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 ethically 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.

Impartial ethics review is designed to maintain the highest ethical standards of practice in research, to protect participants in research and research-workers from harm or exploitation, to preserve participants' rights, 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, 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, amending Directive 2001/83/EC, Regulation

[1] World Medical Association. (2001). World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bulletin of the World Health Organization, 79 (4), 373 - 374. World Health Organization. https://apps.who.int/iris/handle/10665/268312

(EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

- Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU
- S.I. No. 260/2021 - European Union (National Research Ethics Committee for Clinical Investigations of Medical Devices) Regulations 2021
- 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

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 an 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 an 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: In relation to a clinical trial or clinical investigation, the 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 in accordance with European Communities (Clinical Trials on Medicinal Products for Human Use) Directive 2004 (S.I. No 190 of 2004), European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2014 (S.I. No 041 of 2022) the Medical Device Regulation (MDR) (EU) 2017/745 (S.I. 260 of 2021) and the In Vitro Diagnostic Medical Device Regulation (IVDR) (EU) No 2017/746 (S.I. 257 of 2022).

2. The scope of remit for each NREC are outlined in its Terms of Reference, which are determined by the Minister of Health.

3. Each Chairperson, in consultation with the National Office, will ensure the membership equips the Committee to address all relevant considerations arising from a research ethics application. This may on occasion necessitate the consultation of an external expert in a specific area.

4. Each NREC comprises a minimum of 15 and a maximum of 28 members, of which a minimum shall be one quarter ‘lay’ members.

5. Where there is any doubt as to the category of membership (expert or lay) that a member addresses, the National Office will determine this categorisation for operational purposes.

6. A Chairperson and Deputy Chairpersons are appointed for an initial term (duration depending on the Terms of Reference for the particular NREC) from the date of appointment by the Minister.

7. The Chairperson is responsible for the conduct of Committee business and for ensuring that the Committee reaches clear decisions on all matters. The Chairperson will ensure that all members’ views are equally heard. The Chairperson will endeavour in so far as possible to ensure the Committee reaches its decisions through agreement by consensus; if consensus is unlikely, decisions may be made by a voting majority, with the Chairperson having a casting vote where necessary.

8. Quorum is required for all main NREC meetings. A quorum consists of seven members, one of whom must be the Chairperson and/or Deputy Chairperson, one expert member and one lay person.

9. If the Chairperson and Deputy Chairpersons are simultaneously absent from a meeting, another member of the NREC will be nominated by the appointed Chairperson as acting Chairperson for the purposes of the meeting.

10. Committee members will be appointed for an initial term by the Minister in line with the respective NREC Terms of Reference. Committee members may serve for consecutive terms on appointment by the Minister.
11. All members are appointed for their independent contributions and not in a representative capacity.
12. All members are expected to maintain confidentiality regarding meeting deliberations, applications, information on research participants and all related matters. Each member will sign and adhere to a confidentiality agreement and declaration of interest in relation to their work on any given NREC.
13. The National Office in collaboration with the Chairperson will produce an annual report on the Committee's activity, training, and attendance.
14. Committee meetings may be conducted virtually or in person. Members will attend virtual meetings using the video conferencing and electronic tools provided. On occasion and with advanced notice, members may be expected to attend face-to-face meetings.
15. Committee members will be required to attend a minimum of eight meetings per year. Members who are frequently absent may be asked to resign by the Chairperson. Special consideration for scheduled absences, e.g. maternal or paternal leave, sick leave, will be given.
16. The Chairperson, in consultation with the National Office, will give due consideration to the impact of repeated absences and/or inactive participation of individual members on both the individual's maintaining of sufficient committee experience and the functionality of the Committee as a whole.

3.2 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 agreed by 31 May in the previous year.
3. The closing dates for valid applications should normally be a minimum of 13 calendar days prior to each NREC meeting.
4. Documents for the meeting should be distributed to Committee members as soon as possible after the agenda is finalised and applications are validated, and in any case no later than 5 working days prior to the scheduled meeting.

5. All correspondence with the NRECs should be directed to the National Office.

3.3 Application validation

1. Applicants should normally receive notification of whether their application is ‘valid’ or ‘invalid’ within seven calendar days of validation, in line with the operational requirements of the particular NREC review process.

2. Invalid applications will require resubmission if ethics review is to proceed.

3. To be deemed ‘valid’, supporting documents must be marked with version numbers and dates in the case of the research protocol, information sheets, consent forms, letters to participants or others with an interest in the research, and any other documentation to be used in the research that is not already scientifically validated and referenced.

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. Revisions to applications that have been validated will be rejected. Applicants will have the option to withdraw their application and resubmit.

3.4 Review process of new applications

1. Valid applications for an ethics assessment should, where possible, be considered at a main meeting of an NREC.

2. All NREC 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 an NREC assessment report, which is submitted to the National Office.

4. Where an NREC 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. A committee 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. 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 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.

7. Only in very exceptional circumstances may an applicant be invited to attend an NREC meeting to inform the Committee's discussion of their application.

8. Minutes for every NREC meeting will be captured and added to the website in a timely manner after their approval. See Section 3.11 for more information on meeting minutes.

3.5 Conflicts of interest

1. All committee members and National Office staff will 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. 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.

4. 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).

5. 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.

6. Where a National Office staff member has a conflict of interest with a particular application, they may need to recuse themselves from any 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.
7. All conflicts of interest will be recorded in the minutes. See Section 3.11 for more information on meeting minutes.

3.6 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. Any external queries on the NREC operations or decisions should be directed to the National Office.

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.

3.7 Decisions

1. The NREC 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 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 NREC.
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.
6. NREC decision letters will be issued In line with requirements specified within the S.I. 260/2021, S.I. 41/2022, S.I. 99/2022 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.
7. Applicants will be asked to acknowledge receipt and acceptance of the NREC opinion and the associated conditions.
8. The National Office will ensure that that the minutes clearly record the decisions taken by the NREC and further information requested from applicants.
9. All final decisions will be made publicly available on the National Office website.

3.8 Study modifications

1. Substantial modifications will be assessed by the NRECs. Substantial modifications are those changes that are likely to have a bearing on the ethical aspects of a study, and include but are not limited to changes to:

    a. The physical or mental integrity of the study participants,

    b. The scientific value and significance of the study,

    c. The implementation of study protocols,

    d. The quality or safety of investigational products.

2. It is the responsibility of the applicant to determine whether an amendment is a substantial or non-substantial modification.

3. 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.

4. 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.

5. Substantial modifications may be reviewed as appropriate by:

    a. the Chairperson,

    b. an NREC sub-committee,

    c. a division of the NREC,

    d. at a main meeting of the NREC.

6. Substantial modifications should be submitted with a cover letter and NREC substantial modification form with a summary of the main contents of the updates/changes along with any relevant supporting documentation, including the study protocol, using tracked changes (not highlighting) where the changes are being made. If the changes listed are unclear in the view of the National Office, the modification may be marked as invalid and further information requested.

7. NREC decisions on substantial modifications will be issued in line with requirements specified within the S.I. 260/2021, SI 41/2022 and S.I. 257/2022.

3.9 NREC sub-committees

1. NREC sub-committees will be routinely 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. NREC sub-committee meetings can take place at a virtual meeting or in-person meeting, as appropriate.

3. 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.

3.10 Annual progress reports

1. The submission of an Annual Progress Report on the conduct of a study may be an NREC condition of approval.

2. When applicable, applicants should submit an Annual Progress Report to the NREC within 30 days following the anniversary of the date on which approval was given and for every year thereafter for the duration of the study.

3. End-of-Study reports must be submitted to the National Office within one year of the conclusion of the research study.

4. The submission of reports will be acknowledged by email by the National Office.

5. The NREC will be notified of the receipt of reports in the NREC Committee Business Report which will be shared with NREC committee members at main NREC meetings.

6. Templates for the Annual Progress Report and End-of-Study report are located on the National Office website.

7. Annual Progress Reports will be acknowledged and summarily reviewed by the National Office, and made available to the NREC members as a matter of procedure. When reviewing Annual Progress Reports, the National Office should escalate any concerns about the study to the Chair in the first instance. Copies or summaries may be distributed to members on request.

8. Under the Clinical Trials Regulations, there is no requirement for the submission of an Annual Progress Report and it will not be a requirement of the NREC-CT.

3.11 End of Study Reporting

1. Sponsors must submit must notify the National Office once a trial has ended in Ireland.

2. Sponsors must notify the National Office of the global end of a clinical trial.

3.12 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 present for the review,

    b. Any member or National Office staff conflicts of interests,

    c. The submission of written comments by members unavailable to attend the meeting,

    d. The substance of any advice given by the committee,

    e. The opinion that the NREC returns on the application,

    f. A summary of the main ethical considerations,

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

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

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

    j. Where an unfavourable opinion is given on a substantial modification, the reasons for the decision.

2. Minutes from any given meeting will be reviewed and formally approved by the NREC at the next subsequent meeting.

3. Minutes will be uploaded to the National Office website within 14 calendar days of NREC approval.

3.13 Site suitability

1. Applicants must provide the NREC with a completed Site Suitability Form signed by the principal investigator for each site. The principal investigator is the chief authorised health care professional responsible for the conduct of the study at a site.

2. The principal investigator for each site sign-off must confirm that the site has sufficient facilities, personnel, and resources to conduct the particular clinical trial or clinical investigation.

3. It is the role of the NREC to assess the adequacy of the site, including the support staff, available facilities, and any emergency procedures.

4. The responsibility for ensuring that the correct permissions have been sought at each site will lie with the applicant.

5. The NREC at its discretion may a request a site visit to inform its deliberations.

3.14 Insurance & indemnity cover

1. NRECs are not expected to undertake detailed expert scrutiny of the insurance policies pertaining to the research described in the applications they review. The responsibility for ensuring that cover is sufficient and complete lies with the applicant.

2. The NREC should receive an assurance from the applicant that there are adequate insurance or indemnity arrangements in place for the potential legal liability arising from the research, and that provisions in proportion to the risk for compensation or treatment in the event of injury, disability or death attributable to participation, have been considered.

3. In particular, this information should evidence that:

    a. the insurance arrangements cover the research study concerned,

    b. the sponsor and, except for Phase 1 trials, all protocol authors, investigators/collaborators and, where applicable, Site Management Organisations will all be protected by insurance or indemnity arrangements,

   c. the arrangements will provide adequate cover to meet the potential liability assessed by the sponsor.

4. Where a site, sponsor or Investigator come under the Clinical Indemnity Scheme, the sponsor and/or Investigator is responsible for notifying the State Claims Agency of the study.

4.0 SPECFIC PROCEDURES FOR CLINICAL TRIAL DIRECTIVE (Clinical Trials Directive (EC) No. 2001/20/EC)

4.1 Scope of the NREC-CT

1. The scope of the remit of the NREC-CT is determined by its Terms of Reference.
2. For operational reference purposes, the NREC-CT will only accept applications for review related to:
    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).
3. Non-interventional studies and trials without medicinal products are out-of-scope for the NREC-CT.
4. If out-of-scope applications are received, they will be deemed 'Invalid' by the National Office.

4.2 Documentation requirements

1. Applicants must complete the designated Clinical Trials Application Form (either the NREC specified template or the Department of Health template) as part of the application of a CTIMP for ethics review.
2. Applicants must provide the following information, if relevant to their clinical trial:
    a. An outline of the anticipated benefits and risks to the study participants,
    b. The clinical trial protocol,
    c. An outline of the suitability of the investigator and supporting staff,
    d. The investigators' brochure,
    e. An outline of the clinical trials facilities at each site,

f. The arrangements for the recruitment of subjects,

g. Materials involved in the recruitment of participants such as patient information leaflets, advertisements, invitation letters etc.,

h. The participant consent forms,

i. The provision made for indemnity or compensation in the event of injury or death attributable to the clinical trial,

j. The provision made for insurance or indemnity to cover the liability of the investigator and sponsor,

k. Statement outlining how the trial complies with data protection legislation,

l. Data Protection Impact Assessment (DPIA) with comments from the Data Protection Officer, if a DPIA is required for the study,

m. The terms of any agreement between the sponsor and the owner or occupier of the trial site which are relevant to the arrangements

n. Proof of fee payment.

3. Any supporting documentation must be marked with version numbers and dates in the case of the research protocol, information sheets, consent forms, letters to participants or others with an interest in the research, and any other documentation to be used in the research that is not already scientifically validated and referenced.

4.3 Notification of conclusion or early termination

1. 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.

2. 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.

3. 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.

4. Sponsors must submit an End-of-Study Report to the NREC-CT within one year after completion of the trial.

5. The End-of-Study Report will be acknowledged in writing by the National Office.

4.4 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.

4.5 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 an 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.

4.6 Payment of fees for NREC-CT

1. The procedure for payment of fees for review is outlined in the “National Office for Research Ethics Committees – Payment of Fees[2]” guidance document.

[2] https://www.nrecoffice.ie/wp-content/uploads/National-Office-Applicant-procedure-for-payment-of-fees-V2.pdf

5.0 SPECIFIC PROCEDURES FOR CLINICAL INVESTIGATIONS OF MEDICAL DEVICES AND PERFORMANCE STUDIES OF IN VITRO DIAGNOSTIC MEDICAL DEVICES

5.1 Scope of the NREC-MD

1. The scope of the remit of the NREC-MD is determined by Regulation (EU) 2017/745 (S.I. 260/2021) 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. Applicants are requested to state in the application cover letter to which Article of the MDR/IVDR their application relates, and to contact the competent authority (the Health Products Regulatory Authority) if necessary to confirm which article applies to a study.
5. If out-of-scope applications are received, they will be deemed ‘invalid’ by the National Office.
6. Applicants should familiarise themselves with their regulatory application obligations to the competent authority (the HPRA) under the MDR/IVDR.
7. 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).

5.2 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), were permitted to continue but, since that date, they 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. reporting, including safety reports, device deficiencies, and annual reporting (as applicable),
   b. any other matter that requires an ethical decision, such as substantial, modifications, or
   c. any other matter that requires notification, such as non-substantial modifications.
3. In practice, all clinical investigations of medical devices must report to the NREC-MD for research ethics purposes. The requirement for a decision by, or report or notification to, the NREC-MD will be the 'trigger' for transfer of the relevant historical documentation on studies approved by a local REC to the National Office for the records of the NREC-MD.

5.3 Substantial modifications

1. For those ongoing medical device studies approved by local RECs under the Medical Device Directives that require a substantial modification after the date of MDR implementation (26th May 2021), applicants will need to apply for ethics review by the NREC-MD.
2. Substantial modifications to studies originally approved under the MDR/IVDR must continue to be reviewed by the NREC-MD.

5.4 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.

3. Documents must be numbered, marked with version numbers and dates.

5.5 Notification of conclusion or early termination

1. Applicants must inform the NREC-MD of the completion of the study within 90 calendar days of the completion date. A definition of completion should be included in the study protocol.
2. If a study is discontinued prematurely, notification must be submitted within seven calendar days to the NREC-MD. The notification must specify the reasons for discontinuing the study prematurely.
3. When the applicant halts a study temporarily, the NREC-MD should be notified within seven calendar days by submission of a substantial modification. 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.
4. The applicant must submit an End-of-Study Report to the NREC-MD within one year after completion of the study.
5. The End-of-Study Report will be acknowledged in writing by the National Office.

5.6 Urgent safety measure

1. The applicant 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 applicant 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.

5.7 Monitoring the safety of clinical investigations/performance studies

1. It is the primary obligation of the applicant to monitor the ongoing safety of a study.

2. The applicant must ensure that data on serious adverse reactions/device deficiencies occurring in the concerned study at any site in Ireland are reported, in writing (by email), to the NREC as soon as possible after first becoming aware of them.

3. The NREC-MD will be notified of safety reports. The NREC-MD, an NREC-MD subcommittee or the NREC-MD Chairperson may:
    a. Assess the continued safety of the concerned study,
    b. Assess the continued 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.

4. Where an NREC has concerns about any of the above, the Chairperson or Deputy-Chairperson should express these in writing (by email) to the study's Principal Investigator. The Principal Investigator should respond as soon as possible, after which the NREC will need to be satisfied that its concerns have been addressed adequately.

5. If evidence of adverse events gives rise to suspicions that the safety of participants has been compromised, the National Office can refer the matter to the competent authority/regulatory body. In Ireland, the Health Products Regulatory Authority (HPRA) is the designated national competent authority and market surveillance authority for medical devices and in vitro diagnostic medical devices.[3]

6. Safety reports will be acknowledged by the National Office in writing (by email) and will be included in the NREC Committee Business report which is provided to NREC-MD members for information, at each meeting of the Committee.

7. 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 a previously given favourable opinion. Typically, such information, if it had been received with the initial application, would not have

[3] https://www.hpra.ie/homepage/medical-devices/regulatory-information/medical-devices-regulation/clinical-investigations

resulted in an NREC favourable opinion. Where the NREC revisits or revokes its original opinion, the applicant will be informed and reasons provided. Where the NREC revokes its original opinion, it will inform the HPRA.

5.8 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.

5.9 Appeals process

1. Following NREC-MD decision, applicants will be asked to notify the Committee in writing (by email) not later than 10 days (for medical devices) after the notification is sent whether they

    a. accept the decision,

    b. intend to resubmit the application,

    c. plan to appeal the decision.

2. Where an applicant is unsatisfied with an unfavourable opinion, in the first instance the applicant is advised to speak with the National Office.

3. Applicants are encouraged to resubmit the original application with a statement clearly outlining why the original application should be re-reviewed by the NREC.

4. An official appeal of an NREC decision should be submitted by the applicant to the National Office within 28 days of receipt of notification of the NREC's final decision for medical devices, and within 30 days after the date on which the sponsor was given notice of a decision for in vitro diagnostic medical devices. The applicant should clearly state the justification(s) for appeal in addition to submitting all documentation which was reviewed by the NREC.

5. The appeal of an NREC decision will be considered by an independent appeals panel convened by the National Office. No member of the NREC that reviewed the application will sit on the appeals panel. The appeals panel may consult with any person which it believes could assist in the consideration of the appeal.

6.0 SPECIFIC PROCEDURES FOR CLINICAL TRIAL REGULATIONS (Clinical Trials Regulation (Regulation (EU) No 536/2014))

6.1 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.

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

6.2 Clinical trial application assessment

6.21 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 Clinical Trial Information System (CTIS) portal.
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.

6.23 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. Signed CV template

   Suitability of facilities

   h. Signed site suitability template for each individual site

   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. Signed 'Declaration of Interest' template

   Collection, storage and use of biological samples

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

   Evidence of compliance with data protection laws

   o. National statement of compliance template
   p. Optional study-specific Data Protection Impact Assessment (DPIA)

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.

6.23 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.

6.24 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.

6.25 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.

6.3 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.

6.4 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.

6.5 Monitoring and supervision of trials

6.51 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.

6.52 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.

6.53 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.

6.6 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.

6.7 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