interventional trials. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioral treatments, process-of-care changes, preventive care, etc.”

Starting from this broad definition, clinical trials can be divided in different categories. Major categories are: trials on the development of medicinal products, trials on medical devices, therapeutic trials, diagnostic studies, interventional clinical research and epidemiology research (see table 1).

Table 1: clinical research categories and trial examples

clinical research category	includes
medicinal product	Phase I to IV trials, biotherapy trials, biopharmaceutical trials, vaccine trials, fixed combination of medicinal products, multimodal trials
medical device	devices alone, devices combined with medicinal products
other therapeutic trial	radiotherapy, surgery, transplantation, transfusion, trials with cell therapy, physical therapy, psychotherapy
diagnostic study	diagnostic or imaging studies without medicinal product/medicinal device
other interventional clinical research	complementary or alternative medicine, collection of blood or tissue samples or other fluids, physiology studies, pathophysiology studies, psychology studies
epidemiology	interventional and non interventional pharmacoepidemiology/epidemiology, retrospective studies, registries of patients

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Each category encompasses a different set of methodological approaches. As an example, for the development of a novel medicinal product, such as a novel drug, four different trial phases are further differentiated. Phase I trials analyse basic pharmacological aspects of a substance applied to the human organisms, such as its safety and tolerability, its pharmacokinetics and pharmacodynamic aspects. In phase II, the focus shifts to a drug's therapeutic usefulness tested with an explorative methodological approach, whereas in phase III its therapeutic usefulness must be confirmed. In the last phase, phase IV, which takes place after the drug is formally approved and already available on the market, the drug's therapeutic use is further analysed (see table 2).

Table 2: Description of phase I to phase IV trials

phase	description
1	human pharmacology <i>(initial safety and tolerability, pharmacokinetics, pharmacodynamics)</i>
2	therapeutic exploratory
3	therapeutic confirmatory
4	therapeutic use <i>(after drug approval)</i>

Clinical trials in a narrow sense often refer to clinical trials on medicinal products. These may be defined as

“any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy”
(EU Directive 2001/20/EC)

A trial “sponsor” is responsible for the trial. A sponsor is an individual, company, institution or organization, which takes responsibility for the initiation, management and/or financing of a clinical trial.

It is important to note that clinical trials need not necessarily involve commercial companies.

A clinical trial is called an “Investigator-driven clinical trial” if

- a pharmaceutical company/device company is not acting as the sponsor for the purposes of the clinical trial application
- a pharmaceutical/device company is not fully funding the conduct of the study, that is, making payment to the relevant hospital or investigator
- the clinical trial addresses relevant clinical questions and not industry needs
- the principal investigator or the hospital/institution is the primary author and custodian of the trial protocol

<http://www.health.qld.gov.au/ohmr/> (Office of Health and Research, Queensland Health)

A Clinical Trial may be mono- or multicentric. This means the trial is either conducted only at one study site or at multiple study sites. In multicentric trials, all study sites use the same protocol, while multiple investigators are involved. A multinational clinical trial is conducted in more than one country, and is thus multicentric by definition.

The need for investigator-driven clinical research in Europe

In the years 2004-2010, only 12% of all applications for multinational clinical trials in Europe were investigator-initiated. In stark contrast to this small number, clinical research is not only highly important for public health care systems, as these serve to transfer scientific

findings into novel therapeutic applications, but, notably, the monetary investment also pays off. A health economic analysis showed that the total health and GDP gains of medical research in the field of mental health sponsored by public institutions summed up to a total return rate of 30%. Regarding cardiovascular disease research, a total health and GDP gain of 40% was calculated. When taking a longer term view, gains even increase: in the US, 28 clinical trials funded by the US National Institutes of Health produced costs of about 335 M\$, but, taking into account a period of 10 years, were estimated to pay back a net benefit to society of about 15.2 Billion \$.

Moreover, industry-sponsored trials and alliances of clinical investigators and pharmaceutical industry may bring along certain drawbacks. Naturally, industry has a commercial interest in the study outcome and may prefer to report positive results found in a study. In turn, selective reporting practices may cause considerable biases. It was estimated that a positive result reported by a commercial trial was four times more likely than a positive result reported by a non-commercial trial. Also in alliances of clinical investigators and pharmaceutical industry, doubts exist that published results might be tipped towards industry interests. Further concerns may be raised. Industry-sponsored trials may not necessarily address patients' interests. In consequence, a considerable number of topics which are not a primary interest for commercial companies desperately need attention to date:

- More trials on rare disease are required. More than 6.000 different types of rare diseases exist, as compared to only 41 drugs available for their treatment. About 480 drug candidates are described, which are currently not further studied due to scarcity of funding opportunities.
- Trials on the optimization of already available treatments are needed. Once approved for market entry, further studying a medicinal product is not the primary focus for industry. However, it is highly important for patients.
- Fragile populations should be included in clinical trials; to date information on treatment effects in children or the elderly is often not available. For instance, about half of all paediatric drugs have in fact never been tested in children.
- Pharmaceutical interventions dominate treatment strategies. However, non-pharmacological treatments might be as efficient and should be studied in a similar manner.
- Methodologically, in commercial research, a tendency towards equivalence/non-inferiority trials prevails. There is a need to examine the comparative effectiveness of treatments and therapeutic strategies.

Regarding investigator-driven clinical trials, multinational approaches may have a number of advantages as compared to national ones: They can provide adequate patient numbers more easily, shorten the overall time needed for conducting a trial, improve the generalisability of study results, support the implementation of innovative trial designs and bring together specific resources and expertises.

Recommendations for encouraging and improving multinational investigator-driven clinical research in Europe

Despite some great attempts, also several aspects regarding multinational investigator-driven clinical trials urgently need improvement to date, such as methodological issues, administrative regulations, career opportunities, infrastructure, and funding possibilities.

Methodology: Today, in the EU, only quality, efficacy and safety must be demonstrated in clinical research. However, there is a need for studying the comparative effectiveness of treatments and therapeutic strategies. Furthermore, sufficient sample sizes should be involved in trials to ensure statistical power. Transparency of trials must be reinforced, such as making raw data publicly available (anonymised) and optimise data use and analysis.

Regulations: The administrative burden for conducting a clinical trials is quite heavy: Clinical Trial authorisation, ethics committee requirements and insurance issues for multinational trials are quite a challenge for researchers today – it would be highly

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recommendable to simplify such issues, e.g. through harmonization of documents for approval. Furthermore, risk-based approaches should be adopted, to allow for a reduction in workload and cost.

Infrastructure: An adequate infrastructure supporting investigator-driven multinational clinical trials on the national, European and global is recommended to overcome the above mentioned obstacles.

Funding: Funding of translational research, investigator-driven clinical trials and independent health care research should be increased through public Europe-wide funding initiatives. Importantly, the European Commission funds investigator-initiated multinational clinical trials on some health-related topics, such as childhood-onset neurodegenerative diseases, therapeutic interventions in the elderly or for the management of cardiovascular diseases (see FP7 HEALTH.2011).

Education, training and career options: Education, training and career opportunities urgently need improvement to attract researchers to the field.

II. Need for support and for funding of multinational investigator-driven clinical trials: the role of ECRIN

Prof. Dr. Jacques Demotes, France

Jacques Demotes-Mainard, MD-PhD, is a neurologist and Professor of Cell Biology with a background in clinical neurology and basic neuroscience. Jacques Demotes-Mainard is coordinator of the “European Clinical Research Infrastructures Network” (ECRIN) and promotes multinational clinical research in Europe. He is Deputy Director of the Biology and Health Research Department at the Ministry of Higher Education and Research in France.



Abstract

ECRIN, the European Clinical Research Infrastructures Network, encourages and supports multinational clinical research in the European Research Area. Creating a single area for clinical research in Europe will provide access to patients and expertise all across Europe, thus boosting the efficiency and competitiveness of clinical research in Europe. This however requires defragmentation of the infrastructure, which is the main mission of ECRIN. Moreover, harmonisation of the legislation, and defragmentation of funding is required.

ERA-Nets may be a suitable tool for funding multinational clinical trials. However, critical issues have to be addressed, when setting up a funding activity:

- the need for a critical mass of participating countries,
- the need to involve the right partners, as in some countries the funding source for clinical trials are distinct from the funding agencies for basic neuroscience,
- the need for significant levels of funding, i.e. 1 to 3 million € for a clinical trial is a minimum, with high costs in the coordinating country,
- the question of whether the same panel of experts can assess both basic and clinical research (as the evaluation is protocol-based and requires specific expertise in methodology),
- the need to avoid multiple evaluations (a possibility would be to use the ECRIN scientific board for both access to funding and to the infrastructure),
- the need to avoid “parallel” trials, and to ensure that it will be a single trial with the same sponsor, same protocol, same amendments, same management, same database, same EudraCT number,
- the need to define which category of investigator-driven clinical research should be supported: As such, one could consider focussing on rare neurological diseases or on a common disease area. Furthermore, funding could concentrate on trials for developing innovative products, on repurposing trials (=trials exploring new indications of marketed drugs), and/or on treatment optimisation trials using already marketed products.

ECRIN – the European Clinical Research Infrastructures Network

The “European Clinical Research Infrastructures Network” (ECRIN) is a sustainable, not-for-profit initiative supporting multinational clinical research projects in Europe (www.ecrin.org). ECRIN is one of several ESFRI initiatives developing a common research infrastructure in Europe (ESFRI = European Strategy Forum on Research Infrastructures). ECRIN was launched in 2006, together with five further ESFRI initiatives (i.e. BBMRI, EATRIS, ELIXIR, INFRAFRONTIER, and INSTRUMENT), and is supported by the European Commission.

Goal of ECRIN. The goal of ECRIN is to make Europe a single area for clinical research. Therefore, ECRIN provides a Europe-wide infrastructure for clinical research in any disease area. ECRIN offers coordinated services to multinational clinical research in Europe, and aims at facilitating access to patients and to expertise despite the fragmentation of health, legislative and funding systems in Europe.

Organisation of ECRIN. Partners from 14 European countries take part in ECRIN, i.e. Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Poland, Spain, Sweden, Switzerland and the United Kingdom.

Each partner country is represented by a European Correspondent. The ECRIN Management office in turn coordinates the network of the European correspondents. The European Correspondents are key contact points and act as a local relay in ECRIN activities. They collaborate with a national hub of clinical trial units and clinical research centres and they are responsible for the organisation and management of ECRIN pilot projects in their country. In particular, they maintain updated knowledge, provide information and consulting, and provide tools and documents for the set-up and management of multinational studies and for coordinating the support and services.

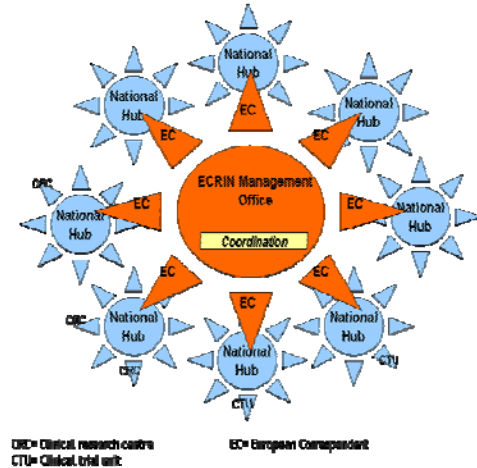


Figure 1: Organisation of ECRIN

Currently, ECRIN is preparing a change in its organisational structure in order to become a sustainable, partner-country driven “European Research Infrastructure Consortium” (ERIC).

Core activity: Services to multinational clinical research

In the beginning of the ECRIN project, the ECRIN consortium assessed the most important needs of researchers conducting multinational clinical research with a thorough survey. Accordingly, ECRIN identified and developed its subsequent core activities:

1. **ECRIN provides information and consultancy during the preparation of the clinical research project.** In particular, ECRIN supports the adaptation of the study protocol to local context, and information on regulatory and ethical requirements, clinical trial sites/units, participant recruitment, insurance issues, cost evaluation models, funding opportunities, and contracting issues.
2. **After a positive evaluation by the Scientific Board, ECRIN provides services during the conduct of the project:** ECRIN promotes the submission of the proposal to, and the interaction with, competent authorities and ethics committees, provides support with insurance contracting, performs adverse event reporting, monitoring, and data management issues, and gives support on investigational medicinal product management.

Access to the ECRIN services and acceptance criteria. Access to the ECRIN services is based on scientific excellence judged by the ECRIN scientific board. The scientific board consists of 7 members (3 ECRIN members, 4 external members). In addition, three external peer-reviewers assess each protocol. By May 2011, six projects were accepted, four projects were rejected and nine were under review.

In order to be accepted by ECRIN, a trial must fulfil several criteria: The proposal must be a multicentre trial in at least two European countries and its topic must be of high clinical relevance and/or must have a marked impact on public health. The project’s rationale must be based on an up-to-date systematic review of clinical data or, if not available, of preclinical data on the experimental intervention and comparator. Methodologically, the overall trial design must be appropriate to the clinical question, including for example an appropriate and justified experimental intervention and comparator, and an adequate sample size with

supporting power calculation. Outcome measures for efficacy and safety with clinically meaningful benefit for the patient should be chosen as well as a relevant patient population; appropriate inclusion and exclusion criteria should be specified and an adequate setting, duration of treatment and follow up period should be selected (see also section “ECRIN recommendations for setting up a multinational trial” below).

Furthermore, it is mandatory that rules for transparency are followed. As such, applicants must commit themselves to register the trial in a public register before inclusion of the first participant (i.e. on <http://www.clinicaltrials.gov/>), to publish results irrespective of positive or negative findings, to make raw anonymised data sets available to the scientific community upon legitimate request to the sponsor or principal investigator once the trial is completed, and to declare any conflicts of interest.

ECRIN: Impact and added value

ECRIN has achieved quite considerable progress in the field of multinational clinical research. As such, ECRIN has compiled and compared national requirements across participating countries on important aspects, such as ethics regulations, competent authorities, sponsors or insurance regulations. Politically, ECRIN had a high impact on the regulation and revision of the 2001/20/EC Directive and on training in the field of medical research. ECRIN furthermore attaches much importance to render clinical research visible to the public: ECRIN invests in the communication with patients and citizens and promotes transparency in clinical research through requiring a registration of trial protocols, reporting of results, open access to data). Moreover, ECRIN provides training of patient associations to clinical trials methodology and involves patient associations in protocol designs.

Besides, the importance of clinical research is increasingly acknowledged by the European Commission and funding is growing. Clinical trials even became a health priority for funding calls of the European Commission in 2011: Specific support for investigator-driven clinical trials will be foreseen, such as trials for the optimisation of treatment in the elderly, on paediatric/adolescent diabetes medicines, and on orphan drugs (treatments for rare diseases). More than 20 upcoming calls in the 7th Framework Program of the EC will focus on clinical research.

Further Europe-wide funding opportunities may potentially be provided through the Innovative Medicines Initiative, Joint Programming Initiatives, the International Rare Diseases Research Consortium, ERA-Nets, or the ECRIN-Integrating Activity.

Critical issues for funding multinational clinical trials via an ERA-Net call

An ERA-Net is a highly interesting instrument for funding multinational clinical research. When launching a call on multinational clinical trials by an ERA-Net, certain issues should be considered:

- **Funding organisations:**
 - A critical mass of participating countries / funding organizations should be supporting the call
 - Relevant partners with experience in funding clinical trials should be on board
- **Funding:**
 - a total funding sum of > 1 million € and up to 3 million € per clinical trial should be considered
 - keep in mind that costs in the coordinating country are higher than in participating countries
- **Proposal evaluation:** Multiple scientific evaluations should be avoided:
 - The review board should be able to evaluate both basic and clinical research. In proposals with clinical trials detailed trial protocols are required.
 - One suggestion was to use the scientific board of ECRIN
- **Trial design:** “Parallel” trials should be avoided: The study must be completely comparable at every site, by using the same protocol, database, EudraCT, management tools, sponsor, and protocol amendments

- **Eligible trial categories:** Decide on which category of investigator-driven clinical studies to be supported:
 - Only therapeutic trials or other clinical studies?
 - Trials on innovative products, repurposing trials exploring new indications, or treatment optimization studies?
 - Focus on selected disease areas? Disease priorities? Rare diseases or common diseases?

ECRIN recommendations for setting up a multinational trial

ECRIN highly recommends considering state-of-the-art methodological and statistical approaches when planning a multinational clinical trial. As such, the following aspects should be considered:

- A randomized superiority design is preferable for efficacy assessment rather than conducting a non-inferiority trial.
- Attention should be paid to select the best available comparator.
- The primary outcome measure must be most suitable for patient and public health interests.
- The sample size calculation should be based on the primary outcome measure, while power calculation for other important outcome measures should be included as well.
- Adverse events must be adequately recorded.
- Strategies must be elaborated to reduce or control possible biases, for instance, central randomisation, blinding of all parties (at least assessors, statisticians), intention-to-treat analysis for efficacy in superiority trials, blinded conclusions drawn before breaking the allocation code, and the independent interpretation of, and decision to publish results. Potential risks and solutions to overcome such risks must be described, including involvement of and charter for independent data monitoring and safety committee.
- A well-elaborated governance structure distributing the responsibility for coordination, data analysis, and independent monitoring should be established. Attention should be paid to adequately describe indications of feasibility, for example, by stating the number of committed clinical sites, expected participant recruitment to meet sample size, resources and funding, and logistics of delivering the intervention(s).
- Finally, pertinent patient organisations (if available) should be involved in the protocol design.

III. A psychiatrist's perspective on multinational clinical trials

Prof. Dr. René S. Kahn, The Netherlands

René Kahn, MD-PhD, is Professor of Psychiatry. Since 2002 he is chairman of the Division of Neuroscience at the University Medical Centre in Utrecht, The Netherlands, which combines the departments of (child and adolescent) psychiatry, neurology, neurosurgery, neurophysiology, pharmacology and rehabilitation medicine. René Kahn is a Member of the Royal Netherlands Academy for Arts and Sciences.



Abstract

As an example of a successful multinational clinical trial in the field of psychiatry, the EUFEST trial was presented. EUFEST, the “EUropean First Episode Schizophrenia Trial”, was an open-label randomized clinical trial comparing the effectiveness of several already registered pharmacological treatments (i.e. the first generation antipsychotic haloperidol against four second generation antipsychotics amisulpride, quetiapine, olanzapine and ziprasidone). 50 treatment centres in 14 European countries and Israel participated in the trial. About 500 first episode schizophrenia patients were enrolled in the trial, all meeting DSM-IV criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder, and having had only minimal prior exposure to antipsychotic treatments.

The trial was successfully conducted showing that second generation antipsychotics were superior to haloperidol treatment regarding the treatment retention time.

“Classic hurdles” encountered while conducting the multinational clinical trial were: setting up an appropriate trial design, acquiring sufficient funding, developing an appropriate trial management structure, ensuring comparable quality standards across all study sites, finding appropriate ways of payment between countries, and defining authorship rules for scientific publications.

EUFEST: The study in a nutshell

Rationale and results

The reason for conducting this multinational clinical trial were doubts on the effectiveness of second generation antipsychotics, such as amisulpride, quetiapine, olanzapine and ziprasidone. Most results on the effectiveness of such drugs were based on patients with chronic schizophrenia, highly selective samples and on clinical trials conducted by pharmaceutical companies promoting the drugs. Thus the principal question was whether such second generation antipsychotics were as effective as a low dose administration of the first generation antipsychotic haloperidol for treating schizophrenia.

The primary objective of the study was to compare one year retention of haloperidol treatment vs. treatment with one of the four second generation antipsychotics in patients with recent onset schizophrenia, schizoaffective and schizophreniform disorder. Retention was defined as the time to discontinuation of drug intake, and a period of one year was investigated. Likely reasons for a loss of retention are an inefficient clinical result, bad treatment tolerability or insufficient acceptance of the treatment. Secondary aims of the study were several aspects of treatment efficacy and safety, such as changes in psychopathological symptoms, side effects, compliance rates, quality of life, substance abuse or alterations in cognitive functions.

The study showed that one-year retention was better for all atypical drugs than for haloperidol. However, other important secondary outcomes such as symptom improvement or hospi-

tal admissions did not differ between treatments. In conclusion, second generation antipsychotic drugs appear to be a clinically useful treatment for first-episode schizophrenia.

Methodological aspects

The EUFEST consortium chose a pragmatic “naturalistic” study design with the subsequent characteristics:

- **Non-selected sample:** Patients included in the study were not selected according to a highly pre-defined set of criteria, but the inclusion threshold was relatively low: Inclusion criteria were age (18-40 years) and recent onset (< 2years) of schizophrenia, schizophreniform disorder or schizoaffective disorder. Lifetime intake of antipsychotics was restricted to < 6 weeks, with 2 weeks in the previous year. As compared to many other studies, drug-abusing patients were accepted in the study.
- **Low dose comparator treatment:** The first generation drug haloperidol served as the comparator treatment; haloperidol was administered in a low dose (< 4mg haloperidol eq).
- **Long-term follow up:** The follow-up period was long (i.e. one year)
- **Realistic outcome measures:** Realistic outcome measures were selected, such as retaining subjects in the study or readmission to a hospital.
- **Open label trial:** EUFEST was an open-label trial; accordingly, both patients and investigators knew which drug was administered and the assessment of treatment and outcome measures was not blinded - as is the situation in real life medical care.

EUFEST is registered as an International Standard Randomised Controlled Trial, number ISRCTN68736636.

Hurdles to overcome when conducting a multinational clinical trial

Conducting EUFEST was a highly successful trial but some “classic” problems were met, summarized as follows.

1. Open-label vs. double-blind trial design?

When planning the trial, investigators must principally agree on whether to conduct an open-label or a double blind trial. In open label trials, both the researchers and participants know which treatment is being administered, whereas in double-blind trials both researchers and participants are blind to the treatment.

Both approaches carry advantages and disadvantages: Open-label trials (as in EUFEST) are practical and closer to real life conditions. Double-blind trials instead are better protected against biases, such as performance biases (i.e. patients may be systematically treated differently by the investigators) or ascertainment biases (i.e. the measurement of outcome variable may differ according to treatment arms). If deciding for an open-label trial, biases should be measured and analysed themselves. As an example, in EUFEST, the investigators’ belief in the study outcome was compared to the later factual outcome of the study. Hence, it could be shown that the primary outcome variable “Time to treatment discontinuation” was in fact unrelated to the investigators’ expectations.

2. Where do you get the money?

In principal, there are two sources of funding for clinical trials: Funding by industry support or funding by public support such as by grants from the European Commission. If deciding for industry commitment, different approaches can be set up, such as free drug provision by the industrial partner. In such cases, for scientific interests, it is crucial to minimize the degree of influence by the commercial partner.

3. How much do you measure?

Statisticians highly recommend restricting the number of outcome measures. Still, it is often hard to define the most important end point of a study, the most relevant follow-up period (still pragmatically realisable), the most critical symptom, and the best clinical tool for meas-

uring it. Besides, each measure must be applicable in all languages in question, while also producing comparable results.

4. How do you organize the trial?

In EUFEST, 14 countries, with a total number of 50 sites were involved. How do you coordinate such a huge consortium? How to make sure all national regulations are met and communication between participants runs smoothly? To overcome this problem, in EUFEST, national coordinators responsible for the overall study management were nominated. Furthermore, a central steering group was established to manage the trial.

5. Do you pay each country the same amount per patient?

Obviously, salaries and living standards differ between countries. Accordingly, if granted the same amount of compensation per patient regardless of the study site country, study participation might easily be biased by the relative value of monetary compensation. When planning a study, these relations should well be taken into account.

6. How do you go about writing papers and deciding about authorship?

When planning a study, it is highly recommendable to spend some thoughts on future result exploitations. Principally, the scientific merits should be fairly distributed – however, given huge consortia, papers with never-ending lists of authors are not necessarily the best solution to this. In EUFEST, papers were divided into “first” and “second” papers, with first papers being of highest scientific quality. For these, only the steering group had authorships, whereas the whole group was foreseen for the second papers.

7. How can you guarantee comparable high-level standards in over 50 study sites all over Europe?

It is of utmost importance that work conducted at the different study sites is performed in a comparable manner. It is recommendable that study monitors frequently visit the study sites to ensure compliance with the study regulations, that they are paid per visit and that they check charts for quality controls.

8. Conclusions

It is most important to set up strict rules both regarding the role of industry involved in the trial and regarding the quality standards for each site. Payments should be done on performance basis and authorship rules should be clearly defined before starting the study.

IV. A neurologist's perspective on multinational clinical trials

Prof. Dr. Wolfgang H. Oertel, Germany

Wolfgang Oertel, MD-PhD, is Professor of Neurology and Chairman of the Department of Neurology at the Philipps-University in Marburg, Germany. Currently, Wolfgang Oertel is President of the German Neurological Society. He founded the 'German Competence network Parkinson (CNP)' from which the German Parkinson Study Group emerged.



Abstract:

Investigator-initiated clinical trials are highly needed in the field of neurological research. In particular, trials on high risk compounds, drug repurposing trials, active comparator trials, and long-term studies on disease modification are necessary.

Based on experiences with the German Parkinson Study Group (GPS), which was initiated in 2003 and involved in several multicentre and multinational clinical trials, a set of recommendations for funding multinational clinical trials in a framework like the ERA-Net-NEURON may be derived. It is important...

- to select a disease with a considerable burden for patients and care-giving relatives,
- to identify a scientific core group of 3 to 4 leaders within a consortium, who, ideally, already have experience in conducting clinical trials,
- to ensure that study protocols are simple, pragmatic and allow smaller European countries to participate,
- to promote fair rules of authorship and of democratic rotation of key functions in the study group,
- to make sure that a study group is well prepared to address issues of European diversity in administrative regulations, standards and mentality.

The need for investigator-initiated clinical trials in neurology

Due to new diagnostic and therapeutic advances, neurology is one of the fastest growing specialities in medicine. It includes a broad array of conditions, such as cerebrovascular diseases (ischemia, haemorrhage), dementias, epilepsies, movement disorders (including Parkinson syndromes, restless legs syndrome and essential tremor), muscle-nerve-disorders, neuroimmunology (including multiple sclerosis), neurointensive care, neurooncology, headaches including migraine and other pain syndromes, neurorehabilitation, neuroorthopedic surgery, neurotraumatology, neurological sleep disorders and vertigo.

Multinational clinical therapeutic trials in the field of neurology are mainly planned and sponsored by pharmaceutical or biotechnological companies. Only a few independent clinical study groups work on the above mentioned indications at the national and multinational level in Europe. Thus there is a tremendous need to establish and maintain supporting infrastructure in order to encourage multinational clinical research independent of industry in Europe. Furthermore, funding of clinical research is necessary, particularly in the following fields:

- Studying innovative and/or high risk compounds, as these may not be attractive for industry from an economic point of view
- drug repurposing studies,
- active comparator trials (old versus new drug), and
- long-term studies on disease modification or neuroprotection.

Experiences from the German Parkinson Study Group

From 1999 to 2009, the German Federal Ministry for Education and Research (BMBF) supported the creation and status of the “German Competence network Parkinson (CNP)”. The funding started with high levels of funding in the beginning and decreased to very little funding in the last 3 to 4 years. One task for the CNP was to create a sustainable business structure for continuation after 2009 without BMBF support.

As a result, the German Parkinson Study Group was established in late 2003. The GPS consists of more than 40 academic centres, public hospitals and a few private practices with a special experience in how to perform diagnostic and therapeutic trials in Parkinson syndromes (Parkinson’s Disease, Dementia with Lewy Bodies, Multiple System Atrophy, Progressive Supranuclear Palsy). Its central office is at the Department of Neurology at the University of Marburg. The GPS closely collaborates with the Coordination Centre for Clinical Trials (KKS) in Marburg, an academic Clinical Research Organisation. In 2004, the GPS managed to receive a commercial contract with pharmaceutical industry for a large phase IIb trial examining a new AMPA-receptor blocker to be tested in advanced Parkinson patients. The trial was successfully completed and all predefined time lines were met, such as the ethical approval of the study, level and speed of recruitment, date of data lock and date of final data analysis.

After this important achievement, the GPS received numerous offers from industry, set up successful international collaborations and acquired important grants. For instance, the GPS is supported by the Michael J. Fox Foundation to conduct a double blind placebo controlled prospective bi-continental study (US, Germany) and the GPS participates as one of the main partners in a global trial on the potentially disease modifying effect of an oral “trophic factor inducing” agent (PYM50028) in de novo Parkinson’s Disease. In summary, since 2004, the GPS initiated, conducted and/or participated in one phase Ib trial, in ten phase IIa and phase IIb trials, and in more than 20 phase III trials on Parkinson’s Disease. Currently, the GPS focuses on the “REM sleep behaviour disorder”, a sleep disorder which converts into Parkinson’s disease in 80 % of all cases within 15 to 20 years. This particular research activity is to lay the ground for future trials on disease modifying or even neuroprotective compounds in the field of Parkinson’s disease.

Recommendations for a funding scheme in the ERA-Net framework

Based on the experiences with the GPS, a set of simple recommendations for funding of multinational clinical trials can be derived:

- It is important to select a disease with a high burden for patients and spouses / relatives. The disease, however, does not need to be very common.
- A core group of 3 to 4 leaders with a proven record of collaboration should be established within a research consortium. Forming a fully functional study group is not trivial; this phase may easily take more than a year in large consortia, and, today, there is no point in starting a study group from scratch. This core group should agree on a common goal beyond national interests.
- It is of advantage if such a group already has past experiences in conducting clinical trials: The group should have agreed on a minimal data set for clinical documentation, have experience on how to effectively collaborate with a commercial or academic clinical coordination centre, and has used or even implemented an electronic data entry system for a given disorder.
- The study protocol should be simple, pragmatic and should allow researchers from small European countries to participate. The study design has to fulfil quality criteria which allow publishing the study, even if the results are negative.
- Rules of authorship and rules of democratic rotation of key functions in the study group should be clearly defined – in order to avoid any “neuropolitical” uncertainty over the given funding period.
- The group should be prepared to deliberately handle issues of European diversity. Differences in the quality of documentation, in ethical committee regulations, in data safety, in the legal framework on biosample sharing, in conflict of

ERA-Net NEURON

interest rules, in public and industrial funding procedures, and in the relative value of financial incentives are very common.

The keys to success are to 1) identify a group of clinician scientists who think in European terms rather than in local or national terms, and 2) to sufficiently fund one project so that the group can prove itself as a successful and reliable consortium for future public funding agencies or industrial partners. Once the group has established its reputation with one excellent trial, this fact nearly guarantees the sustainability in their field of expertise.

V. The position of E-Rare, the ERA-Net for research in rare diseases, on funding clinical trials

Dr. Sophie Koutouzov, France

Sophie Koutouzov, PhD, is the Secretary General of the GIS-Institut des Maladies Rares (Rare Diseases Institute - Paris, France) and, since 2006, the Coordinator of the ERA-Net E-Rare. Sophie Koutouzov was Research Director at INSERM (French National Institute of Health and Medical Research) and she was engaged in research on rare diseases herself, with a special focus on immunological mechanisms in systematic lupus erythematosus.



Abstract

The ERA-Net E-Rare coordinates research programmes on rare diseases and funds, through the launch of Joint Transnational Calls, collaborative research projects on these pathologies. Twelve main European research funding bodies (agencies and ministries) form the E-Rare consortium.

So far, E-Rare has favoured collaborative, transnational research on the aetiology, natural history, pathophysiology, and the development of pre-therapeutic studies in the field of rare diseases. Clinical trials, instead, were excluded from the scope of the E-Rare funding calls for several reasons:

- The evaluation procedure is already complex due to the great heterogeneity of the proposals. The evaluation of proposals on clinical trials would add further complexity and burden.
- Funds from participating countries to the calls are limited and would lead to further splitting of resources.
- Not all E-Rare partners are legally able to fund clinical trials.

However, an important task for the future will be to develop E-Rare projects towards a more immediate medical and health benefit for patients suffering from rare diseases. Therefore, possibilities will be explored to expand research topics towards clinical trials. This will crucially depend on overcoming the bottlenecks described above and on developing adequate procedures for funding transnational clinical trials.

The ERA-Net “E-Rare”

The ERA-Net for Research Programmes on Rare Diseases “E-Rare” aims at coordinating national or regional research programmes on rare diseases (see also <http://www.E-Rare.eu/>). To this end, 16 research funding agencies and ministries from twelve EU Member States and Associated States collaborate to develop joint and strategic activities, such as harmonising and developing synergies between national research programmes on rare diseases, developing common research policies on rare diseases and implementing transnational research funding activities (joint calls) in Europe. Like



other ERA-Nets, E-Rare is supported by the European Commission.

Participating organisations are FWF from Austria, FNRS from Belgium, ANR and GIS/INSERM from France, BMBF/PT-DLR from Germany, KEELPNO and GSRT from Greece, UNIPECS from Hungary, CSO-MOH from Israel, ISS from Italy, ZonMW from the Netherlands, MDS and FCT from Portugal, ISCIII from Spain, and TÜBİTAK from Turkey. E-Rare is coordinated by GIS/INSERM.

The ERA-Net E-Rare was initiated in 2006 within the 6th Framework Programme (FP6) of the European Commission and was supported for a 4-year funding period. In the beginning, E-Rare started with ten partners from eight EU member states or Associated States. Due to its success and necessity, the network considerably expanded and the European Commission prolonged its support and granted a second funding phase to E-Rare for the years 2010-2014.

Within its first funding period, E-Rare achieved significant goals. The E-Rare partners...

- systematically exchanged information and best practice models on national rare diseases funding programmes,
- defined relevant strategic priorities for funding rare diseases by conducting focussed thematic workshops. Among these a workshop on “Clinical Trials in Rare Diseases” was organized (see below),
- published free access papers on national rare diseases research programmes and on the needs of rare disease research funding,
- published free access catalogues on high throughput drug screening platforms and supported programmes for opening rotational positions in research,
- conducted two joint transnational calls with six and ten participating countries respectively. The scope of both calls was relatively broad, including human and social sciences, genetics, physiopathology and pre-clinical therapeutic research, such as studies on therapeutic targets, innovative biotechnological research, or drug toxicology. However, clinical trials were not covered.

The position of the ERA-Net E-Rare towards clinical trials funding

Considering that, in rare disease research, only 2% of all studies are clinical studies as compared to 20% preclinical research and 78% basic research studies, clinical trials are strongly needed.

For this reason, the E-Rare consortium discussed during a workshop in 2008 whether to expand their funding initiatives to clinical trials. Specific problems in the field of research on rare diseases are: Efforts for patient recruitment are considerably higher as compared to common diseases - costs for the development of novel drugs, however, are essentially the same as for common diseases. Clinical trials in the field of rare disease are thus relatively more costly. Moreover, as the natural history of rare disease is poorly understood and epidemiological data is scarce, it is very difficult to define appropriate clinical end-points.

Moreover, there are obstacles to funding multinational clinical trials within the E-Rare scheme:

- The E-Rare proposal evaluation procedure is already complex to date due to the heterogeneity of submitted proposals; the evaluation of clinical trials in turn requires again additional expertise and would even further complicate the procedures.
- With a total funding volume of approximately 9-10 million € per call, available funds are limited, with variations across funding organisations participating in the call.
- Splitting of resources does not appear adequate.
- National experiences show quite a heterogeneous picture regarding bottom-up demand for investigator-initiated trials.
- Not all agencies within E-Rare can fund clinical trials.

Still, one aim of the second phase of E-Rare will be to widen transnational funding programmes and to fund projects with a more immediate medical and health benefit for patients. To achieve this, several pre-conditions should be met:

ERA-Net NEURON

- More funds should be assigned to E-Rare by the national funding agencies to allow expansion towards (costly) clinical trials.
- Additional funding agencies should be recruited for E-Rare, as currently some of the national agencies are unable to fund this type of research.
- Additional countries with a strong tradition in clinical studies need to be involved, as well as charities.
- Procedures for funding transnational clinical trials need to be developed (potential collaborations with EATRIS, ECRIN).

Sustainable funding strategies shall be developed beyond the run-time of the ERA-Net E-rare to render the success of E-Rare long-lasting.

Conclusions of the Round Table Discussion

The goal of the Round Table Discussion was to analyze the status quo of the ERA-Net NEURON funding scheme and to discuss the possibility of widening it to cover clinical trials. For this, the needs of the scientific community in the field of disease-related neurosciences were discussed on the basis of the talks presented beforehand.

The Round Table discussion was attended by the five speakers of the workshop and by members of the NEURON consortium. The following aspects were discussed:

Status Quo: Funding scope of ERA-Net NEURON calls

So far, no multinational clinical trials are funded by the ERA-Net NEURON. However, in NEURON calls, clinical studies are eligible up to the point of "proof of concept" studies. Concerning trials on medicinal products "proof of concept" studies usually refer to phase I and phase IIa trials. In general, however, this term is not restricted to medicinal product trials but refers to all sorts of interventions.

Needs of the scientific community in the field of disease-related neuroscience

Several needs of the scientific community regarding clinical trials were pinpointed during the Round Table Discussion:

- **Type of trial and theme of trial:** It became clear that, in the field of disease-related neuroscience specific types of trials are especially needed, such as multinational treatment optimization studies or treatment comparison studies, repurposing studies of already available treatments (i.e. trials testing new indications for available treatments) and small scale-high risk studies. A lack of funding opportunities for these studies was recognized. In contrast, placebo-controlled randomized clinical trials are often covered by industrial sources and may not be the instrument of choice to be funded under the umbrella of an ERA-Net.
Thematically, multinational, investigator-initiated clinical trials on rare neurological/psychiatric diseases appear highly important. Two strategies appear most promising in this regard: a) developing novel drugs for rare diseases and b) conducting repurposing studies on drugs already on the market but not approved yet for the disease in question. For funding of projects in the field of rare neurological diseases, collaborating with the ERA-Net E-Rare-2 might be of particular interest.
- **Funding volume:** A gap was identified for funding clinical trials with small to middle-sized budgets. Within its 6th and 7th Framework Programme, the European Commission funded a number of large-scale trials, usually with high budgets (about 10 million €). However, funding opportunities for small to middle sized grants (i.e. about 1-2 million €) are comparably scarce. Such grants, usually for smaller consortia, would also meet researchers' requests for less administrative requirements, fast track application procedures, and easier trial management. Large consortia may even be disadvantageous, as small countries might be neglected and personal collaborations might not be as close. The volume of funding required for a clinical trial is related to the size and type of the trial. For statistical reasons, large effects of an intervention can be detected by testing relatively small samples and both budgetary and time efforts are small. The opposite is true for small intervention effects.
- **Funding bodies:** Funding of clinical trials by several sources, such as health system institutions, industry, charities, and ERA-Nets may also be considered.

- **Project run-time:** A project run-time of 3 to 5 years appears feasible for small to medium clinical trials. For small consortia, a project duration of about 3 years appears realistic, whereas for middle-sized consortia, rather 5 years appears adequate.

Methodological requirements for multinational clinical trials

Recommendations on methodological criteria as outlined by ECRIN appear highly useful (cp. p. 11). For instance, the registration of trials should be required by funding organisations. The implication of ECRIN itself appears very helpful and recommendable for researchers conducting clinical trials.

Funding multinational clinical trials and the ERA-Net scheme

The ERA-Net NEURON may be a vehicle for offering funding opportunities for small to middle sized clinical trials. However, certain obstacles require consideration and may speak against funding multinational clinical trials:

- **Participating funding organisations:** Not every funding organization is legally able to fund clinical trials. Therefore, a funding initiative on clinical trials should be tailored to the needs and legal possibilities of the funding organizations. New funding organizations already active in the field of funding clinical trials may be approached.
- **Funding model:** ERA-Net joint transnational calls, like the ERA-Net NEURON calls, are usually based on the virtual common pot model. In this model, each funding organisation is responsible for funding its regional/national applicants participating in a research consortium. Cross-border funding (e.g. funding of researcher of another country) is not possible for many funding organisations. Multinational clinical trials have specific funding requirements:
 - a) The coordination unit of a trial needs considerably more money than the remaining partners; it was estimated that the coordination unit would require about 50% of the total budget of a consortium. However, as some funding organisations can allocate only a limited budget per call, only researchers from funding organisations with a high budget would be able to coordinate a trial.
 - b) The coordination unit should ideally be able to control the money flux to study sites involved in the trial. In particular, the coordination unit should be able to react flexibly to potential problems during patient recruitment in order to distribute money according to the sites' performance and success. However, considering multinational trials, there are legal restrictions to cross-border money transfers.

A solution may be that funding organisations pay the grant according to a contingency plan, based on a stepwise payment depending on successful project interim evaluations (i.e. to start with a small budget provision and increase the budget given the project is successful). However, this requires a tight interaction between several funding organisations and the trial coordination unit, and considerable administrative burden for both parties. Moreover, it may well be that a planned budget will not be spent entirely, given that study sites can perform below expectations, while well-performing study sites might be unable to increase their budget.

In summary, the need for funding of multinational clinical trials is widely acknowledged by the NEURON consortium. However, legal and procedural questions remain unsolved. Thus, the question of funding of multinational clinical trials through the ERA-Net NEURON will be further pursued and discussed during the second funding phase of the ERA-Net NEURON.

Annex: List of Participants**Speakers of the workshop**

Name	Institution		Country
Demotes	Jacques	ECRIN / INSERM	France
Kahn	René	University Medical Center Utrecht	The Netherlands
Koutouzov	Sophie	Coordinator ERA-Net E-rare / GIS - Institute of Rare Diseases	France
Ohmann	Christian	ECRIN / Heinrich Heine University Düsseldorf	Germany
Oertel	Wolfgang	University of Marburg	Germany

ERA-Net NEURON participants

Name	Institution		Country
Barbas	Julio	Ministerio de Ciencia e Innovación (MICINN)	Spain
Bergman	Howard	Fonds de recherche Sante - Québec (FRSQ)	Canada
Bourre	Francois	Centre National de la Recherche Scientifique (CNRS) / Institut national de la santé et de la recherche médicale (INSERM)	France
Clark	Jenifer	Agence Nationale de la Recherche (ANR)	France
De Andrés Medina	Rafael	Instituto de Salud Carlos III (ISCIII)	Spain
Dorlöchter	Marlies	Projektträger im Deutschen Zentrum für Luft- und Raumfahrt (PT-DLR)	Germany
Girgenrath	Rainer	Projektträger im Deutschen Zentrum für Luft- und Raumfahrt (PT-DLR)	Germany
Glod	Frank	Fonds Nationale de la Recherche (FNR)	Luxembourg
Goldberg	Joanne	Fonds de recherche Sante - Québec (FRSQ)	Canada
Leshem	Benny	Chief Scientist Office, Israeli Ministry of Health (CSO-MOH)	Israel
Mayer	Herbert	Fonds zur Förderung der wissenschaftlichen Forschung (FWF)	Austria
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Tirronen	Mika	Suomen Akatemia (AKA)	Finland
Zagrean	Leon	National Centre for Programme Management (NCPM)	Romania