

The ethical review process for clinical trials in the European Union

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Overview

- Requirements of the Directive
- Applications to ethics committees
- Ethical review procedures
- Appeals and re-submissions
- Substantial amendments
- Safety reporting
- Role of the Ethics Committee (EC) and collaboration with the Competent Authority (CA)

Overview

- Requirements of the Directive
- Applications to ethics committees
- Ethical review procedures
- Appeals and re-submissions
- Substantial amendments
- Safety reporting
- **Role of the Ethics Committee and collaboration with the Competent Authority**

Introducing the National Research Ethics Service (NRES)

- Research Ethics Committees in **England** (87 committees)
- Operations and management support
- Co-ordination of an integrated system for the **United Kingdom** in collaboration with Scotland, Wales and Northern Ireland
- <http://www.nres.npsa.nhs.uk>

A comprehensive support service

Strategic planning * Stakeholder relations *
Policy * Operational management* SOPs
Central allocation * Training * Guidance*
Queries service * Quality assurance *
Audit and accreditation * Ethical debate*
*Guidance * Financial management *
Integrated Research Application System

Clinical Trials Directive 2001/20/EC

Article 6 - ethical review process

- **Single opinion** for the Member State by a single Ethics Committee
- Opinion to be given within **60 calendar days** of receipt of a valid application (or 90 days for gene therapy; unlimited for xenogenic cell therapy)
- EC may make **single request for further information** during the review – the **clock stops** until this is received

Article 6 - required areas of review

- Relevance of trial
- Trial design
- Risks and benefits
- Protocol
- Suitability of the investigator and supporting staff
- Investigator brochure
- Quality of the facilities
- Subject information
- Consent procedure
- Justification for including minors or adults unable to give informed consent
- Insurance/ indemnity
- Rewards or compensation for investigators and subjects
- Subject recruitment

Commission guidelines

- European Commission guidance on the application to the ethics committee (ENTR/CT2, revision 1, March 2006)

http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm

- Under review by Commission with a view to greater harmonisation of process across Member States

EFGCP working party report

- European Forum for Good Clinical Practice (EFGCP) - guide to ethics committee procedures in all EU Member States:

<http://www.efgcp.be/EFGCPReports.asp?L1=5&L2=1>



Member's area

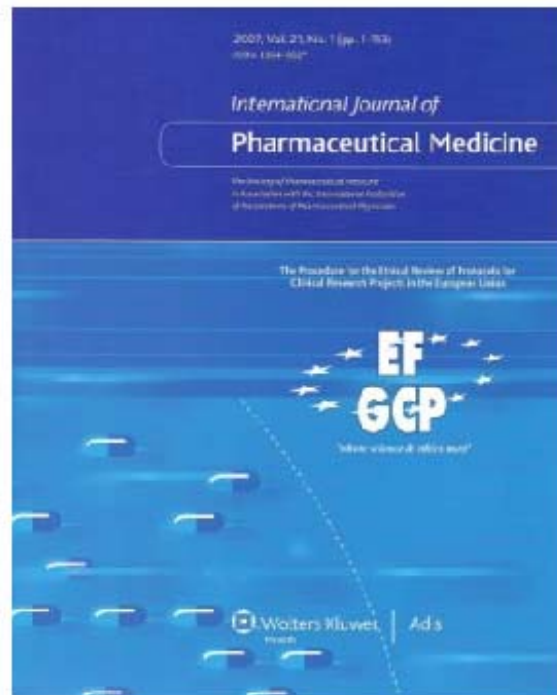
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EFGCP Report on The Procedure for the Ethical Review of Protocols for Clinical Research Projects in the European Union






Every Member State in the European Union has now adopted the EC Directive on Clinical Trials, published in 2001. Based on the principles of Good Clinical Practice, this Directive required Member States to have in place a system of ethical review of research projects that would inspire confidence in the conduct of clinical research throughout Europe. However, sponsors and academic research institutions have had great difficulty in finding out what these systems are, as they are all different. A sub group of the EFGCP Ethics Working Party has tackled the challenge of identifying what over thirty aspects of the ethical review process is for each member state, plus Norway and Switzerland, and has brought this information together in a Report that will be an invaluable reference document for any company, academic department or contract research organisation wishing to conduct clinical research anywhere in Europe.



[Index of the report](#) ▶▶▶



[What they think of the report ...](#)



- CRFocus review, by A. Smith, Editor (vol.18, No 3, March 2007) ▶▶▶
- Pharmaceutical Physician, by Dr. Madhu Devine, Editor (vol.18, No 4, July 2007) ▶▶▶


Index of websites ▶▶▶ 



 Austria ▶▶▶ 



 Bulgaria ▶▶▶ 



 Cyprus ▶▶▶ 



 Denmark ▶▶▶ 



 Finland ▶▶▶ 



 Germany ▶▶▶ 



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 Russia ▶▶▶ 

 Slovakia ▶▶▶ 

 Spain ▶▶▶ 

 Switzerland ▶▶▶ 

 Turkey ▶▶▶ 

Application process

Current application requirements

- CTA application form (Annex 1) - “common module” for CA/EC

plus

- Specific application form for the EC according to national/local requirements
- Supporting documentation

Core documentation

- Covering letter
 - EC application form
 - Annex 1 form (copy)
 - Protocol
 - Investigator Brochure
 - Subject information sheet(s)
 - Consent form(s)
 - List of sites and investigators
 - CV of Chief investigator
 - Evidence of insurance/indemnity
 - *Advertising material**
 - *Subject invitation letter**
 - *Letter to clinician**
 - *Questionnaires**
 - *Patient diary**
 - *Patient card**
- * *if applicable*

Additional documentation?

- Depending on the role of the EC in the Member State, additional documentation may be requested
- E.g. the Investigational Medicinal Product Dossier
- IMPD is not required for ethical review in the UK

Validation

- The 60 day clock starts as soon as a **complete application** has been **received** by the EC
- Any time needed to validate the application and confirm this to the applicant is within the 60 days

Submission arrangements

- Arrangements for booking and submitting applications will vary between Member States
- UK system:
 - Phase 1 trials are booked direct with the EC
 - Other trials are booked via a Central Allocation System
 - Applications must be submitted within 4 days of booking
 - 1 paper copy of application; 6 x protocol; 3 x IB
 - Moving towards **electronic submission** of all documentation

Parallel applications

- Applications to CA and EC may be made in parallel or sequentially, according to the applicant's choice

Integrated Research Application System

www.myresearchproject.org.uk

A graphic element consisting of four overlapping, rounded shapes in light blue, light orange, light green, and purple, arranged in a circular pattern.

IRAS

INTEGRATED RESEARCH
APPLICATION SYSTEM

Aims of IRAS

- Web-based system
- Capture all the information required to apply for relevant permissions and approvals for health research in the UK
- Researchers enter information about their project once
- Use filters to ensure data collected appropriate to the type of study, approvals and permissions required

Applications included in IRAS

- Administration of Radioactive Substances Advisory Committee (ARSAC)
- Gene Therapy Advisory Committee (GTAC)
- MHRA (Devices)
- MHRA (Medicines)
- NHS R&D offices
including NIHR Co-ordinated System for Permissions (CSP)
- National Information Governance Board (NIGB)
- Research Ethics Committees
including Phase 1 RECs established outside the NHS

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including NIHR Co-ordinated System for Permissions (CSP)
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Welcome to the Integrated Research Application System (IRAS)

23 March 2010: IRAS has been updated to version 2.5.1. This update only affects clinical investigations of medical devices that require notification to MHRA. Applicants who have started preparing an application to MHRA Devices but have not yet submitted, are strongly advised to review all of Part B Section 2, PCA1 and PCA2. For full details of the changes please see the [Update page](#) in the Help Section.

Information about all previous updates is available on the Help page. Please check the updates to find out about any changes since you last used IRAS.

The Integrated Research Application System (IRAS):

- Is a single system for applying for the permissions and approvals for health and social care / community care research in the UK
- Enables you to enter the information about your project once instead of duplicating information in separate application forms
- Uses filters to ensure that the data collected and collated is appropriate to the type of study, and consequently the permissions and approvals required
- Helps you to meet regulatory and governance requirements
- Retains familiar aspects of the NRES form system

IRAS captures the information needed for the relevant approvals from the following review bodies:

- Administration of Radioactive Substances Advisory Committee (ARSAC)
- Gene Therapy Advisory Committee (GTAC)
- Medicines and Healthcare products Regulatory Agency (MHRA)
- Ministry of Justice
- NHS / HSC R&D offices
- NRES/ NHS / HSC Research Ethics Committees
- National Information Governance Board (NIGB)
- Social Care Research Ethics Committee

Please Login

If you are a first time user of the Integrated Research Application System please read the information on the [help page](#) before you proceed to login.

Login:

(Your full e-mail address)

Password:

Submit

Reset

Forgotten Password? [Click here](#)

** Passwords are case sensitive.*

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*The Integrated Research Application System uses .pdf files to print. You need to have the free Adobe PDF Reader installed on your computer.
[Click here to download the Adobe Reader](#)*



If you have difficulty installing this software please contact your computer administrator.

3. In which countries of the UK will the research sites be located? *(Tick all that apply)* 

- England
- Scotland
- Wales
- Northern Ireland


3a. In which country of the UK will the lead R&D office be located? 

- England
- Scotland
- Wales
- Northern Ireland


4. Which review bodies are you applying to?

- NHS/HSC Research and Development offices 
- Research Ethics Committee 
- Medicines and Healthcare products Regulatory Agency (MHRA) – Medicines 
- Gene Therapy Advisory Committee (GTAC) 
- National Information Governance Board for Health and Social Care (NIGB) 
- Ministry of Justice (MoJ) 

For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.

5. Will any research sites in this study be NHS organisations? 

- Yes
- No

5a. Do you want your NHS R&D application(s) to be processed through the NIHR Coordinated System for gaining NHS Permission? 

- Yes
- No

If yes, you must complete and submit the NIHR CSP Application Form immediately after completing this project filter, before proceeding with completing and submitting other applications.

Site approvals

- Site approvals are part of the single opinion from the main EC
- “Site-specific assessment” (SSA) = a review of the investigator, supporting staff, facilities, local arrangements, contact points
- Arrangements for SSA will vary between Member States
- May be undertaken by the main Ethics Committee or a local EC
- If undertaken by a local EC, must be undertaken within 60 days for sites listed in initial application, and must **not** be a separate ethical review

Site-specific assessment in the UK

- For **any trial site within the National Health Service (NHS)**, the EC automatically gives approval as part of the opinion, subject to permission from the host organisation before the trial starts at the site (“R&D approval”)
 - **no detailed scrutiny undertaken by the EC**
- For sites outside the NHS, the assessment is undertaken by a local REC for each site and notified to the main EC:
 - within 14 days (Phase 1 trials)
 - within 25 days (other trials)

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 - **within 14 days (Phase 1 trials)**
 - **within 25 days (other trials)**

Initial review of application by main REC

- Review procedures are not defined in the Directive or Commission guidance and vary between Member States
- In the UK, all applications are reviewed initially at a full Committee meeting with a minimum of 7 members, including at least one lay member
- If a “**provisional opinion**” is given with a request for further information, the Chair or a sub-committee may issue the “**final opinion**” following receipt of the information

Attending the REC meeting

- Attending the REC meeting invariably helps to clarify and resolve any concerns
- The Chief Investigator (CI) is always invited to attend REC meetings in the UK
- Sponsor/CRO representative may also attend alongside CI
- All correspondence is copied to both CI and sponsor

Unfavourable opinions

- Arrangements for appeal are a matter for Member States
- Appeals could be reviewed by:
 - a specially appointed panel of the same EC
 - another EC
 - a “national EC”
- Written representations may be permitted
- **Re-submission** of application in modified form may be an alternative to an **appeal** following an unfavourable opinion

Substantial amendments

- Responsibility of the sponsor to determine whether an amendment is substantial; and whether it should be notified to the CA or the EC (or both)
- Amendments are notified to EC using the same form as for the CA (Annex 2)
- Ethics committee must review within 35 calendar days
- If opinion is unfavourable, the amendment may be adapted: in UK, the EC has 14 days to review a “modified amendment”

Safety reporting

- **SUSARs** must be reported in expedited fashion to the EC in the Member State where the event occurred
- *If reports are not sent to ECs in other Member States, Commission guidance recommends a 6 monthly line listing (N.B. guidance is under review)*
- EC must receive **annual safety report** and line listing of all SSARs

Role of the Ethics Committee

Article 6 - required areas of review

- Relevance of trial
- Trial design
- Risks and benefits
- Protocol
- Suitability of the investigator and supporting staff
- Investigator brochure
- Quality of the facilities
- Recruitment procedures
- Subject information
- Consent procedure
- Justification for including minors or adults unable to give informed consent
- Insurance/ indemnity
- Rewards or compensation for investigators and subjects

The EC will normally also review---

- Confidentiality and data protection
- Retention and future uses of tissue samples
- Sub-studies (e.g. genetics)
- Radiation exposure
- Arrangements for notifying other health care professionals
- Criteria for subject withdrawal
- Criteria for early termination
- Data monitoring arrangements
- Exit strategies – continued care of subjects outside trial
- Patient/public involvement in trial design
- Publication/dissemination of results
- Sponsorship arrangements (including legal representative if sponsor based outside EEA)
- Sources of funding

What does the REC not review?

- Role of EC varies between Member States
- Areas where role may differ include:
 - Scientific critique
 - IMP – preclinical and toxicological data
 - Insurance
 - Trial sites
 - Compliance with other legal requirements applying in the MS

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Collaboration between the ethics committees and Competent Authority

Drivers for collaboration

- **GCP Directive 2005/28/EC** requires systems to ensure communication of information between ethics committees and Competent Authority
- Expert Scientific Group Report on the **TGN1412 trial** recommended closer collaboration between MHRA and ethics committees
- European Commission examining roles of EC and CA as part of its **review of the operation of the Directive**

Objectives of collaboration

1. Maintain integrity of ethical review
2. Clarify roles and responsibilities, avoid unnecessary duplication
3. Consistent guidance for researchers
4. Streamline processes – integrated data, parallel review
5. Effective communications between CA and EC

UK Memorandum of Understanding (MoU)

- Version 1 agreed in October 2006:
<http://www.nres.npsa.nhs.uk/applications/guidance/clinical-trials/>
- Version 2 will be published shortly
- Parties to the agreement:
 - Medicines and Healthcare products Regulatory Agency (MHRA)
 - National Research Ethics Service (NRES)
 - Gene Therapy Advisory Committee (GTAC)
 - Appointing Authority for Phase 1 Ethics Committees (AAPEC)

Key provisions of the MoU

- EC may seek advice on safety issues – MHRA will respond within 48 hours
- All EC opinions notified electronically to MHRA via access to national ethics database (for uploading into EudraCT)
- EC should report concerns about safety or non-compliance during a trial to the MHRA
- MHRA notifies regulatory or enforcement action following critical inspection findings or change to safety assessment

Questions welcome

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<http://www.nres.npsa.nhs.uk>