

# EFGCP

## NEWS

The Newsletter of the **European Forum for Good Clinical Practice**  
**'Where Science and Ethics Meet'**

### Annual Conference

Spotlight on misconduct

### Forthcoming events

Dates for your diary

### Drug development

How to involve older people

### Back to back

November sees two EFGCP paediatric conferences

### Working Parties

### ICREL

Update on the impact of European legislation

### PatientPartner

Identifying patient needs

### EudraCT

Inside the Joint Operations Group

### Animals and clinical research

Brussels meeting discusses ethical recommendations

### Ethics Committees

Report from Warsaw workshop on standards

### EFGCP contacts



## Annual Conference

# EFGCP meeting puts the spotlight on research misconduct

EFGCP Annual Conferences have so far taken place in Brussels. Next year there's a break with tradition as the 2009 Conference moves to Prague. The subject: the integrity of biomedical research within Europe. EFGCP Board member Frank Wells explains how the meeting will work, and how it fits into a global discussion about fraud and misconduct.



*EFGCP Annual Conference 2008, Brussels. Next year, Prague will play host.*

The topic of fraud and misconduct in clinical research never completely goes away. Events in Norway and South Korea in the last couple of years remind us of that, and some of us have painful memories of the ways in which our companies, and especially patients, were exploited.

It would be quite wrong to believe that these events are typical or common. Nevertheless, human nature being what it is, we cannot afford to presume that they

will not occur again and experience this year reported by the US Office of Research Integrity confirms that the pharmaceutical industry may still be exploited by rogue researchers.

A highly successful First World Conference on Research Integrity in Lisbon in September 2007 yielded many aspects of fraud and misconduct in scientific research that justify the development of better techniques for the prevention, detection, investigation and >>

» prosecution of such misconduct, throughout the world. Europe has a variable track record in tackling this problem, but many bodies, as well as individuals, have had some success in this objective. It was decided that a Second World Conference should be considered for 2011 but that regional conferences should be held before then, the regions being Europe, South East Asia and the Americas.

Two events that cover this topic are planned for the immediate future: the first, which may already have occurred by the time this edition of the EFGCP Newsletter appears, is the publication of the 4th edition of *Fraud and Misconduct in Biomedical Research*, edited by Frank Wells and Michael Farthing, with chapters from throughout the world. The second is our 2009 Annual Conference,

to be held in Prague on 27 and 28 January, on the theme of *Research Integrity: A European Perspective*, which fulfils the decision to hold such a conference in Europe. The whole programme can be accessed from the EFGCP website ([www.efgcp.be](http://www.efgcp.be)).

### Different national laws

By means of a series of presentations from those experienced in handling this problem, on a world-wide basis, and of workshops, this conference will present an opportunity to explore in depth how individuals and institutions in Europe can demonstrate a commitment to research integrity, specifically in the field of biomedical research.

The workshops cover the roles of the monitor, the auditor, the research ethics

committee, the statistician, the independent enquiry and the national competent authority, and speakers from throughout Europe and the USA will talk authoritatively on historical aspects of research misconduct, whether misconduct really matters, whether it differs from fraud and if so to what degree, how whistleblowers can be protected and what new steps can be taken in the future to minimise its happening.

The Joseph Hoet Memorial Lecture for 2009, entitled "Regulations in Scientific Misconduct: Lessons from the American Experience", will be given by Professor Drummond Rennie of the Department of Medicine at the University of California San Francisco and the Deputy Editor of *JAMA*. We commend this conference as one of lasting interest and importance.

## Forthcoming events

For details of all meetings, see [www.efgcp.be](http://www.efgcp.be), or email [secretariat@efgcp.be](mailto:secretariat@efgcp.be)

### EFGCP Conferences

**Meeting the Challenges of Paediatrics within Oncology Drug Treatment in partnership with ITCC & DIA**  
25 November 2008, Management Centre Europe, Brussels, Belgium

*EFGCP Children's Medicines Working Party 4th Annual Conference*

**EU & US Paediatric Legislation: What is Changing in Practice in Paediatric Drug Treatment, Research & Development?**  
26 November 2008, Management Centre Europe, Brussels, Belgium

**The EFGCP Annual Conference 2009: Research Integrity: A European Perspective**  
27–28 January 2009, Diplomat Hotel, Prague, Czech Republic

### Conferences in partnership with EFGCP

*Conference*

**Impact on Clinical Research of European Legislation – ICREL: Results & Discussion**  
2 December 2008, Diamant Centre, Brussels, Belgium

*AREC–EFGCP Geriatric Medicines Working Party Workshop*

**Research Ethics Committees Complex Cases: Quandaries in Research Projects Involving Older Research Participants**  
15 January 2009, Wildtscheshaus, Basel, Switzerland.

**EFGCP General Assembly Annual Meeting**  
Tuesday 27 January 2009 (17.45–18.45), Diplomat Hotel, Prague, Czech Republic

### EFGCP Board meetings

Monday 1 December 2008 (10.30–16.30), EFGCP Offices, Brussels

Monday 26 January 2009 (16.30–18.30), Diplomat Hotel, Prague, Czech Republic



## Next issue

The next edition of EFGCP News will appear in March 2009. All suggestions for feature articles are welcome, and should be submitted to:

The Editor  
Peter Wrobel  
Clarity in Science Communication  
Tel +44 780 317 6319  
Fax +44 870 130 5680  
[clarity@wrobel.net](mailto:clarity@wrobel.net)

The final date for submission of articles is 16 February 2009.

### EFGCP Working Parties

*Audit Working Party*  
Tuesday 14 October 2008, Brussels

Monday 26 January 2009, Diplomat Hotel, Prague, Czech Republic

*Ethics Working Party*  
Tuesday 14 October, EFGCP Offices, Brussels, Belgium

Monday 26 January 2009  
Diplomat Hotel, Prague, Czech Republic

*Patients' Roadmap to Treatment Working Party*  
Monday 13 October 2008, EFGCP Offices, Brussels, Belgium

---

## Policy

# Elderly people and the development of medicinal products

The EFGCP Geriatric Medicines Working Party has been looking how to include elderly people in drug development. Florian von Raison, Jean-Marc Husson, Jean-Marie Vetel, Michael Bone and Laurence Hugonot-Diener report.

The world population is ageing markedly, especially in industrialised countries, due to a better life, working conditions, and control of diseases as well as improvement of health care. This trend has been observed for several decades and this positive evolution will continue bringing more and more elderly people into the health system with a special need for management of their often multiple co-existing conditions.

In the past and even today the development of most medicinal products does not target in particular older people. Even if elderly people are recognised as a vulnerable population, there are few valid data about the appropriate use of a drug according to specific conditions such as patho-physiological age (rather than calendar age), gender, physical and psychological profiles, adapted pharmaceutical forms with specific dosage and dosage regimen, specific pharmacokinetics, metabolism according to age, drug-drug interactions, contraindications, safety profile and risk management. All these factors are important to ensure effective and safe use of medicines in daily clinical care in this diverse population.

There are of course some exceptions in the development of medicinal products and drugs for degenerative diseases linked to age like Alzheimer's or Parkinson's diseases, osteoporosis and others. The development programmes were able to address all the above aspects as the target population of the indication is an elderly



population per se.

But when is a person considered old? In clinical development or in clinical daily practice? The only international accepted text is the ICH E7 text published in 1993, which defines an arbitrary age at which a person gets old – 65 years – without defining more specific stratification or age classes. A revision of the ICH E7 chapter is ongoing, in an attempt to take into consideration the vulnerability of a person in a more holistic way, as calendar age is not the only component. Factors such as chronic diseases, co-morbidity with physical dependency, social condition,

family life, environment and others are of obvious importance. A precise definition of a frail, weak and fragile person is to be introduced in the new revision of ICH E7. The most vulnerable person should be the “very old frail” patient.

Beyond the lack of proper data for the use of drugs in older people and the absence of age stratification, physicians (both GPs and specialists) are often not aware enough nor sufficiently trained to deliver an adaptive disease management for elderly patients. As a consequence, elderly people are very likely to consume too many medicinal products, in particular common drugs for frequent diseases and conditions. For example, in France patients over the age of 65 take a mean of 3.5 different drugs per day. This figure rises to 8 different drugs for patients older than 75 years.

In order to address the lack of data, specific clinical trials are to be performed in the older populations, because they are the consumers of the common medicinal products such as analgesics, antihypertensive, anti-inflammatory drugs.

The requirement for more data is increasingly recognised as a clear need for the future. The European Commission and certain member states, such as the Netherlands, have already addressed the issue of the lack of clinical trials in the ageing population.

But the lack of elderly people in clinical studies is multifactorial and the list of potential hurdles might be long. Even >>

» in a given study many factors might limit an old patient's access to a study. For example, inclusion criteria not only reflect the requested scientific and medical profiles but also reflect socio-economic factors and a need for a certain degree of comprehension.

Another hurdle for older people entering a study could be the ability to communicate in a particular frail or even demented population (for example, Alzheimer's disease). So the evaluation process must include a measurement of the capacity to take a decision, to ensure the validity of the given consent. Here some tools exist to help the investigator; where that capacity may well be variable from time to time, these tools should be introduced and used in Europe.

Initiatives leading to the improvement of clinical trials in elderly patients are one of the wishes of regulatory authorities,

not only in Europe. Agencies want to rationalise the development plan within this population. In parallel with the Paediatric Investigation Plan (PIP) that has been implemented in Europe, an optional Geriatric Investigation Plan or "GIP" should be created with the following features, acknowledging that recruitment of these subjects is not always simple due to dependence, fragility, frailty, family opposition, etc.

- The GIP should not be a mandatory plan as for children and should not be done for every drug.
- A GIP should target drugs that are used in a geriatric population and have a potential risk with known side effects and metabolism features.
- This GIP should be adapted according to the age stratification, gender, epidemiology and indication : that is, a GIP "à la carte".

• Specific clinical studies for older people should be included with stratified groups according to age, indication and possible co-morbid conditions.

• Pharmaceutical formulations must be adapted to elderly patients in order to improve compliance with drugs.

• Specific pharmacokinetic and pharmacodynamic studies should be performed according to age and other parameters such as physical and psychological autonomy, kidney insufficiency, liver insufficiency, absence of mobility, weight, etc.

• A long term follow-up is needed to look at possible drug-drug interactions.

• The informed consent is per se something specific and ethics committees should include in their group at least one geriatrician. Many elements of informed consent vary with aging, physical and psychological status.

## Back to back: Two EFGCP paediatric conferences

The EU Paediatric Regulation has now been in force for more than 1½ years. Regulatory authorities, clinical organisations and pharmaceutical companies have made their first experiences with preparing, submitting and discussing Paediatric Investigation Plans (PIPs).

The first conference, on 25 November will address the specific challenges that have been encountered with paediatric use of oncology drugs

and will try to find answers to burning questions such as the multitude of new anticancer drugs in development and the fact that cancer in children is rare. Not all new compounds can be clinically tested in patients. This conference is a follow-up to the Paediatric Oncology conference held on 15 November in London. The conference audience will include representatives and participants from regulatory authorities, academic paediatric research, health professionals,

pharmaceutical and biotech companies, and patient and parents' organisations.

The second conference, the following day, will be the 4th Annual Conference of the EFGCP Children's Medicines' Working Party and will make high-level comparisons between the experiences and lessons learned in EMEA and European National Regulatory Authorities, in pharmaceutical companies and academia. It will also address the evolving paediatric research networks and will continue the dialogue on how to further improve child health and paediatric research in Europe.

We shall also be addressing the WHO initiative Make Medicines Child Size and will reflect on how it fits with the US and EU paediatric legislation. Delegates to the conference will have a similar multi-stakeholder profile to those attending the oncology conference that takes place on the previous day.

In the evening of 25 November we will have a social event to which participants of both conference days are invited. This will be a further first-rate opportunity to network with key people and discuss in a relaxed atmosphere.

Details of both conferences can be found under [www.efgcp.be](http://www.efgcp.be)

**Klaus Rose**



# Reports from the Working Parties

Many of the activities of the **Ethics Working Party** this year have been devoted to collaboration with other bodies, such as ECRIN, ICREL and the EudraCT Joint Operations Group, reports on which appear elsewhere in this newsletter. And following on from the workshop devoted to the training of research ethics committees, held last year in Vienna, a successful workshop was held in April, in Warsaw, devoted to the setting and maintenance of standards for research ethics committees – a full though not necessarily final report appears on pages 14 and 15, courtesy of Hugh Davies.

This topic will no doubt be debated at length within member states of the EU, most of which do not currently have schemes in place for the auditing of research ethics committees. The report should provide guidance on this issue.

Also arising from the earlier Ethics Working Party report on the structure and function of research ethics committees, and associated with the above workshop, the Quality Assurance subgroup has produced guidelines for the auditing of research ethics committees which will shortly be published as a separate document.

Meanwhile, the Working Party has collaborated with the Association of Research Ethics Committees in a workshop at which various difficulties that both research ethics committees and clinical trial sponsors have experienced were discussed with a view to providing guiding principles on how to avoid conflict.

The Working Party has taken lead responsibility within EFGCP for collecting and submitting evidence for the proposed revision of the Declaration of Helsinki by the World Medical Association and will continue to address ethical issues and challenges as they arise.

## Frank Wells

On 13 October 2008, in Brussels, the EGAN/EFGCP **Patients' Roadmap to Treatment Working Party** will have its 5th Working Party Meeting. The last meeting took place in Barcelona in June during the European Human Genetics Conference 2008.

The main issues discussed during that meeting were the Working Party's participation in a call of the Innovative Medicines Initiative for Integrated Medicines Development (Training of Non-Experts in drug development) and in the FP7-sponsored PatientPartner Project which is led by VSOP, a Dutch patient organisation belonging to EGAN, the European Genetic Alliance Network (see article, page 6). The PatientPartner project has been approved and the planning activities have started. We have just learned that our consortium has been successful in the Innovative Medicines Initiative and whether we will have to plan the Working Party's activities to train patient organisations in Europe in drug development.

Independently of the Innovative Medicines Initiative, we decided to organise an information day in Prague just before the EFGCP Annual Conference 2008, for regional patient organisations, on patients' potential roles in drug development.

An international workshop entitled "Patients – the Driving Force for Clinical Trials in Europe", in collaboration with other not-for-profit organisations, is planned to take place in 2009. The programme should contain sessions on patient organisations' role in drug development, the problems in the informed consent process, the relevance and suitability of registries for the different stakeholders, and potential changes to the Clinical Trials Directive.

A flyer on the Working Party's vision, mission and activities was discussed and released and can be found on the EFGCP and EGAN websites.

## Ingrid Klingmann

The **Audit Working Party** comprises auditing professionals from all aspects of industry, including the inspectorates. We have run two of our scheduled three meetings so far this year. Attendance has been good (around 15 delegates). We have welcomed several new members to the group, and some of our longer-serving members have moved on and passed the baton to other members of their companies.

Much of our year was taken up in

finalising the "Role of the Quality Assurance Unit" document. This is a guide for those starting new QAUs as to the main aspects of their roles, and some of the pitfalls to avoid. It is complementary to the ENGAGE guideline and therefore does not cover auditing processes in detail. It was encouraging to see this begin to circulate actively through the industry, even while in draft form. We believe this is a document which meets a real need.

Our final meeting of the year will be in collaboration with inspectors from the German and French agencies BfArM and AFSSAPS. They are working on a guideline for risk assessment of studies and processes, and have asked for contributions from the Audit Working Party. This will help to ensure the guidance is based in practical experience, and will therefore be directly useful to industry and non-commercial researchers.

The AWP is working more closely in collaboration with the British Association for Research Quality Assurance, and BARQA will be represented in the discussion with the regulators. We will also be involved with BARQA, Japan's JSQA and the SQA in the United States to develop a global guideline on auditing.

## Paul Strickland

The **Geriatric Medicines Working Party** discussed four priorities for 2008/2009, which it will be following up in the near future.

The first is to support a validation study of a Decision Making Assessment Tool in French, English and potentially other EU languages.

Next, the working party aims to improve the understanding and acceptance by ethics committees of clinical studies and research in elderly people. A joint AREC/EFGCP workshop on understanding the ethical quandaries for older research participants is to be held in Basel on 15 January 2009. If you want to join the working party or to know more about it, please contact either the EFGCP secretariat at [secretariat@efgcp.be](mailto:secretariat@efgcp.be) or Jean-Marc Husson at [jean-marc.husson@efgcp.be](mailto:jean-marc.husson@efgcp.be).

**Jean-Marc Husson and Florian von Raison**

# Impact of European legislation

## ICREL team starts evaluation phase

Ingrid Klingmann reports on progress in the EFGCP-coordinated project

The EFGCP-coordinated ICREL (Impact on Clinical Research of European Legislation) project has received quite a lot of public attention among those involved with developing commercial and non-commercial medicines. In articles and interviews the different stakeholder groups, commercial and non-commercial sponsors, ethics committees and competent authorities were encouraged to complete the respective questionnaires on the EORTC webpage.

The collection of information is now nearly complete, and the evaluation phase has started. In addition, the ICREL Project Team has collected information on experience with the Clinical Trials Directive generated by other research teams. The compiled results will be discussed during a conference on 2 December in Brussels.

After presentations from different highly experienced stakeholders of the needs for a change and the methodology of ICREL, the results from the different questionnaires will be evaluated and discussed in detail in parallel break-out groups. Rapporteurs from all groups will

report the course of the discussions and possible interpretations to the plenary in the afternoon where there will be room for extensive exchange of opinion on these interpretations.

Best practices for the different aspects of different types of clinical trials in different European countries will be identified and compared, and conclusions for recommendations to the European Commission on required changes to the legal environment for clinical trials will be drawn.

Participation at this conference is free of charge, but as there is great public interest in this conference the ICREL Project Team decided to open the discussion to more participants than covered by the ICREL budget by asking industry participants to pay a registration fee of €375 to cover their own costs as well as the costs of one participant from a patient group, ethics committees, competent authorities or academic sponsor groups. Conference programme and registration information are available on [www.efgcp.be](http://www.efgcp.be) as well as the web pages of all consortium partners.

## Genetic disease PatientPartner linking EFGCP with genetic groups



The EFGCP is taking part in PatientPartner, a three-year FP7 project coordinated by VSOP, a Dutch patient organisation belonging to EGAN, the European Genetic Alliance Network, to identify the patients' needs for partnership in the clinical trials context.

The project aims to develop an organised and sustainable communication platform as well as guidelines to enable mutually beneficial interactions between patients and clinical trial professionals. Besides VSOP and EGAN, the consortium also comprises GIG, the Genetic Interest Group, and the EFGCP.

In the first year, the project will use structured interviews with patient organisations all over Europe and reviews of existing literature to define patient needs in the clinical trials context and identify best practices.

Besides providing input to the overall project as part of the Project Coordination Team, through its EGAN/EFGCP Patients' Roadmap to Treatment Working, the EFGCP will organise workshops addressing patients (and patient organisations), researchers and scientists, biopharmaceutical companies, regulators >>



Questionnaire for non-commercial sponsors performing clinical trials in the EU

### Questionnaire

- How many Clinical Trial Applications (CTAs) on medicinal products did you submit to a Competent Authority and/or an Ethics Committee(s) in EU countries in 2007?
- How many of your clinical studies, on smaller (medicinal products, or other) or on last-in-class biotech (investigator/sponsor or the coordinating investigator in non-commercial studies (medicinal products, medical devices, surgery, radiotherapy, diagnosis, observational studies, non-interventional clinical studies) were approved by a Competent Authority and/or received a favourable opinion from Ethics Committee(s) in Europe, for the years 2005 and 2007?

Therapeutic clinical trials*								Other non-therapeutic interventional clinical studies, diagnostic procedures, prevention, incl. biomarkers, genetic markers, imaging	Non-interventional (observational) studies		Only if you were not able to provide the breakdown in the columns on the left: all clinical studies	
Clinical trials on medicinal products		Clinical trials on medical devices		Clinical trials on surgical procedures		Clinical trials on radiotherapy						
Exact number	Approximate number	Exact number	Approximate number	Exact number	Approximate number	Exact number	Approximate number	Exact number	Approximate number	Exact number	Approximate number	
2005												
2007												

\* If you have reported any clinical trials on medicinal products, please also specify the subtype of trials in the following table.

Focus on specific categories of clinical trials on medicinal products					
Clinical trials on advanced therapies (somatic cell therapies, tissue biotechnology, gene therapy)		Clinical trials on biotechnological products (precombination products, monoclonal antibodies etc.)		Clinical trials on orphan diseases or medicinal products with orphan designation	
Exact number	Approximate number	Exact number	Approximate number	Exact number	Approximate number
2005					
2007					

ICREL Questionnaire, MCS final.doc

0-413

The ICREL questionnaire, through which the project has been collecting information.

» and other stakeholders in the clinical trials context.

In these workshops, the conclusions from the interviews, literature studies and best practices will be challenged to draw European-wide viewpoints and consensus.

The discussions will be started in a pan-European workshop, followed by regional workshops in Northern/Western, Southern and \central/Eastern European countries to ensure attention to regional needs and differences.

Finally, the results from these four workshops will be discussed in a final pan-European conference. Attendees will be able to consult the outcomes from both

the investigational phase and previous workshops on a dedicated website.

The third part of the project is the establishment of the European Network of Patients partnering for Clinical Research (EN-PCR). Initially, EN-PCR will be responsible for addressing the high priority issues in this project: paediatric clinical trials, patient registries and biobanks, the Innovative Medicines Initiative and ethical issues.

Later on, the idea is that EN-PCR will guarantee the sustainability of this project, being a permanent structure with a bi-directional purpose: both empowering patients and functioning as a one-stop shop for academic and biopharmaceutical

research.

Further dissemination of the project results will be achieved by a Patient Guide for patient organisations, an Investigator Guide for organisers and sponsors of clinical trials, a List of Recommendations for regulators and a thematic website. The consortium will provide continued support to both EN-PCR and the PatientPartner website after this Coordination Action has ended.

Readers interested in getting actively involved in this project are invited to join the EGAN/EFGCP Working Party. Please contact the Co-Chairs. Ysbrand Poortman ([ypoorntman@zonnet.nl](mailto:ypoorntman@zonnet.nl)) or Ingrid Klingmann ([ingrid.klingmann@efgcp.be](mailto:ingrid.klingmann@efgcp.be)).

## Clinical trials

# EFGCP adds ethical dimension to clinical trial database design

**Frank Wells explains how the EFGCP's Ethics Working Party has become involved in the EudraCT Joint Operations Group**

The EU Database on Clinical Trials – known as EudraCT – is the European Medicines Agency's database that acts as a register of all clinical trials being conducted in the EU. It contains information on every clinical trial, including commencement, termination, content and inspections, and it in theory facilitates communication on these studies between the sponsor and the competent authority.

Some time ago the European Medicines Agency set up a Joint Operations Group, whose remit is to establish business process design and implementation, to ensure that the needs of clinical trial sponsors are represented, and to assess EudraCT design and implementation with regard to confidentiality, security, accessibility, usability, stability, availability and so on.

The EudraCT Joint Operations Group now meets regularly under the chairmanship of Dr Brian Davis, formerly an assessor at the MRHA, the UK's Medicines and Healthcare products Regulatory Agency. Until recently, however, it had nobody on it who in any

way represented ethical interests – and so it was a most welcome step when the EFGCP Ethics Working Party was asked if it would fill this gap by appointing one of its joint chairmen as ethical adviser to the Group. Currently, therefore, Frank Wells fills this role and attends the meetings of the EudraCT JOG, with Ingrid Klingmann as his deputy.

It has become clear that an "ethical presence" is both needed and expected: the European Medicines Agency is keen to ensure that the European public are aware of what clinical research is in progress – and particularly the outcome of such research, with emphasis on the

ethical justification for doing this research.

Since the Ethics Working Party has been represented at the JOG meetings, the latest version of the Clinical Trials Application (CTA) form has been discussed, together with the consultative draft of the Guidance on the information concerning paediatric clinical trials to be entered into the EudraCT and on information to be made public by the European Medicines Agency. Not surprisingly, in view of the introduction of new legislation on trials involving children, the recent meetings of the Joint Operations Group have largely been devoted to paediatric issues where discussion on the ethical issues of information and consent has been able to be initiated and then influenced by an input from EFGCP.

Any ethical issues or concerns that members might wish to express regarding the conduct of clinical trials should be sent to Frank Wells ([frankwells36@aol.com](mailto:frankwells36@aol.com)) so that he may raise them with the Joint Operations Group.





# **The EFGCP Annual Conference 2009**

## **Research Integrity: a European Perspective**

### **Diplomat Hotel, Prague, Czech Republic**

#### **27–28 January 2009**

*In partnership with*

**Czech Science Foundation (CSF)**  
**Czech Ministry of Health (Department of Education and Science)**  
**European Science Foundation (ESF)**  
**Association of the British Pharmaceutical Industry (ABPI)**  
**Association of Clinical Research Professionals (ACRP)**  
**The Institute of Clinical Research**

The First World Conference on Research Integrity, held in Lisbon in September 2007, yielded many aspects of fraud and misconduct in scientific research that justify the development of better techniques for the prevention, detection, investigation and prosecution of such misconduct, throughout the world. Europe has a variable track record in tackling this problem, but many bodies, as well as individuals, have had some success in.

With the help of a series of workshops and presentations from people from around the world experienced in handling this problem, this conference will present an opportunity to explore in depth how individuals and institutions in Europe can demonstrate a commitment to research integrity, specifically in the field of biomedical research. For more information, please email [conferences@efgcp.be](mailto:conferences@efgcp.be) or visit [www.efgcp.be](http://www.efgcp.be).

---

## EFGCP Workshop

# Animal experimentation and clinical studies: Ethical recommendations to ensure participants' safety in early drug development

Report of a workshop held at the Renaissance Hotel, Brussels, on 11 June 2008

## 1. THE WORKSHOP AND ITS AIM

This report summarises the discussion and conclusions of a unique workshop, a first for Europe, that took place in Brussels on 11 June 2008. This Europe-wide meeting, organised by the European Forum for Good Clinical Practice (EFGCP) with support from the European Federation of Pharmaceutical Industries and Associations (EFPIA), drew participants from a particularly broad range of interests – researchers, clinicians, patients, policy makers, regulators, ethicists and proponents of animal welfare. They came together to discuss ethical principles and possible recommendations which can apply when a drug candidate is used in first-in-man trials.

The dilemma faced by industry, ethics committees and regulators is that on the one hand they are trying to reduce animal testing for the sake of animal protection (and to reduce testing costs in order to maintain competitiveness), and that on the other hand they are looking to guarantee the highest possible safety for clinical trial subjects. The workshop's aim was clear, but far from easy, since it tackled one of the most complex and often controversial issues associated with ethics and patient safety in early drug development.

Around 35 invited participants listened to presentations on the dilemmas faced by all the stakeholders, and sought to reach conclusions. It is not in the nature of discussions on such topics that the outcome is a list of unanimous recommendations, and this report does not seek to imply that all participants agreed on all points. Given the widely differing standpoints of the various



Laboratory Brown Norway rat. Picture courtesy [www.genome.gov](http://www.genome.gov)

stakeholders, the concept of a “majority view” would be quite inappropriate.

Opening the workshop, Ingrid Klingmann from the EFGCP said, “We want to have a tangible outcome that we can discuss with the public.” The conclusions on ethical principles that did emerge should, therefore, be seen as items for further discussion – a structuring of the ethical agenda – rather than as a blueprint for legislators.

The meeting took the form of an opening plenary session with a number of keynote introductions focusing on the dilemmas as seen by the various stakeholders. A discussion of the statements and areas of conflict was followed by agreement on the questions to be considered in breakout groups. The

results from these breakout groups were then discussed in a final plenary session, during which some preliminary conclusions and suggestions for further debate (with the provisos above) emerged.

In order to achieve the greatest possible exchange of views, the meeting was conducted under Chatham House rules – that is to say, the contributions of participants are identified only with their consent, and then only in relation to the keynote introductions. In accordance with the spirit of the meeting, this report makes no attempt to attach names to contributions to the general discussions. It was compiled by rapporteur Peter Wrobel, a science writer, in consultation with the meeting's programme committee.

## 2. KEY MESSAGES

The workshop addressed a controversial and, for some, emotional subject – the use of animals in the development of medicinal products for human use – in a broad, deliberately heterogeneous forum. Importantly, the workshop proved not only that such discussion can take place, but that it can also be highly productive.

It also revealed how much ethical common ground there is among researchers, patients and animal welfarists, between industry and policy makers; in fact, among all stakeholders. This common ground is centred around the ethical principles of doing no harm to study participants, and of replacing and avoiding animal use wherever possible in the research and development of new medicinal products.

There should be no secrets about animal research. For example, people taking part in clinical trials should be >>

» informed about prior tests of their clinical trials medication on animals, why the tests were carried out, and about their limitations in predicting absolute safety.

But much as everyone would like to see the use of animals in clinical research phased out, it is clear that this is a long-

## Glossary

**3Rs.** The principles of Replacement, Reduction and Refinement (most often referred to as the 3Rs), first proposed in 1959 by William Russell and Rex Burch as the key strategies for humane experimental techniques.

**EFPIA** represents 32 national pharmaceutical industry associations and 43 leading pharmaceutical companies operating in Europe. Its mission and priorities are to improve the competitiveness within Europe in a regulatory and political environment, which will above all stimulate R&D and reward innovation.

**In vivo** refers to experimentation done in or on the living tissue of a whole, living organism as opposed to a partial or dead one or a controlled environment.

**Pharmacodynamics** is the study of the biochemical and physiological effects of drugs on the body or on microorganisms or parasites within or on the body and the mechanisms of drug action and the relationship between drug concentration and effect.

**Pharmacology** is the study of how drugs interact with living organisms to produce a change in function.

**Toolbox** – the type and duration of animal testing required to be performed during drug development in order to get a marketing authorisation for a medicinal product granted by health authorities

**Scientific Advice procedure.** Regulatory procedure, where health authorities give the industry advice by answering questions connected with the development of medical products.

term goal. If animal use in Europe were to be stopped tomorrow without appropriate alternatives in place, it would have a damaging effect on the safety of new medicines for humans, restrict the number of new medicines coming onto the market and could result in a shift in the research and development of medicines away from Europe.

On the other hand, there are initiatives that have been implemented for some years to reduce the number of animals used in research and drug development, for example by avoiding unnecessary animal tests, ensuring that tests are statistically robust and by developing alternatives to animal use. These ideas are encompassed within the '3Rs principles': reduction, refinement and replacement of animal studies.

In the ongoing discussion about this whole issue, ethics has a central role to play. It is, furthermore, a discussion that must not be confined to those undertaking drug development, animal testing or clinical trials: it is a question for society at large.

### 3. Setting the scene

The question "When is the right moment to start a clinical study in humans?" has no absolute answer. Physicians, ethics committees and regulatory agencies have to make this decision based on data derived from human pharmacological studies and animal experimentation. But research can only go so far: there is never a guarantee. What risk is acceptable to study participants? At what point would it be unethical to continue experiments with animals? This discussion required input from a broad range of views and backgrounds. It cannot be done with "silo thinking", confined to discrete interests and disciplines.

### A policy view

The welfare of animals, including those used for the development of medicines, is a subject that the public is keenly interested in, as Neil Parish MEP, co-chairing the first session, explained: "I get more letters and emails from people concerned about animal welfare than anything else I deal with." As a politician, he would love to be able to say that no animal testing should take place. But it

has to be done, he said, "We do want safe medicines." He added that the more he hears, the more he is torn between the two sides of the argument. As a farmer, he said, he knows how medicines alleviate animal suffering; on the other hand, he does not want to see animals experimented on. So, we have to have a set of rules on how and when to do animal experimentation. What we have to decide is, are the present rules too vigorous, or not vigorous enough? And he had his own take on risk: the patient is the best judge, but can only decide on the basis of the right information.

### A pharma industry view

In a broad review of principles that pharmaceutical companies use to assess the safety of new medicines, Tim Hammond from AstraZeneca, United Kingdom, explained how pre-clinical studies are used to identify potential hazards and assess risk before administering new candidate drugs to humans for the first time. Preclinical studies are used to define the nature of potential toxicity and to define the dose response. There are clear legally binding regulatory requirements that define a minimum set of tests to ensure the highest possible safety of drug candidates. It was recognised that preclinical studies – although imperfect – are the best way currently available to identify toxicity and guide selection of the first dose to be given in first time in man studies. "We would still conduct these studies even without regulatory requirements," he said. First-in-man studies are designed to assess safety and tolerability of new drugs and as such usually dose to the maximum tolerated dose in human volunteers. Consequently, it is essential to understand the full dose response of both the pharmacological and toxicological dose ranges in studies in animals to select a safe starting dose and set clear stopping criteria in the clinical study. As development progresses the clinical knowledge increases and the balance shifts from total reliance on preclinical data to reliance on both preclinical and clinical safety data. Exceptions to this are in assessing reproductive toxicity – the potential to induce adverse effects upon the unborn child – and the risk of the compound inducing tumours. Preclinical

studies remain the only available means to assess risk in these areas. In many areas of toxicity assessment alternative methods are increasingly used, but currently there is no alternative to the integrated assessment that comes from evaluation of in vivo studies.

### An ethics committee view

For John Hudson from the UK Association of Research Ethics Committees, ethics committees were in the “increasingly uncomfortable position” of reaching subjective decisions on the basis of interpreting increasingly complex objective data. And there’s no shortage of data: the problem is turning a 40-centimetre stack of papers into meaningful information for ethics committees and human volunteers to use in the process of informed consent. “Bare statistics are often quite damagingly uninformative,” he said. He pointed to a number of dilemmas in relation to animal testing. For some conditions there are well established animal models, he said, while acknowledging that cutting edge science now raises some unanswered and even unanticipated questions. At the end, he said, there is always a decision to be taken. “It has to be taken in as objective a fashion as possible, but ethical decisions will always be subjective decisions.”

### An animal protection view

Penny Hawkins from the UK Royal Society for the Prevention of Cruelty to Animals (RSPCA) acknowledged that the use of animals in research and testing is “a very broad issue”, because animals are used for a wide range of different purposes. Every project raises its own ethical, scientific and animal welfare issues. The RSPCA’s ultimate goal is to replace or avoid the use of animals in research and testing. In the meantime, recognising that animal experimentation will continue, it wants to see a reduction in animal numbers and suffering, and immediate improvements in animal welfare. Animals are sentient and capable of experiencing pain, suffering and distress, and this matters. Animals do suffer in biomedical research, for example as a result of scientific procedures and their effects. Suffering is also caused by other factors such as the stresses of



Laboratory mice. Image courtesy Caroline Murphy/RSPCA Photolibrary.

transport and laboratory housing, and procedures such as euthanasia using carbon dioxide, which is widely used but can cause pain and distress. Literature from industry groups in support of animal use mentions suffering obliquely, she said, but it does not explain what that suffering is. Animal experiments can lead to medical and veterinary advances, she said, but that “does not detract from serious moral concerns”. “We’re not naïve,” she said, explaining that animal use is intrinsic to veterinary medicine, which the RSPCA uses to treat the many animals in its care.

“Ultimately, animals and humans both matter,” said Hawkins, pointing to “a significant conflict of interest between animals and science”. Avoiding and replacing the use of animals wherever possible has to lead to scientific and societal benefits, and a benefit to animals, she said. “The goal should be to alleviate human suffering without causing animals suffering. That goal is a long way off, but we have to have a positive approach to achieving it.”

### A patient view

Patients, said Cees Smit from the Dutch Genetic Alliance, are interested in the results of good research: “If that can be done without the use of animals, that’s perfect. If animal experimentation is necessary, it must be humane and careful.” From that perspective, patients are not “in favour of animal research”, just like researchers. But if animal experimentation has to be done, then it must be properly regulated, he said. Smit pointed to the fact that almost 15% of animal research was for veterinary medicines – a growing market, with companion animals, for

example, falling victim to typically human illnesses such as diabetes and obesity. There are also crossover diseases, such as bird flu and BSE.

Smit was clearly exasperated with public hearings on research where it seems as if all that is heard is objections to the use of animals on the basis that it is either “only” for fundamental research, or “only” a rare disease, and so on – even that people with genetic diseases should stop having children. The way forward, he said, included greater involvement of patient groups in ethics committees, as well as an international research agenda that would reduce the number of animals used.

Alternatives to animal testing should be validated and internationally recognised. Finally, said Smit, the “more radical” animal protection groups should invest in good relations with other stakeholders in research – and sometimes recognise the value and necessity of research.

## 4. THE DISCUSSION

The key conclusions, suggestions for further debate (see page 13), emerged from four parallel breakout sessions, each considering two key aspects of this broad issue. Each breakout group had a brief to consider the ethical principles involved, and their results were reported back to a plenary session and elaborated in discussion. As said above, there is no suggestion here that all participants were necessarily in agreement on all of the conclusions. Together, though, these conclusions might be seen as a platform for further discussion.



## » The questions

The following questions were provided to the breakout groups:

1. How to define 'risk'? What is acceptable for a trial subject? Who decides? How to ensure the adequate information for trials subjects about the relevance of animal tests performed for their safety?

2. Does the current evidence-base for animal testing justify the present regulatory requirements? What impact would less animal testing have on the conduct of clinical research?

3. Under what conditions might it be possible for regulators to approve a first trial for a medicinal product which has not been tested in animals?

4. Would the objectives of a trial, e.g. pharmacodynamics, efficacy, impact the required amount of animal data? How do you ensure that trial subjects are adequately informed about the relevance of animal tests performed for their safety?

## The answers

**How to define 'risk'? What is acceptable for a trial subject? Who decides? How do you ensure that trial subjects are adequately informed about the relevance of animal tests performed for their safety?**

The answer from the breakout groups was clear: trial subjects must be informed in a meaningful way about all relevant tests performed in animals and about what the results indicate about risks potentially connected to the administration of the new drug. In addition, any limitations of the tests in terms of their predictability of safety need to be pointed out.

**Does the current evidence base for animal testing justify the present requirements of regulators and investigators? In other words, is the current regulatory framework for animal research appropriate?**

The answers provided to these questions were mixed. Some find the current regulatory framework is appropriate. Others believe that the regulatory requirements for doing tests in animals are not always justified, although that does not necessarily mean that the whole "toolbox" is wrong. Many drug candidates drop out during animal

experimentation due to detected safety issues, and the incidence of serious adverse drug reactions in clinical trials is rare; this indicates that, overall, the regulatory framework works. But given the regulatory system for developing a medicinal product and getting a marketing authorisation for it, toxicologists might think it safer to do all the tests rather than only what is necessary.

The current toolbox of experiments was defined by science, not by regulators. So the toolbox should be continuously reviewed in line with progress in biomedical research – and, if appropriate, reduced rather than enlarged. Trial sponsors have to justify when they diverge from the toolbox; and they should stop doing studies in animals that are formally required but known to be useless in this particular situation. It would be, therefore, helpful if the Scientific Advice procedure is more extensively used to enhance early discussion between trial sponsors and regulators about particular animal studies.

Certainly, more harmonisation of requirements both within the EU and between the EU, the United States and Japan would help to reduce the number of animals used in experiments. It was also suggested, controversially for some people, that there should be specialist first-in-man ethics committees that would have the expertise to look at the issues involved. There was agreement, though, on the general principle that ethics committees considering first-in-man trials should have demonstrable access to acknowledged first-in-man experts.

**What impact would less animal testing have on the conduct of clinical research?**

There were several aspects to this particular question. Some animal testing may be redundant, but it is not currently clear how much. Furthermore, some animal models are of limited validity and it would presumably be acceptable to reduce animal use in cases where no suitable animal models exist.

A reduction in animal testing would put additional moral responsibility on ethics committees. They would also need to have a stronger knowledge of pharmacology. It was recommended that ethics committees should be particularly vigilant in examining protocols from less

experienced trial sponsors in order to help the sponsors to better understand the processes and background (which, of course, is already the case now).

However, the key principle is that less animal testing must not impact negatively on patient safety.

**Under what conditions might it be possible for regulators to approve a first trial in humans of, or give marketing authorisation to, a medicinal product that has not been tested in animals?**

Generally, requests for a marketing authorisation without animal testing will be very rare. The view expressed at the workshop was that this might be possible if the product were derived from the patient's own cells, or if there were no suitable animal models or – controversially discussed – if the only suitable animal model were the chimpanzee.

Also, clinical trials for new drugs are very rarely performed without prior animal testing. Exceptions relate to biotechnology-derived products where there is no relevant animal model and no transgenic animal can be produced.

Reduced testing may be appropriate in the development of medicines containing plant extracts or small molecules where toxicological experience had been accumulated over years, or in the development of medicines containing a different salt or ester of a previously tested substance.

Reduced safety data is acceptable in first-in-man trials involving patients suffering from end-stage cancer or other life-threatening diseases – but this can raise special issues with the process of informed consent.

The overall principle is that if sufficiently reliable safety data are available from other types of experiments, regulators should approve the conduct of first-in-man trials with drug candidates that have not been tested in animals before.

The workshop also looked at a hypothetical question: If there were a global ban on animal research and testing tomorrow, what techniques could be used to generate data to provide information about each compound before starting first-in-man trials? The answer was that researchers would have to turn the techniques they use now – in vitro tests and computer simulations, including new

# Suggestions for further debate on ethical principles

- In clinical research it is required to do no harm to study participants. At the same time, animals should be used in research only when necessary and suitable to minimise the risk to the study participants and when unavoidable for the research and development of new medicinal products. As an absolute global ban on animal experimentation would affect the research and development of new medicines and would increase risk for clinical trial participants, the use of animals is today unavoidable to a certain extent.

- It should be accepted that – depending on the medicinal product and the scientific knowledge – it may sometimes be possible to reduce the number of animals used in testing without compromising the safety of volunteers taking part in clinical trials. It should also be accepted that animals and their welfare matter, and that replacing animal use is a legitimate and desirable goal.

- After appropriate information and received consent, reduced safety data is already acceptable in first-in-man trials involving patients suffering from end-stage cancer or other life-threatening diseases.

- In the development of medication targeting vulnerable patient groups such as pregnant women or children, a greater degree of animal experimentation might be necessary to avoid harming them. It is likely that previous adult human data will be available before clinical trials in pregnant women or children are considered. At the same time, everything possible should be done to avoid unnecessary harm to animals as well.

- The “toolbox” used in research and development of medicinal products containing animal testing is to be defined by science rather than by regulation. The current regulatory framework for required animal testing needs to be continuously reviewed and updated along with the

progress made in biomedical research. Harmonisation of the regulatory requirements in all regions needs to be further promoted with the aim of avoiding duplication of animal tests and avoiding animal use in general.

The Scientific Advice procedure should be more extensively used to enhance early discussion between trial sponsors and regulators about particular animal studies.

- Before entering the clinical trial, participants need to be properly informed about the potential risk, about the animal tests that have been performed, and about the limited predictability of such tests.

Ethics committees considering first-in-man trials should have demonstrable access to acknowledged first-in-man experts.

- Researchers in industry and academia do apply, and should be encouraged to apply further, the 3Rs principles; regulators and ethic committees should be vigilant in this respect.

techniques such as QSAR (Quantitative Structure Activity Relationship – though the workshop heard that it will still take “a long time” to make this technique work). One thing was obvious: such a ban, tomorrow, would raise risk for participants in clinical trials, and would reduce the research and development of new products.

**How do the objectives of a trial – for example, pharmacodynamics and efficacy – impact the process of animal testing?**

Considerations of pharmacodynamics – the effect drugs have on the body – affect which animal species are chosen for the study, and the duration of the study. For example, in medical diagnostics, animal studies might be only of two weeks’ duration; in antibiotics, four weeks; longer for drugs that target tumours. But if the drug is intended for pregnant women, for example, then tests would

need to be prolonged in order to assess possible effects on the next generation. Prolonged testing in animals might be needed with drugs intended for very elderly patients as well, or for rare diseases and, very rarely, treatments that involve administering a number of drugs at the same time (so-called multi-drug therapies).

Does it make a difference whether the initial clinical trials in people are intended to be carried out in healthy volunteers or in people who are already ill with the disease to be treated? Yes, in part, was the answer. To some extent, it is possible to derive data on toxicity from cancer patients and, rarely, to move to doses in people that you would not use in animals. Overall, though, the properties of the molecule being tested will determine whether healthy or sick volunteers are sought.

In any event, if you see clinical toxicity in trials, you need to understand the mechanisms. But if you have good

applicable data from humans, the workshop agreed, it is unethical to repeat the experiment in animals just to “tick the boxes” in the list of regulatory requirements. However, researchers warned that it may be necessary to repeat experiments in animals in order to understand the mechanisms and to identify at-risk groups as well as to validate these findings.

The ethical principles are clear: the extent of knowledge about the safety of a drug candidate used for a first-in-man clinical trial may differ between different patient populations. There are especially vulnerable populations, such as pregnant women and children. Testing in these patient populations occurs later in the drug development process, and a greater degree of animal experimentation is necessary to avoid harm to them as much as possible. At the same time, everything possible should be done to avoid unnecessary harm to animals as well.

# Standards for Research Ethics Committees: purpose, problems and possibilities

As the EFGCP survey published last year showed, there is enormous variation among Research Ethics Committees in Europe. But what can or should be done to standardise the way they work? That was the question examined in April by a workshop in Warsaw held by the EFGCP Ethics Working Party hosted by the Bioethics Committee of the Polish Chamber of Physicians and Dentists. Here is a provisional report on the workshop from Hugh Davies, Ethics Adviser to the UK National Research Ethics Service

## Introduction (purpose)

Research Ethics Committees (RECs) now have a recognised place in the regulation of medical research, but if researchers, patients and public are to trust them, and authorities to indemnify them, they need to demonstrate that they do actually protect the dignity, rights, safety and wellbeing of research participants while also not hindering ethical research. One way to do this is to meet agreed standards, the classical process of quality assurance.

The EFGCP Ethics Working Party found striking differences in setting standards for RECs across the European Union (EU) and organised a meeting in Warsaw to explore difficulties for RECs and to exchange experience and resources. Representatives from 27 European countries were invited; 16 countries were represented.

## STANDARDS: The problems

### 1. Limited and variable resources

Funding for RECs across the EU varies and given the cost of establishing processes to measure standards and this variability, progress has been limited to those with resources to support RECs.

### 2. Difficulties setting standards for ethical debate and outcomes

Standards can be set for process, deliberation or outcome. Guidance makes little reference to deliberation or outcome and most current analysis, in line with Coleman and Bouissieu's criticism, has assessed the underlying process rather than results. The majority of unmet standards in recent audit

of RECs in the UK were again those of process. While such audit can assure a consistent and accountable process, it falls short of making any statement on outcome in terms of research safety or acceptability. Academic analyses have pursued the same path. A similar picture is seen in the USA.

This dearth of outcome analysis is understandable. Setting standards for deliberation and outcome, in which we are looking into people's attitudes and skills and the ethical standing of debate, presents much greater challenges. How are we to measure the necessary qualities of a REC member? Even if we can do this, how do we analyse the debate and its outcome? Is research safer and more "respectful" of participants now REC review is established?

While some exploratory work has examined what IRB members consider in their deliberation, most studies of outcome have explored, and demonstrated, variability in the response of RECs. We don't know if they are inconsistently right or wrong!

So while these studies demonstrate variability, they provide no analysis of the outcome that satisfies quality and rigour. Such studies will require a "standard" to be set and may be seen to challenge the independence of RECs, constraining them and "telling them how to think". But autonomy has its boundaries. RECs must work within a framework defined by legislation, standard operating procedures, public views and ethical reasoning. Their independence is primarily to free RECs of any possible conflict of interest or undue influence. It is not intended to divorce them from "due influence" – views in their

community, reason, morality or public opinion. As Angell et al write in *Clinical Ethics* (*Clinical Ethics* 2007 2 92-99): "This is not to say that RECs may do and say as they please; their judgements should function with a notion of there being an answer that reasonable people could accept."

### 4. Measurement alone is not enough; striving for improvement

Given the strength of criticism and the empirical data on REC performance, it is unlikely that critics will be silenced by the measurement of standards alone. RECs need to demonstrate change and improvement. While there were aspirations aplenty, delegates could report no current examples.

### 5. REC members, as volunteers, will resent imposition of standards

Members serve on RECs as volunteers and delegates at the meeting reported lengthy debate and concern about the consequences that standard setting and measurement would have upon recruitment and retention, fearing they would resent such activity, seeing it as implicit criticism of work they are undertaking for the public good, without remuneration. Volunteers may be unwilling recruits to the accountability revolution.

## The possibilities of standard setting and other approaches

Establishing that RECs meet certain standards is not an end in itself. Rather the purpose is to use this record to gain the trust of researchers, research participants,

patients and public by demonstrating to the public, patients and researchers that RECs actually do protect the rights, safety, wellbeing and dignity of research participants and play their part in promoting ethical research. By doing this, an important step will be taken toward maintaining public participation in ethical medical research. It is also the most effective way RECs can respond to current criticism.

Delegates recognised that resources for RECs were limited and therefore discussed other approaches.

### Following the classical “QA path”

The UK National Research Ethics Service has established a programme to share ethical debate between RECs to promote consistency where appropriate and improve ethical review (see <http://www.nres.npsa.nhs.uk/rec-community/quality-assurance/quality-assurance-reports/>).

It is may be possible that participation will become part of committee accreditation. Material can be downloaded and used freely.

### Greater openness

The public know little, if anything, about RECs and their purpose. As a first step the public, patients and researchers need to know what RECs do and why they do it. Greater openness and explanation would be one such route to provide this information and seek their trust. Open debate could put RECs forward as a forum to improve public understanding of research and research ethics. One of the most persuasive arguments to emerge is that a more open REC process, debate and decision making could make a significant contribution to improve patient and subject safety.

### Using routine processes for QA

Given limited funds, how can we use current process to demonstrate ethical standards?

#### (I) Using current multi-centre review as QA

In some states, one REC provides the ethical opinion but local RECs are able to submit their views on the ethics and local issues to the “lead” committee. Formulation

and collection of these opinions, routinely collected, could provide data for QA. All that is required is resource for this analysis. Examples were presented from Belgium and Switzerland.

#### (II) Collecting REC member reports for review

In some states, lead reviewers write ethical summaries of the studies before the REC meetings and lead the debate. In Portugal there is an executive committee that reviews the rep-orts. Again this could provide data for QA.

#### (III) Responding to untoward events

Analyses of these and the review undertaken can be fed back to RECs. As an example CCMO in the Netherlands has looked at outcomes of REC review: conducting reviews on topical themes and specific applications that have given rise to problems, for example review of a trial of probiotics in pancreatitis which found its way into open debate as results indicated such treatment seemed to do more harm than good – see *BMJ* 2008 (9 Feb) 336 p296.

#### (IV) Learning from appeals:

Any fair system should allow a researcher the opportunity to appeal against the REC decision. This could provide an opportunity to reflect on the REC’s deliberation and then disseminate the findings.

#### (V) Feedback from applicants

This can provide data for QA. In the UK this forms part of committee appraisal. See <http://www.nres.npsa.nhs.uk/rec-community/quality-assurance/quality-assurance-reports/>

#### (VI) Other meetings

Most member states hold meetings for REC chairs, members and secretaries, usually for administrative and training purposes.. In Finland committee secretaries and chairs meet annually, in Switzerland the committee presidents meet every month and in Belgium there are two-monthly meetings of representatives from RECs. In the Netherlands the secretary and staff of Medical Research Ethics Committees and the Central Committee on Research Involving Human Subjects (CCMO) meet four times a year; and chairman meetings of the ethics committees and the CCMO twice a year.

There was discussion about how these might be used for QA

### Involving other partners

If REC resources are limited, it might be possible to develop links and cooperate with others involved in research or academic departments of ethics.

### The role of a central authority overseeing RECs

Some member states countries have established a body to oversee RECs. Those that have seem to have made most progress, although this is most likely a consequence of committing resources to RECs and there seems no fair reason against these resources being shared across the EU.

### The place or possible value of a central, national board or ethics committee

The structure of ethical review varies from state to state. Some countries have established a central REC (while the size of some has dictated that is all they need). The form and function of a central committee or board could allow standard setting and deliberation on ethical issues. There was debate about the merits and problems of this and the challenge for member states that have a more devolved structure. In these the prospect of a “higher moral authority” may cause resentment.

### Conclusions

Criticism of research regulation continues, and the relationships between regulator and researcher and public remain under threat. The meeting looked at ways RECs could help build bridges.

If trust in ethical review is to be won, we need to explore how the researcher and public can be assured of the competence, fairness and benefit of ethical review. Setting standards to help RECs improve must be the way forward. Current effort has focussed on process and consistency. We need a more sophisticated analysis that helps RECs meet their fundamental objectives of protecting the rights, safety and wellbeing of research subjects while also promoting ethical research. That is the challenge before all involved in the ethical review of research.

## The EFGCP News

The EFGCP News is an open forum for discussion and information on practices and developments relating to Good Clinical Practice. Comments, letters, contributions and general input are welcome.

Correspondence and items of interest should be addressed to

**The Editor:** Peter Wrobel  
Clarity in Science Communication  
11 Fulready Road  
London E10 6DT, UK  
Tel +44 780 317 6319  
Fax +44 870 130 5680  
[clarity@wrobel.net](mailto:clarity@wrobel.net)

**Copyright:** EFGCP 2008. All rights reserved. No part of this publication may be copied, transmitted or reproduced in any way without the written permission of the EFGCP.

**Disclaimer:** While the Editor and EFGCP try to ensure the accuracy of information presented here, no responsibility can be accepted for subsequent use of the information. The views expressed here are those of individuals and not necessarily those of the EFGCP or of the organisations by which they are employed.

**Printed by:**  
Holbrooks Printers Ltd, Norway Road,  
Hilsea, Portsmouth PO3 5HX, UK

## The EFGCP Website

<http://www.efgcp.be>

## The EFGCP Board

Jean-Pierre Tassignon, Chairman  
[jean-pierre.tassignon@efgcp.be](mailto:jean-pierre.tassignon@efgcp.be)  
Jacques Demotes-Mainard, Vice-Chairman  
[jacques.demotes@efgcp.be](mailto:jacques.demotes@efgcp.be)  
Yves Geysels, Treasurer & Membership Officer  
[yves.geysels@efgcp.be](mailto:yves.geysels@efgcp.be)  
Michael Bone, Secretary  
[michael.bone@efgcp.be](mailto:michael.bone@efgcp.be)  
Susan Trainor, Publications & Organisation Development Officer  
[susan.trainor@efgcp.be](mailto:susan.trainor@efgcp.be)  
Ingrid Klingmann, Conferences Officer, Co-Chairperson, Ethics Working Party & Co-Chairperson, EGAN-EFGCP Patients' Roadmap to Treatment Working Party  
[Ingrid.klingmann@efgcp.be](mailto:Ingrid.klingmann@efgcp.be)  
Frank Wells, Ethics Officer & Co-Chairperson, Ethics Working Party  
[frank.wells@efgcp.be](mailto:frank.wells@efgcp.be)  
Olga Kubar, Education Officer  
[olga.kubar@efgcp.be](mailto:olga.kubar@efgcp.be)  
Vesna Vujaklija, Chairperson, Education Working Party  
[vesna.vujaklija@efgcp.be](mailto:vesna.vujaklija@efgcp.be)

## The EFGCP Secretariat

Fanny Senez, Chief Operating Officer  
Pauline Havelange, Administrative Assistant  
Corinne Gaillard, ICREL Project Assistant Coordinator  
EFGCP Secretariat  
Square de Meeùs  
Rue de l'Industrie, 4  
BE-1000 Brussels, Belgium  
Tel +32 2 732 87 83  
Fax +32 2 503 31 08  
[secretariat@efgcp.be](mailto:secretariat@efgcp.be)

Paul Strickland, Chairman, Audit Working Party  
[paul.strickland@efgcp.be](mailto:paul.strickland@efgcp.be)  
Klaus Rose, Chairman, Children's Medicines Working Party  
[klaus.rose@efgcp.be](mailto:klaus.rose@efgcp.be)  
Jean-Marc Husson, Co-Chairman, Geriatric Medicines Working Party  
[jean-marc.husson@efgcp.be](mailto:jean-marc.husson@efgcp.be)  
Florian von Raison, Co-Chairman, Geriatric Medicines Working Party  
[florian.vonraison@efgcp.be](mailto:florian.vonraison@efgcp.be)  
Ysbrand Poortman, Co-Chairman, EGAN-EFGCP Patients' Roadmap to Treatment Working Party  
[ysbrand.poortman@efgcp.be](mailto:ysbrand.poortman@efgcp.be)  
Jozef Glasa, Board Member  
[jozef.glasa@efgcp.be](mailto:jozef.glasa@efgcp.be)  
Gerard J. Marsat, Board Member  
[gerard.marsat@efgcp.be](mailto:gerard.marsat@efgcp.be)  
Thierry Nebout, Board Member  
[thierry.nebout@efgcp.be](mailto:thierry.nebout@efgcp.be)  
JanHasker G. Jonkman, Board Member & Coordinator of the Training Modules Accreditation Panel  
[janhasker.jonkman@efgcp.be](mailto:janhasker.jonkman@efgcp.be)  
Jean-Pierre Girre, Board Member  
[jean-pierre.girre@efgcp.be](mailto:jean-pierre.girre@efgcp.be)

## EFGCP Silver Corporate Member



## EFGCP Bronze Corporate Member



[www.efgcp.be](http://www.efgcp.be)