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The European Science Foundation acts as a catalyst for the development of science by bringing together leading scientists and funding agencies to debate, plan and implement pan-European initiatives.

Foreword

We are all aware that controlled clinical trials of both drugs and therapies are essential elements in the development of medical research and its transfer into medical practice.

We are also aware that such trials need to be performed on as wide a base of patients as possible and, also, can be very costly. In addition, there are a number of issues in the application of therapeutic or preventive interventions or the testing of so-called 'orphan' drugs where action is necessary within the non-commercially funded sector of research.

This is where ESF and its Member Organisations have a distinctive role to play and where the added value of moving from the national to the European level in such trials is self-evident. In this policy statement, ESF sets out the arguments not only as to why we should operate at the European level but also practical suggestions for future actions by both ESF and its Member Organisations.

Naturally, I hope that these recommendations will be put into practice and ESF has already embarked on an ambitious development within its ESF Collaborative Research Programme (EUROCORES) scheme to initiate controlled clinical trials at a European level.

I am confident that such actions will provide an important contribution to the improvement of health care in Europe.

Enric Banda
ESF Secretary General

Introduction

Controlled clinical trials are essential to assess the benefits of interventions designed to improve health care. Not surprisingly, therefore, the European Science Foundation (ESF), in particular, its European Medical Research Councils (EMRC) Standing Committee, is interested in promoting controlled clinical trials.

Many controlled trials are designed and run by the pharmaceutical industry, and mechanisms and organisations exist to foster and regulate these. Important questions however, which concern effects of interventions intended to improve health, may be of no interest to the commercial sector but are of great importance for public health. This is why the Medical Research Councils in Europe have to take the responsibility to support research intended to lead to improvements in health. Examples of questions that are of public importance, but in which industry has little or no interest, include the effects of aspirin for acute myocardial infarction; magnesium sulphate for eclampsia; indomethacin for early dementia; corticosteroids in head injury; carotid endarterectomy for cerebral ischaemia; chiropractic for low back pain; and counselling for psychological distress.

The reason that interest in controlled trials is required at a European level is because collaboration in multicentre trials can increase recruitment to trials and the size of the trials which yield statistically more reliable estimates of the effects of health care interventions, both overall and for relevant subgroups. In addition, estimates of these effects, which have been derived from investigations of the same question in a variety of circumstances internationally, can provide insights relevant to the applicability of research results in practice.

It is against this background and rationale that the ESF will take a variety of steps to promote pan-European collaboration in controlled trials. This statement constitutes the first step, and refers to two further steps that can be implemented without substantial investment from the limited resources available.

Coordination of public funding for European clinical trials

Although the need for pan-European clinical trials addressing questions that do not interest the commercial sector has been recognised, very little has been done to support this type of research at a Europe-wide level, compared to the support given by the public sector in the USA, mainly through the National Institutes of Health (NIHs) and the Veterans' Administration. The ESF survey carried out in 1999 (see below), showed that clinical trials in Europe are mainly funded on a national basis, and that the annual total investment is of the order of 180 million euros. A number of these trials would be much more valuable if organised on a larger scale across Europe and drawing on national funding from several countries. A reasonable percentage of current investment at the national level should be coordinated and devoted to such pan-European clinical trials.

Therefore, recognising the need for pan-European clinical trials, the ESF

- **Recommends the coordination of public and charitable funding for non-commercial clinical trials in Europe as an essential first step in promoting such trials at a European level by removing one of the most important current barriers.**
- **Recommends that, in order to implement this approach, those agencies with responsibilities for the promotion of such clinical research at the national level, should jointly explore ways in which European coordination may be achieved.**

Harmonisation of clinical trial administrative constraints

Besides the funding issue, those undertaking non-commercial clinical trials in Europe face several problems due to the heterogeneity of laws and regulations across European countries, which consumes time and manpower. Industry can address these problems because it has sufficient resources. Two examples of such heterogeneity are: i) the review by research ethics committees, which is centralised in some

countries at the national level, and which is regionally-based or institutionally based in others; ii) insurance premiums and indemnities, which vary by a factor of >10 across Europe. These issues lead to delays in the initiation, prosecution, and dissemination of research, and increase the total resources needed for carrying through the research to completion.

The recently published European directive on good clinical practice in clinical trials is designed primarily to address the needs relevant to licensing new drugs, and it therefore emphasises regulatory issues. In its present version it does not take account of the constraints of non-commercially funded clinical research and is not appropriate to non-commercially funded clinical trials. It is of the utmost importance that the views of the research community on the applicability of this directive to clinical trials other than drug approval trials is clearly expressed, and that 'trialists' concerns are considered.

ESF should:

- **Monitor developments on measures to be taken for the European directive on clinical trials, to ensure that proper account is taken of the whole domain of this research activity, and not only new chemical entity evaluation.**
- **Monitor any other related development in the EU with a view to commenting from the viewpoint of publicly funded trials.**
- **Promote harmonisation of the process of ethical review, through limitation to one ethical review submission per country.**
- **Establish dialogue, at the European level, with the insurance companies to explore a system for harmonising public clinical trial premiums.**

Appropriate implementation of Good Clinical Practice (GCP) guidelines in the context of non-commercial clinical trials

Although meeting the GCP guidelines, as elaborated by the International Conference on Harmonisation (ICH), consumes time and money, considerations of ethics and applicability

of research mean that the underlying principles should be observed. It is important, therefore, to recommend the implementation of simpler procedures, which, while being able to ensure the quality of every aspect of the trials, promote publicly funded research at an acceptable and realistic cost. The challenge is thus to apply the rules in ways faithful to their spirit, but adapted to each research situation.

ESF should contribute to the:

Preparation of guidelines on how to put ICH recommendations into practice.

Promoting preparation and maintenance of systematic reviews of existing controlled trials*

Embarking on new research without first preparing systematic, scientifically rigorous reviews of relevant existing evidence is indefensible, on both scientific and ethical grounds. Reflecting this, the Danish Research Ethics Committee System has ruled that:

“For a research ethical evaluation of scientific experiments involving man it is crucial that all relevant literature has been reviewed by the research group before submission. This will be a precondition when the evaluating committee is judging the originality of the project and, for example, the permissibility of using placebo and not an already known treatment in a control group.”

Similarly, the UK Medical Research Council requires people applying for support for new controlled trials to:

“Give references to any relevant systematic review(s) and discuss the need for your trial in the light of the(se) review(s).

If you believe that no relevant previous trials have been done, give details of your search strategy for existing trials.”

Furthermore, once a trial has begun recruiting participants, maintenance of systematic reviews is required to enable data monitoring committees to take informed and ethical decisions.

The ESF endorses the view that embarking on new research without first preparing systematic reviews of relevant existing evidence is indefensible on scientific and ethical grounds, and recommends that its Member Organisations should:

- **Require applicants for support of new trials to refer to scientifically defensible reviews of relevant existing trials, or demonstrate that no other relevant controlled trials exist.**
- **Require data monitoring committees to take account of new evidence accumulating in updated systematic reviews.**

Registration of planned, recruiting and unreported controlled trials*

Why should research funding agencies be interested in promoting registration of controlled clinical trials? First, because registration is essential for good financial management, good scientific practice, and good ethical practice. Research funding agencies need to take their decisions in the light of information about relevant ongoing research to avoid duplication of effort, to promote appropriate replication, and to promote collaboration, for example, in multi-centre trials and/or prospective meta-analyses.

In addition, registration of trials is required because patients, clinicians and other decision makers wish to be informed about trials in which they can participate, or to which they can contribute in other ways; and because people using evidence from controlled trials to guide policies and practice and decisions about further research need to be confident that they are aware of all the trial evidence relevant to a particular question.

Accordingly, the ESF endorses calls for prospective registration of controlled trials, and recommends that its Member Organisations should:

- **Require registration as a condition of releasing funds for supporting randomised trials.**
- **Contribute core data items from their registers of randomised controlled trials to the international metaRegister of Controlled Trials at: www.controlled-trials.com**
- **Support the development and use of an International Standard Randomised Controlled Trial Number (ISRCTN).**

* Chalmers I. Using systematic reviews and registers of ongoing trials for scientific and ethical trial design, monitoring, and reporting. In: Egger M, Davey Smith G, Altman D (eds.) Systematic Reviews in Health Care: Meta-Analysis in Context. 2nd Edition of Systematic Reviews. London: BMJ Books, 2001, pp 429-443.

Clinical trials in Europe

funded by national public agencies and/or charities

Country ¹	Organisation ¹	Clinical trials ² Type Number/year	Funding Agency	Patient Recruitment	Peer review	Grant by grant/ Core fund ³	Data bank	Funding per year (kEuro)
AUSTRIA	• Austrian Science Fund (FWF)	Phase 4 3 - 5	Public	National	Yes	Grant by grant	No	100
DENMARK	• Danish Medical Research Council	? 100	Public	National	Yes	Both	No	2,500
FINLAND	• Academy of Finland	Any 0 - 2	Public	National	Yes	Grant by grant	Yes	100
FRANCE (10)	• A.N.R.S.	Phase 4/3/2/1 10	Public	International	Yes	Core fund	No	12,000
	• Fondation pour la Recherche Médicale	Surgery 13 over 3y	Charity	National	Yes	Grant by grant	No	1,830 Total over 5 years
	• F.N.C.L.C.C.	Any 25	Fed/any	International	Yes	Grant by grant	Yes (FNCLCC)	1,864
	• Institut Curie (IC)	Any 120	Any	International	Yes	Grant by grant	Yes (IC)	1,500
	• Institut Gustave Roussy	Any 70 - 80	Any	International	Yes	Grant by grant	?	7,143
	• Institut Paoli-Calmettes	Any 70	Fed/any (IPC)	National	Yes	Grant by grant	Yes	4,573
	• Association «Vaincre la Mucoviscidose» (AFLM)	Any 3 - 4	Charity	International	Yes	Grant by grant	Yes (Agence Med)	95
	• INSERM	Phase 4/2 Surgery ?	Public	National	Yes	Both	Yes	2,640
	• Délégation à la Recherche Clinique – AP-HP	Any ≅ 125	Any	International	Yes	Both	Yes (Ministry of Health)	about 5,000
	• Direction des Hôpitaux (Mission PHRC)	Any 100	Public	International	Yes	Grant by Grant	No	12,000
GERMANY (2)	• Deutsche Forschungsgemeinschaft (DFG)	Any 30	Public	National	Yes	Grant by grant	No	5,000
	• Bundesministerium für Bildung und Forschung	Any 30	Public	National	Yes	Grant by grant	No	?
HUNGARY (2)	• Hungarian Scientific Research Fund (OTKA)	Phases 1/2 10	Public	International	Yes	Grant by grant	No	20
	• Ministry of Health	Phases 1/2 210	Public	International	Yes	Grant by grant	Yes	1,020

Country ¹	Organisation ¹	Clinical trials ² Type Number/year	Funding Agency	Patient Recruitment	Peer review	Grant by grant/ Core fund ³	Data bank	Funding per year (kEuro)
ITALY	● Istituto "Mario Negri" (Milan)	Phases 3/4 10	Charity	International	Yes	Grant by grant	Yes (Dpt Health)	5,000
NETHERLANDS (2)	● College voor Zorgverzekeringen (Health Insurance Council)	Phase 3/ non-drug trials 8	Individual /Public	National	Yes	Grant by grant	No	8,000
	● Nederlandse organisatie voor wetenschappelijk onderzoek (NWO)	Non-drug trials <10	Public	National	Yes	Grant by grant	No but setting up	8,6 (in 2000)
NORWAY	● The Research Council of Norway	Any 1 - 2	Public	National	Yes	Grant by grant	No	200
SPAIN	● Fondo de Investigacion Sanitaria	Phases 3/4 /surgery 25	Public	National	Yes	Grant by grant		1,000
SWEDEN	● Swedish Cancer Society	Any 30	Charity	Yes	Yes	Grant by grant	No	200
TURKEY	● TÜBITAK	Any 5	Public	National	Yes	Both	Yes (Ministry of Health)	21
UNITED KINGDOM (6)	● British Heart Foundation	? 13 <i>(currently)</i>	Charity	International	Yes	Grant by grant		7,000 (current)
	● British Diabetic Association	Phases 3/4 /non drug trials 2 - 4	Charity	National	Yes	Grant by grant	No	183
	● Cancer Research Campaign	Phases 1/2/3/4 25- 30	Charity	National	Yes	Both	Yes (UKCCCR)	8,000
	● National Health Service	Phases 3/4 /non-drug trials 46	Public	International	Yes	Both	Yes nascent	90,000
	● Arthritis Research Campaign	Phases 1/2 ?	Charity	International	Yes	Grant by grant	No	5,700 (for next 5 years)
	● Medical Research Council (MRC)	Any 120 <i>(on-going)</i> + 15 <i>(new)</i>	Public	International	Yes	Both	Yes	15,000 (in 1997 and 1998)

Legend:

¹ Public Agencies and Charities from 18 European countries have responded to the questionnaire that was sent in July 1999. The table only summarises the responses from those organisations that are funding clinical trials. It was finalised in July 2000, after consultation with respondents.

² As indicated, the type of clinical trials funded could be drug trials (phase 1 studies, phase 2 studies, randomised phase 3 and/or phase 4 studies) and/or non-drug trials (surgery, diagnosis, immunotherapy, radiotherapy, epidemiology, etc.). The approximate number of clinical trials funded per year is given in italic.

³ Funding mechanisms used by an organisation could be via grants on a trial-by-trial basis (grant-by-grant) or by core funds provided to key "trial centres" (core funds)

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The **EMRC** is the ESF Standing Committee with overall responsibility for initiating and co-ordinating scientific activities in the domain of biomedical sciences including fields such as:

- Diagnostic and therapeutic medicine
- Neurology
- Immunology
- Psychology
- Clinical studies
- Toxicology
- Human genetics
- Medicinal biotechnology

and for providing expert advice on issues of science policy relevant to the biomedical sciences.

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