



**GUIDANCE ON THE APPLICATION FOR  
RECOGNISED ETHICS COMMITTEE OPINION AND THE ETHICAL REVIEW  
OF CLINICAL TRIALS ON MEDICINAL PRODUCTS FOR HUMAN USE**

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## **Section 1: Introduction**

### ***1.1 Legal Basis***

Good clinical practice (GCP) is a collection of international ethical and scientific standards for designing, conducting, reporting and recording trials involving human participants. All clinical trials on medicinal products for human use should be carried out in accordance the principles of GCP. Compliance with GCP assures the protection of the rights and safety of research participants, which were established in the Declaration of Helsinki<sup>1</sup>.

On 1<sup>st</sup> May 2004 the Department of Health published the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, (S.I. 190 of 2004), which implemented the EU Clinical Trial Directive on Good Clinical Practice in Clinical Trials (2001/20/EC). The regulations establish procedures relating to the conduct and review of clinical trials on medicinal products for human use and in so doing replace the Control of Clinical Trials Acts, 1987 and 1990 in respect of those trials.

On 12<sup>th</sup> July 2006, the above Regulations were amended by the European Communities (Clinical Trials on Medicinal Products for Human Use) (Amendment No. 2) Regulations 2006 (S.I. No. 374 of 2006). The primary purpose of these Regulations is to implement Commission Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use. Those Regulations also lay down detailed guidelines on the documentation relating to clinical trials, archiving, qualification of inspectors and inspection procedures. A codified copy of these Regulations for working purposes is available on the Department's website<sup>2</sup>.

These guidelines also take account of the Communication from the Commission - Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use. (2011/2 172/01) The functions of the Ethics Committee Supervisory Body currently lie with the Minister for Health and are being undertaken by officials in the Department of Health, supported by any necessary external expertise. The Minister is, therefore, responsible for recognising and monitoring ethics committees.

### ***1.2 Scope***

The aim of this guidance booklet is to assist investigators and Recognised Ethics Committees (RECs) in their work by establishing standard operating procedures for the making of

<sup>1</sup> World Medical Association, *Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Human subjects* (1964; 1975; 1983; 1989; 1996; 2000).

<sup>2</sup> [http://www.dohc.ie/issues/clinical\\_trials\\_2004/6](http://www.dohc.ie/issues/clinical_trials_2004/6)

applications for an ethics committee opinion and the ethical review of clinical trials involving medicinal products for human use.

The guidance considers the documentation necessary to constitute a valid application for ethical review as well as the documentation which should be used by both investigators and ethics committee members throughout the duration and at the end of a clinical trial. The guidance also provides advice, which should facilitate and support the progress of research and the efficient ethical review of research.

### ***1.3 Definitions***

The definitions used in this guidance are those provided in the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004 (S.I. 190 of 2004).

**Clinical trial:** any investigation in human subjects, other than a non-interventional trial, intended –

- (a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more investigational medicinal products, or
- (b) to identify any adverse reactions to one or more such investigational medicinal products, or
- (c) to study absorption, distribution, metabolism and excretion of one or more such investigational medicinal products, or
- (d) to discover, verify, identify or study any combination of the matters referred to at subparagraphs (a), (b), and (c), with the object of ascertaining the safety or efficacy of such products, or both.

**Multi-centre clinical trial:** a clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in a single Member State, in a number of Member States or in a Member State or Member States and a third country or third countries.

**Non-interventional trial:** any study of one or more medicinal products, which have a marketing authorisation, where the following conditions are met–

- (a) the products are prescribed in the usual manner in accordance with the terms of that authorisation,
- (b) the assignment of any patient involved in the study to a particular therapeutic strategy is not decided in advance by a clinical trial protocol but falls within current practice,
- (c) the decision to prescribe a particular medicinal product is clearly separated from the decision to include the patient in the study,
- (d) no diagnostic or monitoring procedures are applied to the patients included in the study, other than those which are ordinarily applied in the course of the particular therapeutic strategy in question, and
- (e) epidemiological methods are to be used for the analysis of the data arising from the study.

**Trial site:** a hospital, nursing home, health centre, surgery or other establishment or facility at or from which a clinical trial, or any part of such a trial, is conducted.

**Board:** the Irish Medicines Board established by section 3 of the Irish Medicines Board Act 1995 (*No. 29 of 1995*).

**Chief Investigator:**

- (a) in the case of a clinical trial conducted at a single trial site, the investigator for that site, or
- (b) in the case of a clinical trial conducted at more than one trial site, the authorised health care professional, whether or not he or she is an investigator at any particular site, who takes primary responsibility for the conduct of the trial.

**Investigator:** the authorised health care professional responsible for the conduct of a clinical trial at a trial site and if a trial is conducted by a team of authorised health care professionals at a trial site, the investigator is the leader responsible for that team.

**Authorised health care professional:** a registered medical practitioner or registered dentist.



**Sponsor:** in relation to a clinical trial, the person who takes on responsibility for the initiation and management (or for arranging the initiation and management) of, and the financing (or arranging the financing) for that clinical trial.

**Investigator-Sponsor:** means, in relation to a clinical trial, a chief investigator who is also acting as the sponsor for that clinical trial.

**Unexpected adverse reaction:** means, in respect of an investigational medicinal product, an adverse reaction, the nature or severity of which is not consistent with the information about that medicinal product as set out:

- (a) in the case of a product which is the subject of a marketing authorisation, in the summary of product characteristics for that product,
- (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the particular clinical trial.

**Serious adverse event or serious adverse reaction:** any adverse event or adverse reaction that at any dose –

- (a) results in death,
- (b) is life-threatening,
- (c) requires hospitalisation or prolongation of existing hospitalisation,
- (d) results in persistent or significant disability or incapacity, or
- (e) consists of a congenital anomaly or birth defect.

## **Section 2: Making an Application for Ethical Review**

### ***2.1 How to make an application***

All applications for the ethical review of a clinical trial must be made using the standard application form (**Form 1**) and standard applicant's checklist (**Form 2**).

The applicant must complete the application form ensuring that all of the various boxes have been filled correctly. The application form must be signed by the Chief Investigator, - i.e. the investigator who takes primary responsibility for the conduct of the clinical trial.

An application for ethical review should be submitted together with all the necessary supporting documents, which are listed in the standard checklist. One copy of each document must to be submitted except where otherwise indicated in the standard checklist.

In accordance with Regulation 12 (4) (a) of the Clinical Trials Regulations the “Chief Investigator’s Declaration” (page 18 of the application form) must be signed by the Chief Investigator and forwarded to the REC (together with the requisite fees) for ethical review. The standard fee for an ethical review involving a single site is €1,150 (i.e. €1000 for the application + €150 for the site). A further fee of €150 is payable for each additional site. The Supervisory Body envisages that these fees will cover most of the administrative costs, which arise during the review of a clinical trial.

The secretary of the REC will write to the Chief Investigator confirming that the application is valid and stating the date on which an ethical decision can be expected.

## ***2.2 Site Specific Assessment***

The EU Directive and the Clinical Trials Regulations, 2004 provide that there should be only one ethical review of a clinical trial per member state, irrespective of how many sites are participating in the study.

The site specific assessment (SSA) form (**Form 3**) must also be completed and submitted with the standard application form and supporting documentation in order for an application to be valid.

In the case of a single-centre clinical trial, the SSA form should be completed and the “Declaration of the Chief Investigator/Investigator” should be signed by the Investigator at that site.

In the case of a multi-centre clinical trial, the SSA form should be completed and signed by the Investigator at each site in Ireland, e.g. if there are six sites to be involved in the clinical trial then there must be six completed SSA forms (i.e. one for each site).

The Investigator at each site in Ireland must forward the SSA form to the Chief Investigator of the clinical trial. The Chief Investigator should submit all of the SSA forms, together with all other supporting documentation. An application for an ethical review will not be valid unless the SSA form for each of the proposed sites has been submitted.

## ***2.3 Seeking Permission from the Site to conduct a clinical trial***

The Investigator at each site is responsible for obtaining permission for the clinical trial to be conducted at his or her specific site from the site CEO or person acting on his or her behalf.

It is the view of the Supervisory Body that the SSA form contains all the necessary information required by the CEO or person acting on his/her behalf to decide whether to give permission for the clinical trial to be conducted at the site.

The CEO or person acting on his/her behalf is only being asked to decide whether the site has sufficient facilities, personnel and resources to conduct the particular clinical trial at the site.

Where aspects of the clinical trial conflict with the particular ethos of the site, the CEO or person acting on his/her behalf cannot request any changes be made to the clinical trial. He or she can only grant or refuse permission for the clinical trial to take place at that site.

If the CEO or person acting on his/her behalf is satisfied that the site is in a position to conduct the clinical trial then he or she should sign the “Declaration of CEO or person acting on behalf of CEO” and return it to the site Investigator (Chief Investigator in the case of a single-centre clinical trial). In the case of a multi-centre clinical trial, each site Investigator must forward the SSA form signed by the CEO or a person acting on his/her behalf to the Chief Investigator who must then forward them to the REC for its file.

A clinical trial cannot commence at a site until the CEO or a responsible person acting on his/her behalf at that site, signs the “Declaration of CEO/ person acting on behalf of CEO” at the end of the SSA form. This is the case irrespective of whether the REC gives a favourable opinion on the trial for that site.

The timelines set out in the Clinical Trial Regulations do not extend to the CEO or to the person acting on his/her behalf and the REC does not need the SSA Form (**Form 3**) with the box entitled “Declaration of CEO/ person acting on behalf of CEO” completed, in order for an application for ethical review to be validated. However, in keeping with the spirit of the Directive and the Regulations, CEOs and persons acting on their behalf, are strongly urged to make a decision and to complete the SSA form as early as possible.

#### ***2.4 Validation of Applications for Ethical Review***

Once an application has been validated, the secretary of the REC will send a letter confirming receipt of the valid application to the Chief Investigator. The letter will state the date on

which the application was validated and an indication of the date on which a decision can be expected.

Where an application is deemed to be invalid, the secretary of the REC will inform the Chief Investigator of this fact. The letter will give the reasons for non-acceptance and invite the Chief Investigator to forward any outstanding documentation to the REC.

## **Section 3: The Review Process**

### ***3.1 Specified Time Periods***

In general the specified time period available for ethical review is normally 60 days

However, in the case of a clinical trial involving a medicinal product for gene therapy or somatic cell therapy or a medicinal product containing a genetically modified organism, the specified time period for ethical review is 90 days. In such cases, where the REC requires external expert advice the time period will be extended to 180 days.

### ***3.2 Request for External Expert Advice***

A REC may seek the advice of an external expert on any aspect of an application for a clinical trial involving a medicinal product, which lies beyond the expertise of its members.

The secretary of the REC should send a letter to the external expert listing the specific points on which advice is sought. The letter will clearly state that the REC is obliged to give an opinion on the application within a specified period and will request that the external expert respond by a particular date.

The clock for ethical review will not be suspended when seeking external expert advice. All external experts should be asked to declare any interest(s) they may have in relation to the clinical trial concerned.

### ***3.3 Request for further Information***

In order to prepare its opinion, the REC may request that the Chief Investigator submit further information. In such cases the secretary of the REC will send a letter to the Chief Investigator listing the points which need to be addressed. The clock for ethical review will stop. The letter will clearly state the date of suspension of ethical review and note that the review will recommence upon receipt of the requested information.

If the further information received is deemed unsatisfactory, then the REC may write to the Chief Investigator asking for a more complete response to the request for further information, listing the points needing further clarification.

Once any further information concerning the proposed clinical trial has been received, the secretary of the REC must send a letter of receipt to the Chief Investigator. This letter will

inform the Chief Investigator that the time period for ethical review has recommenced and indicate the new date on which a decision can be expected.

### **3.4 *Preparing an Ethical Opinion***

In accordance with Article 13 (6) of the Clinical Trial Regulations, 2004, when a REC is reviewing clinical trial applications it must consider the following:

- (a) The relevance and design of the clinical trial being proposed;
- (b) Whether the evaluation of the anticipated benefits and risks is satisfactory and whether the conclusions drawn are justified;
- (c) The clinical trial protocol;
- (d) The suitability of the investigator and supporting staff;
- (e) The investigators brochure;
- (f) The quality and adequacy of the facilities for the trial;
- (g) The adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent to participation in the trial;
- (h) Whether the research, if it includes persons who because they are minors are incapable of giving informed consent, is justified;
- (i) Whether the research, if it includes adult persons who because they are incapacitated incapable of giving informed consent, is justified;
- (j) The arrangements for the recruitment of subjects;
- (k) The provision made for indemnity or compensation in the event of injury or death attributable to the clinical trial;
- (l) The provision made for insurance or indemnity to cover the liability of the investigator and sponsor;

- (m) The amounts and where appropriate the arrangements for rewarding or compensating investigators and trial subjects;
- (n) The terms of any agreement between the sponsor and the owner or occupier of the trial site which are relevant to the arrangements referred to in subparagraph (m).

### **3.5 *Giving an Ethical Opinion***

When reviewing an application for a clinical trial, a REC may form any of the following:

- (a) Favourable opinion, allowing a Chief Investigator to conduct the clinical trial as outlined in the research protocol.
- (b) Favourable opinion subject to conditions, allowing a Chief Investigator to commence the clinical trial subject to revisions being made to the protocol or answers given to questions posed by the REC.
- (c) Unfavourable opinion, meaning the trial may not go ahead.

The secretary of the REC must inform the Chief Investigator of the outcome of an ethical review within 5 working days of a meeting being held.

Where a REC gives a favourable opinion which is subject to conditions, a list of those conditions must be enclosed with the letter informing the Chief Investigator of the outcome of the review. The Chief Investigator will address the conditions and forward any outstanding documentation to the REC.

In situations where a REC gives an unfavourable opinion for a clinical trial the confirmation letter must state clearly the reasons for rejecting the application.

Where a REC gives a favourable opinion for a multi-centre clinical trial, the letter from the secretary of the REC should include a list of all the sites in Ireland for which a favourable opinion has been given.

The Chief Investigator is responsible for informing the clinical trial Sponsor and the investigator at each site in Ireland of the outcome of the review.

## **Section 4: Substantial Amendments to Clinical Trials given a Favourable Opinion**

### ***4.1 Application for a Substantial Amendment***

Once a clinical trial has begun, a trial Sponsor may wish to make amendments to the protocol. A Sponsor may make an amendment to a clinical trial protocol, other than a substantial amendment, at any time.

However, if a Sponsor wishes to make an amendment, which has the potential to impact on the safety of the clinical trial participants or alter the interpretation of the supporting documentation, then he or she must complete and sign the substantial amendment application form (**Form 4**). The Sponsor must submit the form together with all the necessary supporting documentation, including revised numbers and dates which are listed in the checklist at the end of the form.

The standard substantial amendment application form can be used for both new amendments and modified amendments. The Sponsor should mark clearly which type of amendment being applied for by ticking the appropriate box in section A.2 on the form.

### ***4.2 Validating an Application for a Substantial Amendment***

Once an application for a substantial amendment has been validated, the secretary of the REC will send a letter confirming receipt of the valid application to the Sponsor. This letter will state the date on which the application for a substantial amendment was validated and an indication of the date on which a decision can be expected.

Where an application for a substantial amendment is deemed invalid, the secretary of the REC will inform the Sponsor of this fact. The letter should cite the reasons for non-acceptance and invite the Sponsor to forward any outstanding documentation to the REC.

### ***4.3 Review of an Application for a Substantial Amendment***

When reviewing an application for a substantial amendment (either new or modified) for a clinical trial, a REC may form any of the following:



- (a) Favourable opinion, - allowing the Sponsor to implement the substantial amendment as outlined in the notification.
- (b) Favourable opinion subject to conditions, - allowing the Sponsor to implement the substantial amendment subject to revisions being made to the notification or answers to questions posed by the REC.
- (c) Unfavourable opinion, - meaning the substantial amendment cannot be implemented.

The secretary of the REC will inform the Sponsor of the outcome of an ethical review of a substantial amendment within 5 working days of a meeting being held and within 35 days of the notification being validated. In the case of a modified substantial amendment, the REC must provide the Sponsor with an ethical opinion within 14 days of validation.

Where a REC gives a favourable opinion, which is subject to conditions, a list of those conditions must be enclosed with the letter informing the Sponsor of the outcome of the review.

In situations where a REC gives an unfavourable opinion for a substantial amendment, the confirmation letter must state clearly the reasons for rejecting the notification.

A sponsor may modify a substantial amendment in order to address the concerns posed by the REC in its unfavourable opinion of a substantial amendment. If a Sponsor wishes to do this s/he must submit an application for a modified substantial amendment no later than 30 days after receiving the RECs concerns and no later than 14 days before the modified amendment is due to be implemented.

Where a Sponsor's modified substantial amendments are rejected, the amendments may not be made and the clinical trial must continue in accordance with the documentation as previously approved.

In the case of these applications, the Sponsor is responsible for informing the Chief Investigator and, in the case of multi-centre clinical trials, the investigator at each site in Ireland, of the outcome of the review.

#### **4.4     *Urgent Safety Measures***

The Investigator or Sponsor may at any time implement urgent safety measures in order to protect research participants against immediate risks to their health or safety. Urgent Safety Measures do not require REC approval before they can be implemented. If such measures are implemented, the Sponsor must inform the REC, in writing, no later than three days after implementation and explain the circumstances, which led to that implementation.

## **Section 5: Monitoring the Safety of Clinical Trials**

### ***5.1 Expedited Safety Reports on Adverse Reactions***

It is the principal obligation of the Sponsor to monitor the ongoing safety of a clinical trial, for which he or she is responsible. A Sponsor must ensure that data on suspected unexpected serious adverse reactions (**SUSARs**) occurring in the *concerned* clinical trial at any site in Ireland and which are fatal or life-threatening are reported, in writing, to the REC as soon as possible and no later than seven days after first becoming aware of them. Within eight days of filing this initial report, the Sponsor must, where necessary, send any additional information to the REC.

In the case of SUSARs occurring in the *concerned* clinical trial at any site in **Ireland** and which are not fatal or life-threatening, the Sponsor must report them, in writing, to the REC as soon as possible and no later than 15 days after first becoming aware of them.

There is no standard format for submitting expedited reports. However, Sponsors are expected to include the REC reference number on all documentation related to the report, which should then be posted to the REC.

### ***5.2 Review of Expedited Safety Reports on Adverse Events***

Expedited safety reports, and any further information relating to them, should be acknowledged in writing and filed by the secretary of the REC.

RECs do not have access to the Eudravigilance database nor do they have sufficient resources or expertise to analyse the safety data contained therein. Therefore the responsibility of RECs in this context is inevitably limited. RECs are, however, responsible for ensuring that the consent of research participants remains valid and based on accurate and up-to-date information on the risks and benefits associated with the clinical trial.

### **5.3 Submission of Annual Safety Reports**

As well as expedited reports, the Sponsor should provide the REC with an annual safety report on the concerned clinical trial.

Annual safety reports should be submitted to the REC using the standard safety report cover form (**Form 5**). The annual reports will consist of line listings which must be accompanied by an analysis of safety information related to the concerned clinical trial, highlighting the main points for ethical consideration i.e. changes to the benefit-to-risk ratio or validity of research participant's consent.

These reports must include line listings of SUSARs occurring in the *concerned* clinical trial **worldwide**. The line listings must be accompanied by an analysis of the safety information relating to the concerned clinical trial, highlighting the main points for ethical consideration i.e. changes to the benefit-to-risk ratio or validity of research participant's consent.

### **5.4 Review of annual safety reports**

Annual safety reports must be reviewed by at least the Chair of the REC and, where necessary, an expert adviser e.g. a clinical pharmacologist, a pharmacist or a specialist in the concerned disease.

Annual reports should be reviewed in order to:

- (a) Assess the continued safety of the concerned clinical trial,
- (b) Assess the accuracy of the benefit-to-risk ratio analysis contained in the protocol,
- (c) Consider the need for new research participant information and renewal of consent.

Where a REC has concerns about any of the above, the REC Chair should express these in writing to the trial Sponsor. The Chair may request further information from the Sponsor and, where deemed necessary require the Sponsor to address the issues of concern.

The Sponsor should respond to these requests as soon as possible and confirm to the REC that its concerns have been addressed adequately.

## **Section 6: The End of a Clinical Trial**

### ***6.1 Conclusion of a clinical trial***

The sponsor must inform the REC of the end of the a clinical trial within 90 days of its conclusion (i.e. last person last visit), using the standard declaration of the end of a clinical trial form (**Form 6**).

The declaration of the end of a clinical trial form applies to both the normal conclusion and premature termination (i.e. before the date specified in the protocol) of the concerned clinical trial. The sponsor should clearly indicate the circumstances for the ending of the clinical trial by ticking the appropriate box in (section C) of the form.

In the case of a clinical trial being prematurely terminated, the Sponsor must send the declaration form to the REC within 15 days of the trial being terminated, and should state clearly the reasons for the termination.

### ***6.2 Final research report***

The Sponsor must provide the REC with a final research report within 12 months of the concerned clinical trial being completed (i.e. last person last visit) or terminated. The standard final research report cover form, should be submitted together with the full report.

The final research report should be acknowledged in writing and filed by the secretary of the REC.

## **Section 7: Transitional Arrangements**

The transitional arrangements that provide for the continuation of clinical trials granted permissions by the Irish Medicines Board (IMB Permissions) before 1<sup>st</sup> May 2004 will cease to have effect on 1<sup>st</sup> May 2006. It is therefore necessary for Sponsors to arrange for applications to be made to the Board and to a REC, under the Clinical Trials Regulations, 2004. For applications to RECs, the necessary standard application form and documentation should be used. The RECs will respond using the standard letters (see appendix 2). It is also recommended that Sponsors should ensure that early applications are made to the Irish Medicines Board and to the RECs well in advance of the cessation of the transitional arrangements in order to avoid suspension of the clinical trials.

In the case of a single-centre or a multi-centre clinical trial where the REC(s), which gave the original approval for the clinical trial, has/have not been recognised under the Clinical Trials Regulations, 2004 a new single application to a REC should be made and submitted in the normal manner.

In the transitional arrangements, it is the responsibility of the Chief Investigator to submit the new application to a REC. Where in the case of some multi-centre clinical trials, there may be no Chief Investigator, a Chief Investigator should be nominated by the Sponsor and given the responsibility for submitting the application.

The Sponsor should immediately transfer hard copies of all safety reports, and any other relevant documentation deemed necessary for the review of the clinical trial, to the REC concerned.

Where a REC has given an opinion for one of these clinical trials, the local ethics committee, which had given the original approval for the clinical trial, ceases to be responsible for the monitoring of the trial concerned. In those circumstances, it should arrange for the orderly transfer of that responsibility to the relevant REC.

In the case of a single-centre or a multi-centre clinical trial, where the ethics committee which gave the original approval for the clinical trial, has been recognised as a REC under the Clinical Trials Regulations, 2004, a new application will have to be made if the trial is to continue after 1<sup>st</sup> May 2006.

In the case of a single-centre clinical trial, the Chief Investigator should make this application to the newly appointed REC, which in this situation had given the original approval.

In the case of a multi-centre clinical trial, where two or more of the ethics committees which had given the original approval have been recognised as RECs, the Chief Investigator should decide which of those RECs the application should be made to. Where there is no Chief Investigator, the Sponsor should nominate one of the investigators as the Chief Investigator who will then become responsible for submitting the application to one of the RECs for ethical review.

With effect from 1<sup>st</sup> May 2006, any local ethics committee which may have given its approval originally for a clinical trial and which has not been recognised as a REC by the Supervisory Body, should cease to monitor the clinical trial concerned as it is no longer legally entitled to do so.

The same situation would apply in the case of those local ethics committees, that have been recognised as RECs by the Supervisory Body, and which have been monitoring clinical trials on the basis of IMB Permissions granted before the 1 May 2004.

In all cases where approval has been granted by a REC under the Clinical Trials Regulations 2004, all Local ethics committees having responsibility for monitoring the trial should be informed by the Chief Investigator (or by the sponsor) of the new situation and arrangements made for the orderly transfer of responsibility for the monitoring of the trials concerned to the relevant REC.

## **Section 8: Retention of documents by RECs**

RECs are required to retain the essential documents relating to a clinical trial for at least three years after the completion of the trial.

## **Section 9: Requirement for REC to submit an Annual Report**

Under the Regulations, RECs are required to submit an annual report to the Supervisory Body, to its Appointing Authority and to the Irish Medicines Board, within six months from the end of each calendar year (i.e. 31<sup>st</sup> December). In these reports, details should be provided on all applications received by the REC during the calendar year concerned and on the associated decisions that were made.

## **Appendix 1:**

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- Form 2: Applicant's Checklist.
- Form 3: Site Specific Assessment
- Form 4: Application for a Recognised Ethics Committee (REC) Opinion on a Substantial Amendment to a Clinical Trial on a Medicinal Product for Human Use (including Modified Substantial Amendments).
- Form 5: Cover Form for Annual Safety Reports to the Recognised Ethics Committee on a Clinical Trial on a Medicinal Product for Human Use.
- Form 6: Declaration of the End of a Clinical Trial on a Medicinal Product for Human Use to the Recognised Ethics Committee (REC) (including Premature Termination).

## APPLICATION FORM

### **Application for a Recognised Research Ethics Committee (REC) Opinion on a Clinical Trial on a Medicinal Product for Human Use.**

This application form should be completed and submitted by the Chief Investigator (the person who takes primary responsibility for the conduct of the clinical trial). It should be filled out in language comprehensible to a lay person.

#### A. TRIAL IDENTIFICATION

<b>A.1</b>	
EudraCT No.	
Title of Clinical Trial	
Submission Date	

<b>A.2 Trial Duration</b>			
Proposed Start Date	<i>(first person first visit)</i>		dd/mm/yyyy
Proposed End Date	<i>(last person last visit)</i>		dd/mm/yyyy
Expected Duration	<i>(years / months)</i>	Years	Months

#### B. APPLICANT IDENTIFICATION

<b>B.1 Chief Investigator</b>	
Name:	
Title:	
Position:	
Qualifications:	
Address:	
Tel:	
Fax:	
E-mail:	
<i>(Please submit a 2 page CV for the Chief Investigator)</i>	

<b>B.2 Sponsor</b>	
Name:	
Status of Sponsor:	
Commercial:	Non-Commercial
Address:	
Tel:	
Fax:	
E-mail:	

#### C. DETAILS OF THE CLINICAL TRIAL

<b>C.1</b>	
Has this or a similar application been previously submitted for review to this or any other Ethics Committee in the Republic of Ireland?	<input type="checkbox"/> Yes <input type="checkbox"/> No
<i>If yes, please give details</i>	

<b>C.2 Multi Centre Clinical Trials</b>	
Is this trial a Multi-Centre Trial?	<input type="checkbox"/> Yes <input type="checkbox"/> No
<i>If Yes, please submit a list of all proposed sites in Ireland and proposed Investigators including contact no./e-mail.</i>	

Does this trial involve third countries?	<input type="checkbox"/> Yes <input type="checkbox"/> No
--	--



Have you received permission from each of the above sites in Ireland to conduct this trial?	<input type="checkbox"/> Yes <input type="checkbox"/> No
---	--

(Please note that a site specific assessment for each site in Ireland must be submitted before the committee can validate an application for ethical review.)

<b>C.3</b>
Please name the substance/medical device, which you propose to administer during the clinical trial. <i>(Please include details of all medicinal products including placebo.)</i>
<input type="text"/>

If the clinical trial does not involve Somatic Cell Therapy, Gene Therapy or Genetically Modified Cells please skip to C. 6.

<b>C.4 Somatic Cell Therapy</b>
If the clinical trial involves Somatic Cell Therapy (no genetic modification) please specify the origin of cells:
Autologous <input type="checkbox"/> Yes <input type="checkbox"/> No
Allogeneic <input type="checkbox"/> Yes <input type="checkbox"/> No
Xenogeneic <input type="checkbox"/> Yes <input type="checkbox"/> No
If <i>xenogeneic</i> , please specify the species of origin <input type="text"/>

<b>C.5 Gene Therapy or Genetically Modified Cells</b>
<b>C.5.1</b>
If the clinical trial involves <b>Gene Therapy</b> please specify the gene(s) of interest.
<input type="text"/>

<b>C.5.2</b>
Please specify the type of gene therapy involved.
<i>In vivo</i> gene therapy <input type="checkbox"/> Yes <input type="checkbox"/> No
<i>Ex vivo</i> gene therapy <input type="checkbox"/> Yes <input type="checkbox"/> No

<b>C.5.3</b>
Please specify the gene transfer product that will be used.
<b>Nucleic acid (e.g. plasmid)</b> <input type="checkbox"/> Yes <input type="checkbox"/> No
If Yes, please specify: <input type="checkbox"/> Naked <input type="checkbox"/> Complexed
<b>Viral Vector</b> <input type="checkbox"/> Yes <input type="checkbox"/> No
If Yes, please specify the type (e.g. adenovirus): <input type="text"/>
<b>Others</b> <input type="checkbox"/> Yes <input type="checkbox"/> No
If Yes, please specify: <input type="text"/>

<b>C.5.4</b>
If the clinical trial involves Genetically Modified Cells please specify their origin.
Autologous <input type="checkbox"/> Yes <input type="checkbox"/> No
Allogeneic <input type="checkbox"/> Yes <input type="checkbox"/> No
Xenogeneic <input type="checkbox"/> Yes <input type="checkbox"/> No
If <i>xenogeneic</i> , please specify the species of origin <input type="text"/>

<b>C.5.5</b>
Please specify the type of genetically modified cells (e.g. hematopoietic stem cells).
<input type="text"/>

<b>C.6</b>
Please specify the primary research question/objective.
<input type="text"/>

--

<b>C.7</b>
Please specify the secondary research questions/objectives.

<b>C.8</b>
What is the scientific justification for the clinical trial?

<b>C.9</b>
Give a brief description of the methods and design of the proposed clinical trial e.g. randomised, controlled. This should also include details of the duration of research participant involvement and exactly what procedures they will undergo.

<b>C.10</b>
Will treatment be withheld from research participants as a result of taking part in the clinical trial? <input type="checkbox"/> Yes <input type="checkbox"/> No
<i>If Yes, please give details</i>

<b>C.11</b>
What are the potential adverse effects, risks or hazards for research participants either from giving or withholding medications, devices, ionising radiation, or from other interventions, which may cause inconvenience or changes to lifestyle?

<b>C.12</b>
What are the potential benefits for research participants?

<b>C.13</b>
What procedures are in place to monitor the health of the research participants during the trial or when they are no longer involved in the trial?

#### D. DETAILS OF TRIAL PARTICIPANTS

<b>D.1</b>
How many research participants and controls are expected to participate at each site in Ireland?

<b>D.2</b>
How will research participants/controls be identified and recruited?
<i>(If recruitment includes advertisements or written correspondence please provide copies and/or TV/radio scripts and letters.)</i>

<b>D.3</b>
What are the inclusion criteria?

<b>D.4</b>
What are the exclusion criteria?

<b>D.5</b>
What criteria exist for withdrawing research participants prematurely? <input type="text"/>

<b>D.6</b>	
Will the participants be from any of the following groups? ( <i>tick as appropriate</i> )	
Children under 16 <input type="checkbox"/>	Adults with learning disabilities <input type="checkbox"/>
Adults who are unconscious <input type="checkbox"/>	Adults who have a terminal illness <input type="checkbox"/>
Adults in emergency situations <input type="checkbox"/>	Adults with mental illness <input type="checkbox"/>
Pregnant women / women of child bearing age <input type="checkbox"/>	Prisoners <input type="checkbox"/>
Adults suffering from dementia <input type="checkbox"/>	Health volunteers <input type="checkbox"/>
Those who could be considered to be vulnerable or have a particularly dependent relationship with the investigator, e.g. those in care homes, medical students. <input type="checkbox"/>	
Please justify their inclusion, outlining how the trial is expected to benefit research participants. <input type="text"/>	

**(NB. Parts 4 and 5 of Schedule 1 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 clearly outline the conditions and principles which apply in relation to the treatment of Minors or Incapacitated Adults who are participants in medical research.)**

<b>D.7</b>
Will research participants be reimbursed for expenses? <input type="checkbox"/> Yes <input type="checkbox"/> No
If Yes, please clarify <input type="text"/>

<b>D.8</b>
Will they receive any incentives for taking part in the clinical trial? <input type="checkbox"/> Yes <input type="checkbox"/> No
If Yes, please clarify <input type="text"/>

<b>D.9</b>
Will the participant's general practitioner be notified of his or her participation in the trial? <input type="checkbox"/> Yes <input type="checkbox"/> No
If No, please clarify <input type="text"/>

**E. INFORMED CONSENT**

<b>E.1</b>
Will written informed consent be obtained <input type="checkbox"/> Yes <input type="checkbox"/> No
If Yes, who will be responsible for obtaining (qualifications and experience)? <input type="text"/>
If No, please justify. <input type="text"/>


<b>E.2</b>
Give details of the manner in which consent will be obtained. <b>Please attach copies of both the Information leaflet and Consent form.</b>


<b>E.3</b>
What arrangements have been made for research participants who might not adequately understand verbal or written information? <input type="text"/>


**F. CONFIDENTIALITY**


**NB. Investigators should be aware of their responsibilities as provided for in the Data Protection Acts 1998 and 2003.**

<b>F.1</b>	
Does the proposed clinical trial involve the retention of biological material (tissue, bodily fluids) or data derived from them?	<input type="checkbox"/> Yes <input type="checkbox"/> No
If Yes, for what period of time will the biological material and/or data be retained?	


<b>F.2</b>
How will data security be maintained?


<b>F.3</b>
Who will have access to the biological material and/or data?


<b>F.4</b>
If biological material and/or data are to be disposed of please explain how and by whom this will be done?


<b>F.5</b>
How will the results of the clinical trial be reported and disseminated (e.g. peer-reviewed journal, research participants)?


**G. FINANCIAL ARRANGEMENTS**

<b>G.1</b>
What arrangements have been made for compensation in the event of a claim made by or on behalf of a participant?


<b>G.2</b>	
Is indemnity in place for the conduct of this clinical trial?	<input type="checkbox"/> Yes <input type="checkbox"/> No
<i>If yes, please submit a copy to the REC.</i>	

<b>G.3</b>	
Has funding for the clinical trial been secured?	<input type="checkbox"/> Yes <input type="checkbox"/> No
If Yes, give details of funding organisation(s) and amount secured and duration:	
Organisation:	
Contact name:	
Address:	
Tel:	
Fax:	
E-mail:	
Amount:	
If No, what arrangements have been made to cover the cost of the research?	

<b>G.4</b>	
Does the Chief Investigator or any of the investigators have any direct/indirect involvement in the outcome of the clinical trial that could in anyway be regarded as a possible conflict of interest?	<input type="checkbox"/> Yes <input type="checkbox"/> No
If Yes, please explain.	

<p><b>Declaration of the Chief Investigator</b></p> <p><b><i>This declaration must be signed and sent to the REC together with the requisite fee before the application will be considered as valid.</i></b></p> <ul style="list-style-type: none"> <li>• I certify that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.</li> <li>• I undertake to abide by the ethical principles outlined in the Declaration of Helsinki, and my obligations as set out in the International Conference on Harmonisation's Good Clinical Practice Guidelines (ICH GCP) and the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004 (S.I. No 190 of 2004).</li> <li>• If the clinical trial is approved I undertake to adhere to the study protocol and to comply with any conditions set out in the letter of approval sent by the Recognised Ethics Committee.</li> <li>• I am aware of my responsibility to be up to date and comply with the requirements of the law relating to security and confidentiality of patient or other personal data.</li> </ul> <p><b>Signature:</b> _____</p> <p><b>Print Name:</b> _____</p> <p><b>Date:</b> _____ (dd/mm/yyyy)</p>
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## APPLICANT'S CHECKLIST

<b>REC ref. No:</b>		<b>EudraCT No:</b>	
<b>Title of Clinical Trial:</b>			
<b>CI Name:</b>			
<b>Sponsor:</b>			

**Please complete this checklist and submit it with your application.**

- *Submit a copy of each document*
- *All accompanying documents must bear version numbers and dates (except where shaded)*
- *Delete 'yes / no' as applicable*

ID	Document	Enclosed? D	ate	Version	Office Use
<b>AC.1</b>	Application Form	Mandatory			
<b>AC.2</b>	Clinical Trial Protocol	Mandatory			
<b>AC.3</b>	Summary C.V. for Chief Investigator	Mandatory			
<b>AC.4</b>	Research participant information sheet	Mandatory			
<b>AC.5</b>	Research participant consent form	Mandatory			
<b>AC.6</b>	Evidence of insurance or indemnity	Mandatory			
<b>AC.7</b>	Covering letter on headed paper	<input type="checkbox"/> Yes <input type="checkbox"/> No			
<b>AC.8</b>	Site Specific Assessment Form for each proposed site	<input type="checkbox"/> Yes <input type="checkbox"/> No			
<b>AC.9</b>	Investigator's brochure	<input type="checkbox"/> Yes <input type="checkbox"/> No			
<b>AC.10</b>	Letter of Invitation for participant	<input type="checkbox"/> Yes <input type="checkbox"/> No			
<b>AC.11</b>	Summary, synopsis or diagram (flowchart) of protocol in non-technical language	<input type="checkbox"/> Yes <input type="checkbox"/> No			
<b>AC.12</b>	Details of any Data Monitoring Committee	<input type="checkbox"/> Yes <input type="checkbox"/> No			
<b>AC.13</b>	Sample diary card/patient card	<input type="checkbox"/> Yes <input type="checkbox"/> No			
<b>AC.14</b>	Validated questionnaire	<input type="checkbox"/> Yes <input type="checkbox"/> No			
<b>AC.15</b>	Non-validation questionnaire	<input type="checkbox"/> Yes <input type="checkbox"/> No			
<b>AC.16</b>	Copies of advertisement material for research participants, e.g. posters, newspaper adverts, website. For video or audio cassettes, please also provide the printed script.	<input type="checkbox"/> Yes <input type="checkbox"/> No			

## SITE SPECIFIC ASSESSMENT (SSA)

**Notes:** (1) This form should be completed by the Investigator at each site in Ireland. In the case of a multi-centre clinical trial, the Site Specific Assessment form for each site must be submitted to the Recognised Ethics Committee (REC) by the Chief Investigator for his or her application to be valid.

(2) Before a clinical trial can commence at a site, the CEO or person acting on his/her behalf at that site must have signed the declaration at the end of this form.

A.1 Trial and Site Identification	
EudraCT No.:	
Title of clinical trial:	
REC reference no:	
Submission date:	
Name of site:	

A.2 Who is the Investigator for the research study at this site?	
Name:	
Title:	
Address:	
Tel:	
Fax:	
E-mail:	

A.3 Outline the qualifications and experience of investigators relevant to the current clinical trial.	

A.4 Provide details of other named investigators on the local research team.	
Name:	
Title:	
Position:	
Qualification:	
Role in the research team:	

Name:	
Title:	
Position:	
Qualification:	
Role in the research team:	

Name:	
Title:	
Position:	
Qualification:	
Role in the research team:	

**A.5** Give a brief description of the recruitment of subjects, inclusion and exclusion criteria and the trial methods and design of the proposed research e.g. randomised, controlled. This should also include details of the duration of research participant involvement and exactly what procedures they will undergo.

**A.6** Is indemnity in place for the conduct of this clinical trial at this site?  Yes  No

If yes it is the responsibility of the Investigator to make a copy of the indemnification available to the CEO/ person acting on behalf of CEO.

**A.7** Please outline the facilities and other departments that will be used for the purpose of conducting this clinical trial (e.g. laboratories, radiology, pharmacy etc.).



## SITE SPECIFIC ASSESSMENT (SSA)

### Declaration of Principal Investigator<sup>2</sup> at Site

*This declaration must be signed and submitted to the REC before the main application will be considered valid*

- I am satisfied as to my suitability as principal investigator for the conduct of the research at this site and in respect of the supporting staff available to undertake the research at the site.
- I am satisfied that the facilities at this site are of such quality and adequacy as to conduct the research at this site
- I certify that the information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

**Signature:** \_\_\_\_\_

**Print Name:** \_\_\_\_\_

**Date:** \_\_\_\_\_ (dd/mm/yyyy)

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<sup>2</sup> Where the clinical trial is to be conducted only at a single site, the Principal Investigator is the Chief Investigator.

## SITE SPECIFIC ASSESSMENT (SSA)

### ***Declaration of CEO/ person acting on behalf of CEO***

It is not necessary for this declaration to be submitted to the REC for the main application to be considered valid. However the clinical trial cannot commence at the site until the declaration is signed.

**I hereby declare that, having regard to the information contained in this form, I am satisfied that the clinical trial may be carried out at this site.**

**Signature:** \_\_\_\_\_

**Print Name:** \_\_\_\_\_

**Date:** \_\_\_\_\_ (dd/mm/yyyy)

**Application for a Recognised Ethics Committee (REC) Opinion on a Substantial Amendment to a Clinical Trial on a Medicinal Product for Human Use.**

(This application form should be completed by the Sponsor and submitted via the central allocation system. It should be filled out in language comprehensible to a lay person.)

**A. TRIAL IDENTIFICATION**

<b>A.1</b>	
EudraCT no.:	
Title of clinical trial:	
REC reference no:	
Amendment no:	
Submission date:	

<b>A.2 Please indicate whether this is: (tick as appropriate)</b>	
An application for a substantial amendment	<input type="checkbox"/>
A modified application for a substantial amendment	<input type="checkbox"/>

**B. APPLICANT IDENTIFICATION**

<b>B.1 Sponsor</b>	
Name:	
Organisation:	
Address:	
Tel:	
Fax:	
E-mail:	

**C. AMENDMENT IDENTIFICATION**

<b>C.1 Amendment to Protocol</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<i>(If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.)</i>	

<b>C.2 Amendment to initial request for an ethical opinion</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<i>If yes, please refer to relevant sections of the main application form.</i>	

<b>C.3 Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the clinical trial</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<i>If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.</i>	

<b>C.4 Other</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<i>If Yes, please specify</i>	

**D. DETAILS OF AMENDMENT**

**D.1 Give a description of the amendments being proposed including the reasons for making such amendments**

<b>D.2 Checklist of Documents to be submitted with this application form</b> <i>(Tick as appropriate)</i>	
<ul style="list-style-type: none"> <li>Covering Letter on Headed paper, including list of modified documentation with new version numbers and dates.</li> </ul>	<input type="checkbox"/>
<ul style="list-style-type: none"> <li>Revised Protocol with new version number and date with amended data highlighted</li> </ul>	<input type="checkbox"/>
<ul style="list-style-type: none"> <li>Revised information sheets and consent forms with new version number and dates and amended data highlighted</li> </ul>	<input type="checkbox"/>
<ul style="list-style-type: none"> <li>Other supporting documentation</li> </ul>	<input type="checkbox"/>

### DECLARATION OF SPONSOR

*This declaration should be signed before the application will be considered valid by the REC.*

- I confirm that the information contained in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment to be implemented.
- I undertake to abide by the ethical principles outlined in the Declaration of Helsinki, and the International Conference on Harmonisation's Good Clinical Practice Guidelines (ICH GCP) and the European Communities (Clinical Trials on Medicinal Products for Human Use) regulations, 2004 (S.I. No 190 of 2004).

**Signature of Sponsor:** \_\_\_\_\_

**Print Name:** \_\_\_\_\_

**Date of submission:** \_\_\_\_\_ (dd/mm/yyyy)

**Cover Form for a Safety Report to the Research Ethics Committee on a Clinical Trial on a Medicinal Product for Human Use.**

This cover form should be completed by the Sponsor and should be submitted with any safety reports.

<b>A. TRIAL IDENTIFICATION</b>	
<b>EudracCT No.:</b>	
<b>Title of clinical trial:</b>	
<b>Trial Reference No.:</b>	
<b>Title of Clinical Trial:</b>	
<b>Name of site:</b>	
<b>Name of REC:</b>	
<b>Submission date:</b>	

<b>B. APPLICANT IDENTIFICATION</b>	
<b>Name:</b>	
<b>Title:</b>	
<b>Position:</b>	
<b>Qualification:</b>	
<b>Address:</b>	
<b>Tel:</b>	
<b>Fax:</b>	
<b>E-mail:</b>	

<b>C. LIST OF ENCLOSED DOCUMENTATION</b>	
<b>Reporting Period</b>	
<b>Date of Report</b>	

## Declaration of the End of a Clinical Trial on a Medicinal Product for Human Use to the Research Ethics Committee.

This form should be completed by the Sponsor.  
It should be submitted to the recognised REC, which gave the favorable opinion within 90-days of the conclusion (last person - last visit) of the trial.

### A.1 TRIAL IDENTIFICATION

EudraCT no.:	
Title of clinical trial:	
REC reference no.:	
Name of REC to which report is being submitted	
Submission date:	

### A.2 TRIAL DURATION

Start date	<i>(first person first visit)</i>		dd/mm/yyyy
End date	<i>(last person last visit)</i>		dd/mm/yyyy
Duration <i>(years / months)</i>		Years	Months

### B. APPLICANT IDENTIFICATION

B.1 Sponsor	
Name:	
Address:	
Tel:	
Fax:	
E-mail:	

### C. CIRCUMSTANCES OF ENDING OF CLINICAL TRIAL

<b>C.1 Has this clinical trial ended prematurely?</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
If Yes, please specify the reasons for ending the trial prematurely.	

<b>C.2 Is this a temporary halt to the trial?</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
If Yes, please specify the reasons for temporarily halting the clinical trial and, if possible, identify when you expect the clinical trial to re-start.	

<b>C.3 Are there any potential implications for research participants as a result of terminating/halting the clinical trial prematurely?</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
If Yes, please describe the steps taken to address them.	



**D. FINAL REPORT ON THE RESEARCH**

<b>D.1</b> Is a summary of the final report on the research enclosed with this form?	<input type="checkbox"/> Yes <input type="checkbox"/> No
If No, please submit a copy to the REC within twelve months of the end of the clinical trial.	

**DECLARATION**

*I confirm that the information contained in this form is accurate to the best of my knowledge and I take full responsibility for it.*

**Signature:** \_\_\_\_\_

**Print Name:** \_\_\_\_\_

**Date:** \_\_\_\_\_ (dd/mm/yyyy)

## **Appendix 2**

### **Index of standard letters**

#### ***Validation of Application***

- Letter 1: Confirmation of a valid application  
Letter 2: Confirmation of an invalid application

#### ***Review of Application***

- Letter 3: Request for external expert advice  
Letter 4: Request for further information  
Letter 5: Receipt of further information  
Letter 6: Confirmation that further information not complete

#### ***Confirmation of Opinion***

- Letter 7: Confirmation of favourable opinion  
Letter 8: Confirmation of favourable opinion with conditions  
Letter 9: Confirmation of unfavourable opinion

#### ***Application for Substantial Amendment***

- Letter 10: Confirmation of a valid notice of a substantial amendment  
Letter 11: Confirmation of an invalid notice of a substantial amendment  
Letter 12: Confirmation of a favourable opinion on a substantial amendment  
Letter 13: Confirmation of a favourable opinion on a substantial amendment with conditions  
Letter 14: Confirmation of an unfavourable opinion on a substantial amendment with conditions

#### ***Modified Substantial Amendments***

- Letter 15: Confirmation of a valid notice of a modified substantial amendment  
Letter 16: Confirmation of an invalid notice of a modified substantial amendment  
Letter 17: Confirmation of a favourable opinion on a modified substantial amendment  
Letter 18: Confirmation of a favourable opinion on a modified substantial amendment with conditions

Letter 19: Confirmation of an unfavourable opinion on a modified substantial amendment with conditions

***Monitoring of Approved Research***

Letter 20: Receipt of expedited safety report for fatal or life-threatening suspected unexpected serious adverse reactions (SUSARs)

Letter 21: Receipt of further information for fatal or life-threatening suspected unexpected serious adverse reactions (SUSARs)

Letter 22: Receipt of expedited safety report for non-fatal or non-life-threatening suspected unexpected serious adverse reactions (SUSARs)

Letter 23: Receipt of annual safety report

Letter 24: Receipt of declaration of the end of a clinical trial

Letter 25: Receipt of final research report

***End of Transitional Arrangements***

Letter 26: Receipt of safety reports and other documentation

**Letter 1: Confirmation of a valid application**

**Name of REC**  
**Address**  
**Tel**  
**Fax**

**Name of Chief Investigator**  
**Address**  
**Date**

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates to be reviewed by the Committee)**

Dear [Name],

I hereby acknowledge receipt of your application for ethical review and the cheque for the review fee, which I received on [date]. I confirm that your application is valid and will be reviewed by the Recognised Ethics Committee at the meeting on [date].

The Committee will issue an ethical opinion on this application within a period of [specified number of] days from the date of acknowledgement of a valid application. Therefore a decision will be reached by [date]. You will be informed of the decision within 5 working days of it being made.

Yours sincerely,

[Name]

***Committee Secretary***

E-mail: [Secretary's e-mail address]

**Letter 2: Confirmation of an invalid application**

Name of REC

*Address*

Tel

Fax

*Name of Chief Investigator*

Address

Date

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates to be reviewed by the Committee)**

Dear [Name],

I hereby acknowledge receipt of your application for ethical review, which I received on [date].

Your application is invalid, for the following reason(s):

1. It was not submitted on the standard Recognised Ethics Committee application form
2. The Site Specific Assessment (SSA) form has not been submitted  
[List site(s) for which SSA has not been received]
3. The application form has not been completed  
*[Provide details of questions not completed e.g. B.3, C.1]*
4. The protocol has not been submitted
5. The applicant's checklist has not been filled out or submitted
6. Elements of the checklist have not been submitted  
*[Provide details of documents not received e.g. AC.1, AC.14]*
7. Version numbers and dates have not been entered on the documentation

*[Provide details of documents where this applies]*

- 8. No evidence has been provided of insurance or indemnity to cover the potential liability of the sponsor(s) or investigator(s)
- 9. The Chief Investigator has not signed the application form
- 10. The review fee has not been received by the Committee
- 11. Other

You may re-submit your application to the Committee taking into account the above factors.

Yours sincerely,

[Name]  
Committee Secretary

E-mail: [Secretary's e-mail]

**Letter 3: Request for external expert advice**

**Name of REC  
Address**

***Tel***

***Fax***

**Name of External Expert  
Address  
Date**

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates to be reviewed by the Committee)**

Dear [Name],

The Recognised Ethics Committee has received the above application, which will be reviewed at the meeting held on [date].

In order to give its opinion the Committee would like to seek your views as an external expert on this application. I would be most grateful if you would consider this application and forward any comments that you consider relevant to the review that is being undertaken by this recognised ethics committee.

[List any specific points on which advice is sought]

In order to comply with its obligation to prepare an opinion within [specify number of] days of acknowledgement of a valid application, the committee would appreciate a response from you no later than [date]. If you are unable to respond, could you kindly let me know at your earliest possible convenience?

Would you please declare if you have any personal interest in relation to this research study.

Yours sincerely,

[Name]  
Committee Secretary

E-mail: [Secretary's e-mail address]

**Enclosure      Copy of application documentation**

**Letter 4: Request for further information**

Name of REC  
Address

*Tel*  
Fax

Name of Chief Investigator  
Address  
Date

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates which have been reviewed by the Committee)**

Dear [Name],

The Recognised Ethics Committee reviewed the above application at the meeting held on [date].

The Committee is unable to give an ethical opinion based on the information and documentation received thus far. Before giving its opinion, the Committee requests that you provide further information as listed below.

The time period for review *has* been suspended as of [date] and will recommence on the day the Committee acknowledges receipt of the requested information.

[List of points to be addressed, including any recommended revisions to the application or supporting documentation]

Please forward revised documentation highlighting, where appropriate, the changes you have made and giving revised version numbers and dates.

You will be informed of the outcome of the ethical review within 5 working days of it being reached.

Yours sincerely,

[Name]  
Committee Secretary

E-mail: [Secretary's e-mail address]



**Letter 5: Receipt of further information**

**Name of REC  
Address  
Tel  
Fax**

**Name of Chief Investigator  
Address  
Date**

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates to be reviewed by the Committee)**

Dear [Name],

I hereby acknowledge receipt of further information on the above clinical trial in your letter of [date].

The time period for review, which was suspended on [date] has recommenced as of [date]. Therefore a decision will be reached by [date]. You will be informed of the decision within 5 working days of it being made.

Yours sincerely,

[Name]

***Committee Secretary***

E-mail: [Secretary's e-mail address]

**Letter 6: Confirmation that further information not complete**

Name of REC  
Address  
Tel  
Fax

*Name of Chief Investigator*

Address

Date

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates to be reviewed by the Committee)**

Dear [Name],

I hereby acknowledge receipt of further information on the above clinical trial in your letter of [date].

The further information [and revised documentation] has been considered by the Committee at their meeting held on [date].

The Committee would be grateful for a more complete response on the following points:

[Details of further information/revision still needed – must relate to matters raised by Committee at first review]

The time period for review *has* been suspended as of [date] and will recommence on the day the Committee acknowledges receipt of the requested information.

Please forward revised documentation highlighting, where appropriate, the changes you have made and giving revised version numbers and dates.

You will be informed of the outcome of the ethical review within 5 working days of it being reached.

Yours sincerely,

[Name]

***Committee Secretary***

E-mail: [Secretary's e-mail address]

**Letter 7: Confirmation of favourable opinion**

Name of REC  
Address  
Tel  
Fax

*Name of Chief Investigator*

Address

Date

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates which have been reviewed by the Committee)**

Dear [name],

The Recognised Ethics Committee reviewed the above application at its meeting held on [date].

The Committee has given a favourable ethical opinion for the above clinical trial based on the application form, protocol and supporting documentation.

*In the case of a multi-centre trial:* The Committee undertook a site specific assessment of proposed sites in Ireland. Please see enclosed a list of sites in Ireland, which have been given a favourable opinion. It is your responsibility to notify the Sponsor and the investigator at each site in Ireland of the outcome of the review.

Yours sincerely,

[Name]

*Chair of Committee*

E-mail: [Secretary's e-mail address]

**Enclosures    List of sites in Ireland with favourable opinion**

**Letter 7 (Contd.): Name of Recognised Ethics Committee**

**List of sites with favourable ethical opinion**

**For all clinical trials requiring site-specific assessment, this form is issued by the central REC to the Chief Investigator with the favourable opinion letter.**

**Trial Identification**

Title of clinical trial:
REC reference no.:
EudraCT no.:
Submission date:

This clinical trial was given a favourable ethical opinion on [date]. The favourable opinion is extended to each of the sites listed below. The clinical trial may commence at each site when the CEO/ person acting on behalf of the CEO has signed the declaration at the end of the Site Specific Assessment form.

<b>Investigator</b>	<b>Site</b>

*(Add more pages if necessary)*

Signed:.....

**Chair of Committee**

Date:.....

**Letter 8: Confirmation of favourable opinion with conditions**

**Name of REC**  
**Address**  
**Tel**  
**Fax**

**Name of Chief Investigator**  
**Address**  
**Date**

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates which have been reviewed by the Committee)**

Dear [name],

The Recognised Ethics Committee reviewed the above application at its meeting held on [date].

The Committee has given a favourable ethical opinion for the above clinical trial based on the application form, protocol and supporting documentation. This favourable opinion is given provided that you comply with the conditions set out in the attached document.

*In the case of a multi-centre trial:* The Committee undertook a site-specific assessment of proposed sites in Ireland. Please see enclosed a list of sites in Ireland, which have been given a favourable opinion. It is your responsibility to notify the Sponsor and the investigator at each site in Ireland of the outcome of the review.

Yours sincerely,

[Name]

***Chair of Committee***

E-mail: [Secretary's e-mail address]

**Enclosures    List of approval conditions**  
*List of sites in Ireland with favourable opinion*

**Letter 8 (Contd): Name of Recognised Ethics Committee**

**List of sites with favourable ethical opinion**

**For all clinical trials requiring site-specific assessment, this form is issued by the REC to the Chief Investigator with the favourable opinion letter.**

**Trial Identification**

Title of clinical trial:
REC reference no.:
EudraCT no.:
Submission date:

This study was given a favourable ethical opinion on [date]. The favourable opinion is extended to each of the sites listed below. The clinical trial may commence at each site when the CEO/responsible person acting on behalf of the CEO has signed the declaration at the end of the site specific assessment form.

<b>Investigator</b>	<b>Site</b>

*(Add more pages if necessary)*

Signed:.....

**Chair of Committee**

Date:.....

**Letter 9: Confirmation of unfavourable opinion**

**Name of REC  
Address  
Tel  
Fax**

**Name of Chief Investigator  
Address  
Date**

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates, which have been reviewed by the Committee)**

Dear [Name],

The Recognised Ethics Committee reviewed the above application at the meeting held on [date].

The Committee was unable to give a favourable ethical opinion on the research, for the following reasons:

*[List reasons for rejection]*

*In the case of a multi-centre clinical trial: It is your responsibility to notify the Sponsor and Investigator at each site in Ireland of the outcome of the review.*

Yours sincerely,

[Name]

***Chair of Committee***

E-mail: [Secretary's e-mail address]

**Letter 10: Confirmation of valid application for a substantial amendment**

Name of REC

*Address*

Tel

Fax

Name of Sponsor

Address

Date

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates to be reviewed by the Committee)**

*Amendment number:*

Dear [Name],

I hereby acknowledge receipt of the above application for a substantial amendment, which I received on [date]. I can confirm that this is a valid application for a substantial amendment.

The Committee will issue an ethical opinion on the amendment within 35 days from the date of acknowledgement of a valid application. Therefore a decision will be reached by [date]. You will be informed of the decision within 5 working days of it being made.

Yours sincerely,

[Name]

***Committee Secretary***

E-mail: [Secretary's e-mail address]



**Letter 11: Confirmation of invalid application for a substantial amendment**

Name of REC  
Address

*Tel*

Fax

Name of Sponsor

Address

Date

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates to be reviewed by the Committee)**

*Amendment number:*

Dear [Name],

I hereby acknowledge receipt of the above application for a substantial amendment, which I received on [date].

Your application for a substantial amendment is invalid, for the following reason(s):

1. The application for a substantial amendment form is incomplete.   
*[Provide details of sections not completed e.g.B.1]*
3. The application for a substantial amendment form has not been signed.
4. The supporting documentation is not complete.   
*[Provide details of documents not received e.g. revised research participant consent form]*
5. The fee for review of a substantial amendment has not been received

You may re-submit the substantial amendment to the Committee, taking into account the above point(s).

Yours sincerely,

[Name]

***Committee Secretary***

E-mail: [Secretary's e-mail address]

**Letter 12: Confirmation of a favourable opinion on a substantial amendment**

**Name of REC  
Address  
Tel  
Fax**

**Name of Sponsor  
Address  
Date**

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates which have been reviewed by the Committee)**

*Amendment number:*

Dear [Name],

The Committee has given a favourable ethical opinion on the substantial amendment based on the application for a substantial amendment form and supporting documentation.

*In the case of a multi-centre trial:* It is your responsibility to notify the Chief Investigator and the Investigator at each site in Ireland of the outcome of the review.

Yours sincerely,

[Name]

*Chair of Committee*

E-mail: [Secretary's e-mail address]

**Letter 13: Confirmation of a favourable opinion on a substantial amendment with conditions**

Name of REC  
Address  
Tel  
Fax

Name of Sponsor  
Address  
Date

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates, which have been reviewed by the Committee)**

*Amendment number:*

Dear [Name],

The Committee has given a favourable ethical opinion on the substantial amendment based on the application for a substantial amendment form and supporting documentation.

*This favourable opinion is given provided that you comply with the conditions set out in the attached document.*

*In the case of a multi-centre trial:* It is your responsibility to notify the Chief Investigator and the Investigator at each site in Ireland of the outcome of the review.

Yours sincerely,

[Name]

***Chair of Committee***

E-mail: [Secretary's e-mail address]

Enclosures List of approval conditions

**Letter 14: Confirmation of an unfavourable opinion on a substantial amendment**

Name of REC  
Address  
Tel  
Fax

Name of Sponsor

*Address*

Date

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates, which have been reviewed by the Committee)**

*Amendment number:*

Dear [Name],

The Committee was unable to give a favourable ethical opinion of the substantial amendment, for the following reasons:

*[List reasons for rejection]*

The substantial amendment is therefore not approved. The study should continue in accordance with the documentation previously approved by the Committee.

You may modify or adapt the substantial amendment, taking into account the Committee's concerns. Modified substantial amendments should be submitted, within 30 days of receipt of this letter, on the standard application for a substantial amendment form. The form should indicate that it is a modification of the above substantial amendment (see section A.2 of the application for Recognised ethics committee opinion on a substantial amendment to a clinical trial on a medicinal product for human use form).

Yours sincerely,

[Name]

*Chair of Committee*

E-mail: [Secretary's e-mail address]

**Letter 15: Confirmation of receipt of an application for a modified substantial amendment**

**Name of REC  
Address  
Tel  
Fax**

**Name of Sponsor  
Address  
Date**

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates to be reviewed by the Committee)**

*Amendment number:*

Dear [Name],

I hereby acknowledge receipt of the above application for a modified substantial amendment, which I received on [date]. I note that this is a modification of an amendment rejected by the Committee on [date].

The Committee will issue an ethical opinion on the modified substantial amendment within 14 days from the date of acknowledgement of a valid application. Therefore a decision will be reached by [date]. You will be informed of the decision within 5 working days of it being made.

Yours sincerely,

[Name]

***Committee Secretary***

E-mail: [Secretary's e-mail address]

**Letter 16: Confirmation of an invalid application for a modified substantial amendment**

**Name of REC**  
**Address**  
**Tel**  
**Fax**

**Name of Sponsor**  
**Address**  
**Date**

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates to be reviewed by the Committee)**

*Amendment number:*

Dear [Name],

I hereby acknowledge receipt of the above application for a modified substantial amendment, which I received on [date].

Your application for a modified substantial amendment is invalid, for the following reason(s):

1. The application for a substantial amendment form is incomplete.   
*[Provide details of sections not completed e.g.B.1]*
2. The application for a substantial amendment form has not been signed.
3. The supporting documentation is not complete.   
*[Provide details of documents not received e.g. revised research participant consent form]*

You may re-submit the application for a modified substantial amendment to the Committee, taking into account the above point(s).

Yours sincerely,

[Name]

***Committee Secretary***

E-mail: [Secretary's e-mail address]

**Letter 17: Favourable opinion of modified substantial amendment**

**Name of REC  
Address  
Tel  
Fax**

**Name of Sponsor  
Address  
Date**

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates which have been reviewed by the Committee)**

*Amendment number:*

Dear [Name],

I can confirm that the Committee has given a favourable ethical opinion on the modified substantial amendment based on the application for a substantial amendment form and supporting documentation.

*In the case of a multi-centre trial:* It is your responsibility to notify the Investigator at each site in Ireland of the outcome of the review.

Yours sincerely,

[Name]

*Chair of Committee*

E-mail: [Secretary's e-mail address]

**Letter 18: Confirmation of a favourable opinion of a modified substantial amendment with conditions**

Name of REC  
Address  
Tel  
Fax

Name of Sponsor  
Address  
Date

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates which have been reviewed by the Committee)**

*Amendment number:*

Dear [Name],

I hereby acknowledge receipt of the above-modified substantial amendment, which I received on [date]. I note that this is a modification of a substantial amendment rejected by the Committee on [date].

I can confirm that the Committee has given a favourable ethical opinion on the modified substantial amendment based on the application for a substantial amendment form and supporting documentation.

This favourable opinion is given provided that you comply with the conditions set out in the attached document.

*In the case of a multi-centre trial:* It is your responsibility to notify the Investigator at each site in Ireland of the outcome of the review.

Yours sincerely,

[Name]

*Chair of Committee*

E-mail: [Secretary's e-mail address]

*Enclosures List of approval conditions*



**Letter 19: Confirmation of an unfavourable opinion on a modified substantial amendment**

**Name of REC  
Address  
Tel  
Fax**

**Name of Sponsor  
Address  
Date**

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

**List of documents (including version number and dates, which have been reviewed by the Committee)**

*Amendment number:*

Dear [Name],

The Committee is unable to give a favourable ethical opinion on the above modified substantial amendment, for the following reasons:

*[List reasons for rejection]*

I regret to inform you that the modified substantial amendment is therefore not approved and may not be re-submitted. The clinical trial should continue in accordance with the documentation previously approved by the Committee.

Yours sincerely,

[Name]  
Chair of Committee

E-mail: [Secretary's e-mail address]

***Letter 20: Receipt of expedited safety report for fatal or life-threatening suspected unexpected serious adverse reactions (SUSARs)***

*Name of REC*

**Address**

**Tel**

**Fax**

**Name of Sponsor**

**Address**

**Date**

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

Dear [Name],

I hereby acknowledge receipt of the expedited safety report for fatal or life-threatening suspected unexpected serious adverse reaction (SUSARs) for the above clinical trial, which I received on [date]. Where appropriate, please furnish the Committee with any additional relevant information within 8 days of the making of this report.

Yours sincerely,

[Name]

***Committee Secretary***

E-mail: [Secretary's e-mail address]

***Letter 21: Receipt of further information for fatal or life-threatening suspected unexpected serious adverse reactions (SUSARs)***

*Name of REC*

***Address***

**Tel**

**Fax**

**Name of Sponsor**

**Address**

**Date**

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

Dear [Name],

I hereby acknowledge receipt of further information for fatal or life-threatening suspected unexpected serious adverse reactions (SUSARs) for the above clinical trial, which I received on [date].

Yours sincerely,

[Name]

***Committee Secretary***

E-mail: [Secretary's e-mail address]

***Letter 22: Receipt of expedited safety report for non-fatal or non-life-threatening suspected unexpected serious adverse reactions (SUSARs)***

*Name of REC*

***Address***

**Tel**

**Fax**

**Name of Sponsor**

**Address**

**Date**

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

Dear [Name],

I hereby acknowledge receipt of the expedited safety report for non-fatal or non-life-threatening suspected unexpected serious adverse reactions (SUSARs) for the above clinical trial, which I received on [date].

Yours sincerely,

[Name]

***Committee Secretary***

E-mail: [Secretary's e-mail address]

**Letter 23: Receipt of annual safety report**

*Name of REC*

**Address**

**Tel**

**Fax**

**Name of Sponsor**

**Address**

**Date**

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

Dear [Name],

I hereby acknowledge receipt of the annual safety report for the above clinical trial, which I received on [date]. The Committee will review the report, and I will inform you if any further information is required.

Yours sincerely,

[Name]

***Committee Secretary***

E-mail: [Secretary's e-mail address]

**Letter 24: Receipt of a declaration of the end of a clinical trial**

**Name of REC  
Address**

***Tel***

**Fax**

**Name of Sponsor**

**Address**

**Date**

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

Dear [Name],

I hereby acknowledge receipt of the declaration of the end of a clinical trial, which I received on [date]. The above clinical trial [concluded] [was terminated prematurely] on [date].

As a summary of the final research report should be provided to the Committee within 12 months of the conclusion of the study, I expect to receive same from you no later than [date].

Yours sincerely,

[Name]

***Committee Secretary***

E-mail: [Secretary's e-mail address]

**Letter 25: Receipt of final research report**

*Name of REC*

**Address**

**Tel**

***Fax***

**Name of sponsor**

**Address**

**Date**

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all correspondence)

**Title of clinical trial:**

Dear [Name],

I hereby acknowledge receipt of the final research report for the above clinical trial, which I received on [date]. The Committee will review the report, and I will inform you if any further information is required.

Yours sincerely,

[Name]

***Committee Secretary***

E-mail: [Secretary's e-mail address]

**Letter 26: Receipt of safety reports and other documentation**

**Name of REC  
Address**

***Tel***

**Fax**

**Name of Sponsor**

**Address**

**Date**

**REC reference:**

**EudraCT no.:**

(Please quote REC reference and EudraCT numbers on all future correspondence)

**Title of clinical trial:**

Dear [Name],

I hereby acknowledge receipt of hard copies of all safety reports and other relevant documentation deemed necessary for the review of the above clinical trial, which I received on [date].

Yours sincerely,

[Name]

***Committee Secretary***

E-mail: [Secretary's e-mail address]