NATIONAL OFFICE FOR RESEARCH ETHICS COMMITTEES

Appendix 1

NREC-CT Operational Framework - Clinical Trial Regulation

Clinical trials of investigational medicinal products (CTIMP)-specific procedures under Regulation (EU) No. 536/2014

Title:	**Appendix 1** **NREC-CT Operational Framework - Clinical Trial Regulation**
Document Type:	Procedure
Reference/version no:	1.0
Status:	Draft (Currently awaiting finalisation of National legislation before this Appendix can be considered final)
Last updated:	31/01/2022
Background:	Externally facing procedure for NREC-CT operations

Table of Contents

1.0 Purpose and scope

The Clinical Trial Regulation (CTR) aims to create an environment that is favourable for conducting clinical trials, with the highest standards of patient safety across the EU, through coordination of authorisation procedures cross Member States. Intrinsic to this is the harmonisation of how trials applications are assessed and monitored across Europe. The CTR impacts the way that sponsors submit clinical trial documentation, and how the HPRA and the NREC-CT review, approve and monitor clinical trials.

This Appendix outlines how the National Office and the NREC-CT have adapted their ongoing processes to reflect the changes at a national and European level.

With operational support from the National Office, the NREC-CT continues to review all studies that meet the definition of Clinical Trial of an Investigational Medicinal Product within the Clinical Trial Directive (EU) No. 2001/20/EC and the Clinical Trial Regulation (EU) No. 536/2014.

Under the CTR, all submissions and notifications to the NREC-CT will be managed through the Clinical Trial Information System (CTIS).

2.0 Scope of the NREC-CT

1. The NREC-CT will only accept applications for review related to those studies that fulfil the criteria of 'clinical trials of investigational medicinal products' under Regulation (EU) No. 536/2014:

    a. interventional trials with medicinal products for human use,

    b. low-interventional trials (trials with authorised medicinal products, used in accordance with the marketing authorisation, and additional diagnostic and monitoring procedures not posing additional risk or burden to patients' safety compared to normal practice).

2. Non-interventional studies and trials without medicinal products are out-of-scope for the NREC-CT.

3. If out-of-scope applications are received, they will be deemed 'invalid'.

3.0 Clinical trial application assessment

3.1 Part I – Coordinated assessment

1. The HPRA will lead on the validation of documentation related to Part I submissions. The HPRA may consult with the National Office where it considers necessary.

2. The HPRA will lead on the assessment of Part I of the clinical trial application, and where Ireland is the Reporting Member State, complete the Draft Assessment Report and the Final Assessment Report for upload to CTIS.
3. Where Ireland is the Reporting Member State, the NREC-CT will review the ethics aspects of Part I documentation, in particular the study protocol, and submit its considerations through the CTIS portal for inclusion in the *Request for Further Information*.
4. Responses to considerations raised by the NREC-CT in the *Request for Further Information* will be reviewed by the NREC-CT with support from the National Office.
5. Timelines for assessment will be in line with the Clinical Trial Regulation.

3.2 Part II – National assessment

1. The National Office will lead on the validation of documentation related to Part II submissions.
2. Where a Part II is submitted in conjunction with a Part I, the National Office will notify the relevant Reporting Member State organisation through the CTIS of any considerations it may have related to Part II validation. These may be then included in a *Request for Further Information* at the validation stage.
3. For a Part II submission to be considered valid by the National Office, the following documentation will be required:

<u>Recruitment arrangements</u>

a. Recruitment and informed consent procedure template
b. All other relevant materials

<u>Participant information and informed consent</u>

c. Recruitment and informed consent procedure template (if not submitted under ‘Recruitment arrangements’)
d. Consent / assent forms
e. Participant information materials
f. Additional relevant materials

<u>Suitability of investigator</u>

g. Signed CV template

<u>Suitability of facilities</u>

h. Signed site suitability template for each individual site

<u>Proof for insurance and indemnification</u>

i. Evidence of policy cover

<u>Financial and other arrangements</u>

j. Statement confirming source of funding
k. Compensation for trial participants template
l. Signed 'Declaration of Interest' template

<u>Collection, storage and use of biological samples</u>

m. Compliance with use of human biological samples template
n. Additional materials where relevant

Evidence of compliance with data protection laws

o. Statement outlining measures in place to comply with national and EU legislation
p. Study-specific Data Protection Impact Assessment with evidence of input from Data Protection Officer (or where relevant, statement outlining why a study-specific DPIA is not necessary)

4. Only EMA-endorsed templates or NREC-adapted templates will be accepted for the following:
    a. Compensation for trial participants
    b. Investigator Curriculum Vitae template
    c. Declaration of interest template
    d. Site suitability form
    e. Informed consent and participant recruitment procedure template
    f. Compliance with Member State applicable rules for the collection, storage and future use of human biological samples
5. The NREC-CT will lead on the assessment of Part II of the clinical trial application.
6. The National Office will support the NREC-CT in the completion and upload of the Final Assessment Report to the CTIS.
7. Where Ireland is a Member State concerned, CVs submitted as part of a Part II submission must be signed by the relevant Principal Investigator.
8. Where Ireland is a Member State concerned, Site Suitability templates must be signed by one of the following: Chief Executive Officer, Head of Clinic / Institution, Clinical Director, Director of Research, or delegate at site.
9. Timelines for assessment will be in line with the Clinical Trial Regulation.

3.3 National decision

1. The administrative step of issuing the Single National Decision will be completed by the HPRA.
2. Where there is a negative outcome for Part I, a negative outcome for Part II or a negative ethics opinion, a clinical trial will not be authorised in Ireland.
3. Where there is a negative outcome for Part II or a negative ethics opinion, the National Office will provide justification to the HPRA, which will be uploaded to the CTIS with the negative Single National Decision.

3.4 Substantial modifications

1. The HPRA will lead on the validation and assessment of substantial modifications related to Part I documentation. Where Ireland is the Reporting Member State, the HPRA will be responsible for the completion of Draft and Final Assessment Reports.
2. The NREC-CT, supported by the National Office, will input on the assessment of Part I substantial modifications where the Committees consider it necessary.

3. Where substantial modifications for Part I documentation requires National Office or NREC-CT input, this will be completed through the submission of considerations through the CTIS portal.
4. The National Office will lead on the validation of substantial modifications related to Part II documentation.
5. The NREC-CT, supported by the National Office, will assess substantial modifications associated with Part II documentation.
6. The National Office will support the NREC-CT in the completion and upload of the Final Assessment Report to the CTIS related to a Part II substantial modification.
7. Timelines for assessment will be in line with the Clinical Trial Regulation.

3.5 Withdrawal and resubmission

1. Sponsors may withdraw an application at any stage of the assessment process up until the reporting date. If a Sponsor decides to withdraw an application, they must withdraw the entire clinical trial. Justification for withdrawal must be communicated through the CTIS portal.
2. Sponsors may resubmit an application following a negative national decision or the withdrawal of an application.
3. Where an application receives a negative opinion related to a Part II submission or a negative ethics opinion, the National Office strongly encourages Sponsors to speak to the National Office ahead of resubmission.

4.0 Safety notifications

1. The reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) will be through the Eudravigilance database, and the reporting of Annual Safety Reports will be through the CTIS. These reports and notifications will be monitored and assessed by the HPRA. Neither the National Office nor the NREC-CTs will have routine access to these safety reports or notifications. Where HPRA considers it appropriate it will seek the involvement of the National Office and / or the NREC-CT in the review and assessment of safety reports and notifications.
2. For more information on the requirements of safety reporting and assessment, please review the the Implementing Regulation on coordinated safety assessment in clinical trials (EU) 2022/20.

5.0 Start, end, temporary halt, and early termination of clinical trial

The National Office, as part of its Member State concerned role, must be notified through the CTIS of:

1. Start of a clinical trial in Ireland within 15 days of the trial commencing.

2. Recruitment of the first participant to the trial in Ireland within 15 days of the first visit.
3. End of recruitment in Ireland within 15 days from the end of recruitment at Irish sites
4. End of trial in Ireland within 15 days the trial ending in Ireland.
5. End of trial across all Member States concerned within 15 days from the end of trial in the European Economic Area.
6. End of trial globally within 15 days from the end of trial.
7. Temporary halt or early termination within 15 days from implementation. If a temporary halt or early termination is implemented due to a change of the participant risk-benefit ratio, an outline of the rationale and follow-up measures must be included
8. Restart of a trial after a temporary halt within 15 days of the restart.

6.0 Monitoring and supervision of trials

6.1 Serious breaches

1. The HPRA and the National Office must be notified through the CTIS portal of serious breaches of the rules for the conduct of a particular trial where Ireland is a Member State Concerned. This must be done within 7 days of the Sponsor being made aware of the breach.
2. Where it is considered necessary, the NREC-CT will liaise with the HPRA on the national assessment of a serious breach and will consult with other Member States concerned where appropriate.

6.2 Urgent safety measures and unexpected events

1. The HPRA and the National Office must be notified through the CTIS portal of all unexpected events and urgent safety measures within 15 days from the date the Sponsor became aware of this event.
2. Where unexpected events and urgent safety measures require an urgent modification of a clinical trial, the sponsor and the investigator may take urgent safety measures without authorisation from the NREC-CT or HPRA. If these measures require a temporary halt of the clinical trial, the Sponsor should apply for a substantial modification before restarting the clinical trial.
3. The Sponsor should notify the HPRA and the National Office through the CTIS portal, of the event and the measures taken. This notification should be issued within 7 days from the date the measures were taken.
4. Where it is considered necessary, the NREC-CT will liaise with the HPRA on the national assessment of an urgent safety measure and unexpected events and will consult with other Member States concerned where appropriate.

6.3 Corrective measures

1. Acting as the Member State concerned, the National Office on behalf of the NREC-CT, in partnership with the HPRA may decide to:
    a. revoke the authorisation of a clinical trial.
    b. suspend a clinical trial.
    c. require the Sponsor to modify any aspect of the clinical trial.
2. The National Office on behalf of the NREC-CT, may consult with other relevant Member States concerned before initiating a corrective measure.
3. In the event that the National Office on behalf of the NREC-CT, in partnership with the HPRA, choose to initiate a corrective measure, all other Member States concerned will be notified.

7.0 Appeals

1. In the event that a Sponsor receives a negative outcome on behalf of Ireland as a Member State Concerned due to a negative Part II outcome or a negative NREC-CT opinion, the Sponsor is strongly encouraged to resubmit a new application to Ireland as a Member State concerned through the CTIS, addressing the concerns of the NREC in the first instance.
2. Appeals will be handled outside of the CTIS portal.
3. A request for appeal of a Part II decision or negative NREC-CT opinion should be submitted by the Sponsor to the National Office and the HPRA within 28 days from the date of notification of the negative Single National Decision.
4. The Sponsor should clearly state the grounds for appeal in addition to submitting all original documentation reviewed by the NREC.
5. Appeals must be based on a negative national decision rather than conditions of a favourable national decision.
6. The appeal of an NREC-CT decision will be considered by an independent Appeals Panel convened by the National Office. No member of the NREC-CT that reviewed the application will sit on the Appeals Panel. The Appeals Panel may consult with external experts to inform their deliberations.

8.0 Payment of fees

1. For the assessment of clinical trial applications under the CTR, a single fee payment must be made to each Member State Concerned. In Ireland, this fee must be paid to the HPRA.
2. Please see HPRA website for further details on the fee payment process for clinical trial applications in Ireland - http://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/fin-g0002-guide-to-fees-for-human-products-v27.pdf?sfvrsn=69