National Research Ethics Committees

Operational Framework

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1.0 Purpose and scope

This document sets out the operational framework of procedures for the National Research Ethics Committees (NRECs).

The NRECs are appointed by the Minister for Health (hereafter the 'Minister') to act in the public interest by reviewing and providing opinions on the ethics underpinning those health research areas as defined in their Terms of Reference. The NRECs assess applications submitted to them through the National Office for Research Ethics Committees (hereafter the 'National Office'). The National Office provides operational support to and is responsible for all administrative actions associated with the NRECs, including the issuing of an ethics opinion following a Committee's decision.

Independent ethics review is designed to maintain the highest ethical standards of practice in research, to ensure the dignity, safety and wellbeing of research participants including the right to privacy, and to provide reassurance to the public that these standards are being met. The operational framework supports the NREC system to deliver robust, nationally applicable opinions following independent, thorough ethics review, which will engender the trust and confidence of the health research community, research participants, sponsors, and the wider public.

The decisions from the NRECs are grounded in international best practice and the cornerstone principles of research ethics, including those described in the Declaration of Helsinki[1]. The prevailing role of the NRECs will be the protection of the rights, safety, dignity, and well-being of research participants.

The operational framework seeks to embed operational excellence in the NREC system by laying out transparent, consistent and comprehensive procedures to ensure a robust review, an efficient and predictable process, and a timely decision for applications made to the NRECs via the National Office.

This framework is consistent with Ireland's Member State obligations under the following EU regulations and prevailing national implementing legislation:

- Directive 2001/20/EC for clinical trials of investigational medicinal products (CTIMPs)
- Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use
- Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices
- Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* diagnostic medical devices

[1] World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki/

- S.I. No. 41/2022 - European Union (Clinical Trials on Medicinal Products for Human Use) (National Research Ethics Committees) Regulations 2022
- S.I. No. 99/2022 - European Union (Clinical Trials on Medicinal Products for Human Use) (Principal) Regulations 2022
- S.I. No. 257/2022 - European Union (National Research Ethics Committees for Performance Studies of In Vitro Diagnostic Medical Devices) Regulations 2022
- S.I. No. 671/2023 - European Union (National Research Ethics Committee for Clinical Investigations of Medical Devices) Regulations 2023

This operational framework sets out the generalities of the operations of all the NRECs, and then more specifically for the NRECs within the respective regulatory framework.

2.0 Definitions

Applicant: The individual/entity that is responsible for the preparation, submission, conduct, and administration of a study for NREC review. Applicant is typically a contract research organisation, sponsor or Principal Investigator.

Chairperson: The member of a NREC appointed to be Chairperson by the Minister for Health. Where the Chairperson is unavailable for any reason, s/he may designate his/her role to a Deputy Chairperson.

Clinical investigation: According to Regulation EU No 2017/745, any systematic investigation involving one or more human participants, undertaken to assess the safety or performance of a device.

Clinical trial: According to Regulation EU No 536/2014, a clinical study that fulfils any of the following conditions:

a. the assignment of the participant to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned,

b. the decision to prescribe the investigational medicinal products is taken together with the decision to include the participant in the clinical study, or

c. diagnostic or monitoring procedures in addition to normal clinical practice are applied to the participants.

Commercial clinical investigation/trial: A clinical investigation/trial where a commercial organisation is the study sponsor.

Expert consultation: Consultation with a person or body who gives expert advice to a NREC on an application or any related matter, where it is considered that that person or body has an expertise required by the Committee.

Expert member: A member of the Committee who:

a. is a practising or retired health practitioner, which has the same meaning as it has in the Health Identifiers Act 2014 (No. 15 of 2014),

b. professional qualifications or experience relating to the conduct of, or use of statistics in clinical research, unless the said qualifications or experience relate only to the ethics of clinical research or medical treatment,

c. is involved in the promotion, organisation or conduct of clinical research, or

d. belongs to a class or category of persons prescribed by the Minister for the purposes of this definition for the purpose of membership of a particular NREC.

Investigational medicinal product: A medicinal product for human use, that is being tested or used as a reference, including as a placebo, in a clinical trial.

Investigator-sponsor: Principal investigator who is also acting as the sponsor for that clinical study.

***In vitro* diagnostic medical device:** According to Regulation EU No 2017/746; any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

a. concerning a physiological or pathological process or state,
b. concerning congenital physical or mental impairments,
c. concerning the predisposition to a medical condition or a disease,
d. to determine the safety and compatibility with potential recipients,
e. to predict treatment response or reactions,
f. to define or monitoring therapeutic measures.

Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices.

Lay member: A member of the Committee who is not an expert member. In general, a lay member is not in close professional proximity to the conduct of research under NREC review. A lay member may have a professional qualification, including law, ethics or philosophy, that affords the Committee a specific expertise beneficial to NREC deliberations, and in this regard, the member will be identified as ‘lay’ with a qualification of ‘ethics’ or ‘law’ etc where appropriate. A lay member may be a patient, public, involvement representative member who brings an informed interest in or perspective on health research from the objective standpoint of the general public or a patient.

Low-intervention clinical trial: Regulation EU No 536/2014, a clinical trial that fulfils all the following conditions:

a. the investigational medicinal products, excluding placebos, are authorised
b. according to the protocol of the clinical trial,
    i. the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or
    ii. the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned

c. the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.

Medical device: According to Regulation EU No 2017/745; medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
- providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices:

- devices for the control or support of conception,
- products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.

Medical exposure to ionising radiation: Ionising radiation received by a person as part of their medical diagnosis or treatment. This also includes exposure to radiation for medical or biomedical research purposes as well as carers and comforters exposed to ionising radiation while attending to a patient.

National Office: The National Office for Research Ethics Committees with an independent statutory role in the regulation of health research ethics, and which is a constituent part of the Health Research Board which provides administrative and operational support to the National Office.

National Research Ethics Committee (NREC or 'Committee'): A research ethics committee appointed by the Minister for Health to act in the public interest by conducting research ethics review of applications in prescribed areas of health research, and providing nationally applicable ethics opinions.

Non-commercial clinical investigation/ trial: A clinical investigation/trial for which a commercial organisation is not the study sponsor. Typically, a non-commercial clinical investigation is sponsored by an academic or hospital institution, a scientific

group or society. The National Office reserves the right to query the nature of sponsorship of a study.

Non-interventional study: A clinical study other than a clinical trial.

Non-substantial amendment/modification: An amendment that is not a substantial amendment, and as such, not requiring research ethics review by the NREC.

NREC business report: A report compiled by the National Office to notify NREC members of committee business undertaken or information received, outside of the main NREC meetings. This report will be shared with the agenda ahead of each NREC meeting.

Performance study: According to Regulation EU No 2017/746, a study undertaken to establish or confirm the analytical or clinical performance of a device.

Principal investigator (national): The primary individual responsible for the preparation, conduct, and administration of a research study in any given Member State. The national Principal Investigator takes on the primary responsibility for the study and therefore also for the safety or physical or mental integrity of research participants.

Principal investigator (site): The primary individual responsible for the preparation, conduct, and administration of a research study in a specific study site. The site Principal Investigator takes on the primary responsibility for the site.

Serious adverse event or serious adverse reaction: Any adverse event or adverse reaction, including those for medicinal products 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.

   Not all serious adverse events have a known direct attribution to a medicinal product / medical device.

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

Sponsor: In relation to a clinical trial, clinical investigation or performance study, the individual, company, institution or organisation which 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 or clinical investigation.

Substantial amendment/modification: A change to the research study that is likely to have a significant effect on any of the following:

a. the safety or physical or mental integrity of the subjects of the study,
b. the scientific value of the study,
c. the conduct or management of the study, or
d. the quality or safety of any investigational medicinal product or device used in the study.

Unexpected adverse reaction: In relation to 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.

Validation: An administrative check carried out by the National Office to verify that an application is complete with the documentation sufficient for the NREC to conduct an informed ethics review.

Website: Website for the National Office – www.nrecoffice.ie.

3.0 General procedures

3.1 Membership

1. The NRECs are constituted and operationalised in accordance with European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations (CTR) (EU) No. 536/2014 (S.I. No 041 of 2022), the Medical Device Regulation (MDR) (EU) 2017/745 (S.I. 671 of 2023) and the In Vitro Diagnostic Medical Device Regulation (IVDR) (EU) No 2017/746 (S.I. 257 of 2022).[2]
2. The scope of remit for each NREC are outlined in its Terms of Reference, which are determined by the Minister of Health.

3.2 Conflicts of interest

1. All committee members and National Office staff shall adhere to the NREC Conflict of Interest Policy.
2. Committee members and National Office staff must declare any personal or business material interests that may constitute a real or perceived a conflict of interest in relation to an application for ethics review.
3. Any perceived or actual interest will be managed in accordance with the National Office Conflict of Interest Policy [3]
4. Such a declaration should be made by the member in advance of any consideration of the matter to which the conflict of interest relates. This may be a written declaration to the National Office and Chairperson prior to the meeting or a verbal declaration at the NREC meeting prior to the matter being considered.
5. Where in the opinion of another person an NREC member may have a perceived conflict of interest, the matter shall be discussed by the NREC in advance of any discussion of the matter to which the potential conflict of interest relates. Where there is any doubt as to the existence of a conflict of interest, it will be a matter for the Chairperson to decide (if necessary, in consultation with the National Office).
6. Where a committee member has a conflict of interest with a particular application, they must recuse themselves from the meeting for the duration of the discussion of the matter.
7. Where a National Office staff member has a conflict of interest with a particular application, they may need to recuse themselves from any

[2] https://www.nrecoffice.ie/committees/

[3] National Office Conflict of Interest Policy

administrative aspects of the application and from the meeting for the duration of the discussion of the matter. Where there is any doubt as to the existence of a conflict of interest for National Office staff, it will be a matter for the Chairperson to decide.

8. All conflicts of interest will be recorded in the minutes. See Section 3.7 for more information on meeting minutes.

3.3 Confidentiality

1. All committee members and National Office staff will adhere to the NREC Confidentiality Policy.
2. All committee members are required to protect and treat confidentially all information and documentation that they are privy to in the course of committee work and shall not discuss matters with any third-party external to the National Office or NRECs.
3. Committee members must not discuss matters for consideration at NREC meetings with persons not sitting on the NREC.
4. Committee members should direct any external queries on the NREC operations or decisions to the National Office.
5. Documents shared by way of preparation for and conduct of NREC meetings and ongoing committee work must be treated and stored securely at all times, and any associated information printed or retrieved by individual members must be securely destroyed.
6. Any breach in the security or confidentiality of any documentation, information or material related to NREC work must be reported to the National Office as soon as the member becomes aware.

3.4 Meeting schedule

1. The NREC meeting schedule will be set to ensure that timelines required by EU Regulations can be met. Meetings to review applications to each of the NRECs will normally be held at intervals of one month.
2. The schedule of NREC meetings for the year commencing on 1 Jan will normally be finalised by 30 September in the previous year.

3.5 NREC sub-committees

1. NREC sub-committees may be convened to review substantial amendments, site-specific assessments, safety reporting, other notifications relevant to

approved studies, or to meet any other operational requirements of the NREC deemed necessary by the Chairperson.

2. Decisions made at sub-committee meetings will be shared with other NREC committee members through the NREC Committee Business Report, which will be included in the agenda of main NREC meetings.

3.6 Decisions

1. The NRECs deliver single national ethics opinion for studies carried out under the Clinical Trials on Medicinal Products for Human Use Regulations (CTR) (EC) No. 536/2014 (S.I. No 041 of 2022), the Medical Device Regulation (MDR) (EU) 2017/745 (S.I. 671 of 2023) and the In Vitro Diagnostic Medical Device Regulation (IVDR) (EU) No 2017/746 (S.I. 257 of 2022)
2. All final decisions will be made publicly available on the National Office website and/ or on public EU databases such as Clinical Trials Information System (CTIS).

3.7 Meeting minutes

1. The meeting minutes may include the following information:

a. The members, co-opted members or expert consultation, and observers including National Office staff attending the meeting,

b. Any declared conflicts of interests,

c. A summary of the main ethical considerations,

d. The decision on the application,

e. In the case of a ‘favourable with conditions’ opinion, any conditions set by the NREC,

f. In the case of an ‘unfavourable opinion’, the predominant reasons for the decision are clearly stated,

g. In the case of a ‘request for further information’, an outline of the further information requested by the NREC,

2. Minutes from any given meeting will be reviewed and formally approved by the NREC at the next subsequent meeting and subsequently uploaded to the National Office website.

4.0 Specific procedures for National Research Ethics Committee for Clinical Investigations of Medical Devices and Performance Studies of In Vitro Diagnostic Medical Devices (NREC-MD)

4.1 Scope of the NREC-MD

1. The scope of the remit of the NREC-MD is determined by Regulation (EU) 2017/745 (S.I. 671/2023 and Regulation (EU) 2017/746 (S.I. 257/2022).
2. The NREC-MD will only accept applications for review related to clinical investigations under Regulation (EU) 2017/745 (MDR) involving:
    a. MDR Article 62: Non-CE marked devices being used in a clinical investigation for one or more of the purposes specified:
        i. to establish and verify that a device is suitable for its intended purpose and achieves the performance intended by its manufacturer,
        ii. to establish and verify the clinical benefits of a device,
        iii. to establish and verify the clinical safety of the device and to determine any undesirable side effects under normal conditions of use and assess whether they constitute acceptable risks when weighed against the benefits to be achieved by the device.
    b. MDR Article 74(1): CE-marked devices being further assessed in a clinical investigation (post-market clinical follow-up investigation), within the scope of its intended purpose, and where the investigation would involve submitting subjects to procedures additional to those performed under the normal conditions of use of the device, and those additional procedures are invasive or burdensome.
    c. MDR Article 74(2): CE-marked medical devices being used in a clinical investigation outside the scope of its intended purpose.
    d. MDR Article 75: Substantial modifications to clinical investigations that are likely to have a substantial impact on the safety, health or rights of the subjects or on the robustness or reliability of the clinical data generated by the investigation.
    e. MDR Article 82: Clinical investigations not performed pursuant to any of the purposes listed in Article 62(1).
3. The NREC-MD accept applications for review related to performance studies under Regulation (EU) 2017/746 (IVDR) involving:
    a. IVDR Article 58: Performance study, as specified:

i. in which surgically invasive sample-taking is done only for the purpose of the performance study,

ii. that is an interventional clinical performance study as defined in point (46) of Article 2, or

iii. where the conduct of the study involves additional invasive procedures or other risks for the subjects of the studies.

b. IVDR Article 70(1): CE marked devices being further assessed in a performance study (post-market performance follow up study), and where the performance study would involve submitting subjects to procedures additional to those performed under the normal conditions of use of the device and those additional procedures are invasive or burdensome.

c. IVDR Article 70(2): CE-marked medical device being used in a performance study outside the scope of its intended purpose.

d. IVDR Article 71: Substantial modifications to performance studies that are likely to have a substantial impact on the safety, health or rights of the subjects or on the robustness or reliability of the data generated by the study.

4. If out-of-scope applications are received, they will be deemed ‘invalid’ by the National Office.
5. Applicants should familiarise themselves with their regulatory application obligations to the competent authority (the HPRA) under the MDR/IVDR.
6. The timelines for NREC decisions will be consistent with those outlined in the EU Medical Device Regulation (MDR; EU No 2017/745) and S.I. 260/2021. Applicants submitting to the NREC-MD may expect a decision on valid new applications within 55 days and on substantial modifications within 38 days (45 days if additional expertise is required for review).

4.2 Role of NREC-MD in studies approved under 93/42/EEC Directive

1. Clinical investigations of medical devices that were approved under the Council Directives 93/42/EEC and 90/385/EEC (and their transposing

legislation SI 252/1994 and SI 253/1994 as amended) and were still ongoing on the date of effect (26th May 2021) of the EU Medical Device Regulation (MDR; EU No. 2017/745) must be in conformity with the MDR. It is the responsibility of the applicant to ensure that their studies are compliant with prevailing law, including the MDR.

2. To ensure compliance with the MDR, applicants must, since the 26th May 2021 notify the NREC-MD with regard to:
    a. any other matter that requires an ethical decision, such as substantial, modifications, or
    b. any other matter that requires notification, such as non-substantial modifications.

4.3 Submission and review of applications under MDR/ IVDR

4.3.1 Documentation requirements

1. Applicants must complete the designated NREC-MD application form as part of the application for ethics review of a clinical investigation/performance study.
2. In addition to the NREC-MD application form, applicants must provide the documents specified in the application documentation checklist, available on the website of the National Office, as applicable to a clinical investigation/performance study.

4.3.2 Payment of fees for NREC-MD

1. Applicants must pay the relevant fee in advance of submission to the National Office for Research Ethics Committees. The procedure for payment of fees is outlined on the website of the National Office.

4.3.3 Application validation

1. Applicants should normally receive notification of whether their application is ‘valid’ or ‘invalid’ within seven calendar days of the application submission deadline.
2. Invalid applications will require a full resubmission if ethics review is to proceed.
3. To be deemed ‘valid’, applicants must submit all documentation as requested in the documentation checklist prior to the application submission deadline.
4. If, in the view of the National Office, outstanding information or documentation for an ‘invalid’ submission is relatively straightforward to address or provide in advance of the scheduled meeting, the National Office may informally follow-up with the applicant to request the additional information, and the submission will be marked as ‘validation under consideration’ until all information required

is submitted. If the information is not received ahead of the scheduled meeting, the application will be deemed 'invalid'.

5. If prior to review by the Committee, a valid application is revised by the applicant, said application will need to be withdrawn and resubmitted as a new application.

4.3.4 Review process of applications

1. Valid new applications for an ethics assessment should, where possible, be considered at a main meeting of a NREC.
2. All NREC-MD meetings will normally include a sufficient number of applications to require the convening of the Committee but not so many as to undermine the rigour of the review process. The number of applications to be reviewed at a single meeting will be a matter for the Chairperson, in consultation with the National Office.
3. Each new application will be assigned one lead reviewer and a minimum of one secondary reviewer. Both lead and secondary reviewers will complete a NREC-MD assessment report, which is submitted to the National Office in advance of the NREC meeting.
4. Where a NREC-MD does not have a member with professional expertise in a specific subject matter related to a valid application, the National Office may consult an external expert to provide an expert opinion on an application. The expert consultation either takes place at the meeting or the external expert will submit their written opinion ahead of the meeting. External experts will be required to maintain confidentiality in respect to applications, research participants, deliberations, and all related matters.
5. NREC-MD member who is unavailable to attend a meeting may submit comments in writing on any agenda item ahead of the meeting but cannot contribute to a quorum *in absentia*.
6. Substantial modifications may be reviewed as appropriate by:
    a. the Chairperson,
    b. an NREC-MD sub-committee,
    c. at a main meeting of the NREC.
7. It is the applicant's responsibility to notify interested parties and those to whom the applicant has a reporting obligation (e.g. host institutions, funders, insurers etc.) regarding the study, study modification and associated ethics review. Neither the National Office nor the NRECs are accountable for ensuring that such parties are informed or provided with copies of any documentation required.

4.3.5 Study modifications

1. It is the responsibility of the applicant to determine whether a modification is a substantial or non-substantial modification.
2. If the applicant is satisfied that a modification is not substantial, applicants may notify the National Office of a non-substantial modification for its information.
3. Changes to contact details for the sponsor (or the sponsor's representative), Principal Investigator or other lead contact person are non-substantial modifications, and it is requested the National Office is notified for its information.

4.3.6 Decisions

1. The NREC-MD may reach a decision to provide one of the following opinions:
    a. Favourable opinion,
    b. Favourable opinion with conditions,
    c. Unfavourable opinion.
2. Where a NREC-MD gives a decision of 'favourable opinion with conditions', a list of those conditions will be enclosed with the letter informing the applicant of the outcome of the review. The applicant will address the conditions and forward any outstanding information or documentation to the National Office. The National Office will review the response to conditions and follow up with the applicant if further clarification is required.
3. If a final opinion cannot be reached on an application until further information or clarifications have been received from the applicant, the NREC will issue a 'request for further information'.
4. Where an application is issued a 'request for further information', the opinion letter will clearly outline the clarifications or further information required by the NREC.
5. Applicants issued with a 'request for further information' will be asked to reply to the request in line with submission deadlines for committee meetings. The response to request for further information will be reviewed at full Committee meeting whenever feasible.
6. For NREC-MD, where a 'request for further information' is not responded to within 6 months, the application will be deemed to have lapsed, unless appropriate justification can be provided. In cases such as this a new application must be submitted for committee review.
7. NREC-MD decision letters will be issued In line with requirements specified within the S.I. 671/2023 and S.I 257/2022 including where relevant a statement of conditions and applicable safety reporting obligations. The National Office will normally inform the applicant of the outcome of an ethics review within timelines stipulated by legislation.

4.3.7 Appeals process

1. The process for appeals of NREC-MD decision is outlined in the NREC appeals policy.

4.3.8 Reporting requirements

1. End of Study Report must be submitted to the National Office within 12 months of the end of the trial with a copy of the Clinical Investigation Report (as per ISO 14155:2020)/ Clinical Performance Study Report (as per ISO 20916:2019).

5.0 Specific procedures for National Research Ethics Committee for Clinical Trials (NREC-CT) under the clinical trial regulations (Clinical Trials Regulation (regulation (eu) no 536/2014))

5.1 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. Further information can be found in the Regulation (EU) No 536/2014 Questions & Answers document, Decision Tree, page 120.

If out-of-scope applications are received, they will be deemed 'invalid' by the RMS of that tri.

5.2 Clinical trial application assessment

5.2.1 Part I – Coordinated assessment

1. The HPRA will lead on the validation of documentation related to Part I submissions when Ireland is RMS. 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 Clinical Trial Information System (CTIS) portal.
3. , 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.

5.2.2 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:

   Recruitment arrangements

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

   Participant information and informed consent

   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

   Suitability of investigator

   g. CV template

   Suitability of facilities

   h. Signed site suitability template for each individual site signed by a site delegate

   Proof for insurance and indemnification

   i. Evidence of policy cover

   Financial and other arrangements

   j. Statement confirming source of funding
   k. Compensation for trial participant’s template
   l. 'Declaration of Interest' template

   Collection, storage and use of biological samples

   m. Compliance with use of human biological samples template

   Evidence of compliance with data protection laws

   n. National statement of compliance template

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 on NREC specific template
    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. 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.
8. Timelines for assessment will be in line with the Clinical Trial Regulation.

5.2.3 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.

5.2.4 Substantial modifications

1. The HPRA will lead on the validation and assessment of substantial modifications related to Part I documentation where Ireland is the RMS. 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.

5.2.5 Withdrawal and resubmission

1. Sponsors may withdraw an application at any stage of the assessment process. 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.

5.3 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.

5.4 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.

5.5 Monitoring and supervision of trials

5.5.1 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.

5.5.2 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.

5.5.3 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.

5.6 Appeals

1. In the event that a Sponsor receives an unfavourable 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 processed and managed 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 a 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. For more information please review the NREC appeals policy.

5.7 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

6.0 Specific procedures for National Research Ethics Committee for Clinical Trials (NREC-CT) under the Clinical Trial Directive (Clinical Trials Directive (EC) No. 2001/20/EC)

6.1 Applications under the Clinical Trials Directive

1. New applications under the Clinical Trials Directive (CTD) are no longer accepted by the National Office for Research Ethics Committees and must be submitted under the Clinical Trials Regulation (CTR) using the Clinical Trials Information System (CTIS)
2. All trials authorised under the CTD must end or transition to the CTR by 30 January 2025.
3. Sponsors are advised to submit any necessary outstanding substantial modifications to studies authorised under the CTD to the National Office for NREC review at their earliest convenience, in order to submit their trial for transition to the CTR.
4. Sponsors can use the following guidance available to assist with the transition.

- National Office FAQ: CTR and CTIS FAQs - NREC (nrecoffice.ie)
- The European Commission have published a guidance document for the transition of clinical trials under EudraLex volume 10.
- The Clinical Trials Coordination Group (CTCG) adopted a best practice guide for multinational sponsors of transitional trials.
- Training materials available on the EMA CTIS website under the Transitioning Trials section.

5. Trials which have not yet transitioned to the NREC-CT system from the authorising REC under the CTD can transition directly to CTR. Until the transition is initiated, safety and other applicable reporting should continue to be made to the authorising REC

6.2 Notification of conclusion or early termination

6. Applicants must inform the NREC-CT of the completion of the clinical trial within 90 calendar days of the completion date. A definition of conclusion should be included in the study protocol.
7. If a trial is discontinued prematurely, notification must be submitted within 15 calendar days to the NREC-CT. The notification must specify the reasons for discontinuing the trial prematurely.

8. When the sponsor halts a CTIMP temporarily, the NREC-CT should be notified within 15 calendar days by submission of a substantial amendment. The submission should clearly explain the reasons for the halt and the scope, e.g. stopping recruitment and / or interrupting the treatment of participants already included.
9. Sponsors must submit an End-of-Study Report to the NREC-CT within one year after completion of the trial.
10. The End-of-Study Report will be acknowledged in writing by the National Office.

6.3 Urgent safety measure

1. Applicants may at any time implement urgent safety measures to protect research participants against immediate risks to their health or safety.
2. Urgent safety measures do not require NREC approval before they can be implemented.
3. If such measures are implemented, the sponsor must inform the NREC, in writing, no later than three days after implementation and explain the circumstances that led to implementation of the urgent safety measures.

6.4 Monitoring the safety of clinical trials

1. It is the principal obligation of the applicant to monitor the ongoing safety of a clinical trial for which he or she is responsible.
2. The applicant 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 NREC as soon as possible and no later than seven calendar days after first becoming aware of them.
3. Within 8 calendar days of filing an initial SUSAR report, the sponsor must, where necessary, send any additional information to the NREC.
4. 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 calendar days after first becoming aware of them.
5. Sponsors are responsible for submitting annual safety reports in connection with trials each year to the NREC. 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.

6. The NREC-CT will be notified of annual safety reports. The NREC-CT, NREC-CT subcommittee or NREC-CT Chairperson may:
    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.
7. Where the NREC-CT has concerns about any of the above, the Chairperson or Deputy Chairperson should express these in writing to the trial sponsor. The sponsor should respond to these requests as soon as possible, after which the NREC will need to be satisfied that its concerns have been addressed adequately.
8. If an annual list of adverse effects gives rise to suspicions that the safety of subjects has been compromised, the National Office can refer the matter to the Health Products Regulatory Authority.
9. All safety reports will be acknowledged by the National Office in writing and a description of the safety report may be included in the NREC Committee Business Report to be distributed to NREC members for information.
10. In light of new ethics concerns following any new information received about a trial that may affect the safety, dignity or wellbeing of research participants, the NREC may revisit its opinion. Typically, such information if it had been received with the initial application, would not have resulted in a NREC favourable opinion. Where the NREC revisits or revokes its original opinion, the applicant will be informed and reasons provided. In this regard, such decisions will be taken at a quorate meeting of the full NREC.
    Where the NREC revokes its original opinion, it will inform the HPRA.

7.0 List of changes from previous version

- Updated relevant national legislation from S.I. 260/2021 as amended to S.I. 671/2023
- Overall update and streamlining of the document