NATIONAL OFFICE FOR RESEARCH ETHICS COMMITTEES

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 review applications for ethics review made 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 every application made to the NRECs via the National Office.

This framework is consistent with Ireland's Member State obligations under the under Directive 2001/20/EC for clinical trials of investigational medicinal products (CTIMPs), and Regulation EU No 2017/745 for clinical investigations of medical devices of the European Parliament, and prevailing national implementing legislation, namely the Statutory Instrument No 190/2004 - European Communities (Clinical Trials on Medicinal Products For Human Use) Regulations, 2004 and Statutory Instrument No. 260/2021 - European Union (National Research Ethics Committee for Clinical Investigations of Medical Devices) Regulations 2021.

[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

2.0 DEFINITIONS

Amendment: Any modification made to the study protocol or any other material information coming to pass after the study has started, which may have an impact on the conduct of the study. An amendment can be categorised as substantial or non-substantial (see definitions below).

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

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 medical 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 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 as designated by legislation pertaining to the regulated professions encompassed by the Dentists Act 1985, the Health and Social Care Professionals Act 2005, the Pharmacy Act 2007, the Medical Practitioners Act 2007, and the Nurses and Midwives Act 2011.

(b) has qualifications or experience *directly* relating to the conduct of health research (other than as a member of a research ethics committee) encompassed by the remit of the Committee of which the individual holds membership;

(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 that is being tested or used as a reference, including as a placebo, in a clinical trial.

Investigator: The authorised health care professional responsible for the conduct of a clinical trial / investigation at a site. If a trial is conducted by a team of authorised health care professionals at a trial site, the investigator is the leader responsible for that team and the accountable health care professional for the research at that site.

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

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 PPI (Patient Public Involvement) 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; and

(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: A health product or piece of equipment that a person uses for a medical purpose. Such devices can diagnose, monitor, or treat illness or disease and assist people with physical impairments. Examples include plasters and bandages, wheelchairs, contact lenses, blood pressure meters, pregnancy test kits as well as more complex equipment like related software, incubators, hip implants, and coronary pacemakers.

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, established by the Department of Health as a public office with an independent statutory role in the regulation of health research ethics.

National Research Ethics Committee (or NREC): 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 where 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: An amendment that is not a substantial amendment, and as such, not requiring research ethics review by the NREC.

NREC Committee 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 agenda ahead of each NREC meeting.

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

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 or clinical investigation, the person who or entity that 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: 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) Regulations 2004 (S.I. No 190 of 2004) and the Medical Device Regulation (MDR) (EU) 2017/745 (S.I. 260 of 2021).

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

3. The 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 from time to time necessitate the consultation of an external expert in a specific area.

4. Each NREC comprises a minimum of 15 and a maximum of 21 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. A Chairperson and Deputy Chairpersons may serve for two consecutive terms on 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 of three years by the Minister in line with the respective NREC Terms of Reference. Committee members may serve for two 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 adhere to and sign a Confidentiality Agreement in relation to their work on any given NREC.

13. The Chairperson in collaboration with the National Office 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 will 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 as soon as possible after the agenda is finalised and applications are validated, and in any case no later than 10 calendar days prior to the scheduled meeting.

5. All correspondence with the NRECs should be directed to through 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 straight forward 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 decision should be reviewed 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. Lead reviewers will complete an NREC assessment report with input from secondary reviewers.

4. Where an NREC does not have a member with professional expertise in a specific area related to a valid application (e.g. products involving genetically modified organisms), 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 or vote *in abstentia*.

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, regulators, etc.) regarding the research 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. The Applicant may 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 within 14 days of 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 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 verbal declaration at the NREC meeting prior to the matter being

considered or written declaration to the Chairperson and the National Office prior to the meeting.

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

4. 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.

5. 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 within 14 calendar days from the date of issue of the request for further information. If a response is not received in a timely manner, the National Office, in consultation with the NREC Chairperson, retains the right to consider the application as ‘Withdrawn’. In this instance, the Applicant will be required to resubmit if an NREC opinion is still required.

6. NREC decision letters will be issued In line with requirements specified within the S.I. No 190 / 2004 and S.I. 260 / 2021, including where relevant a statement of conditions and safety reporting obligations. The National Office will normally inform the Applicant of the outcome of an ethics review within five working days of a meeting being held.

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 any further information requested from Applicants.

9. All final decisions will be made publicly available on the National Office website.

3.8 Study amendments

1. Substantial amendments will be assessed by the NRECs. Substantial amendments 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 amendment.

3. If the Applicant is satisfied that an amendment is not substantial, Applicants may notify the NREC of a non-substantial amendment 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 amendments, and it is requested the NREC is notified for its information.

5. Substantial amendments may be reviewed as appropriate by:

    a) the National Office in consultation with the Chairperson,

    b) an NREC sub-committee,

    c) a division of the NREC,

    d) at a main meeting of the NREC where time allows.

6. Substantial amendments should be submitted with a cover letter and substantial amendment form with a summary of the main contents of the updates / changes along with any relevant supporting documentation, including the study protocol, which are clearly marked where the changes are being made. If the changes listed are unclear in the view of the National Office, the amendment may be marked as invalid and further information requested.

7. NREC decisions on substantial amendments will be issued in line with requirements specified within the S.I. No 190 / 2004 and S.I. 260 / 2021.

3.9 NREC sub-committees and divisions

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. Any NREC sub-committee will include the Chairperson or a Deputy Chairperson and a minimum of two additional committee members, one lay and one expert.

3. NREC divisions may be convened to review substantial amendments and new applications for the purposes of an effective and efficient consideration of applications and to meet timelines set out by the legislation.

4. Any NREC division will include the Chairperson or a Deputy Chairperson and a minimum of six additional committee members, ensuring representation of both lay and expert members.

5. NREC sub-committee and division meetings can take place at a face-to-face meeting or virtual meeting, as appropriate.

6. Decisions made at sub-committee / division 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 research study is an NREC condition of approval.

2. Applicants must submit an Annual 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 should be submitted to the National Office within one year of the conclusion of the research study.

4. The submission of all such reports will be acknowledged in writing by the National Office.

5. The NREC will be notified of the receipt of the report in the NREC 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 reviewed by the NREC (or reviewed by the National Office on behalf of the Committee). When reviewing annual progress reports, National Office should escalate any concerns about the study to the Chair in the first instance. The Committee should be notified of the receipt of the report. Copies or summaries may be distributed to members on request.

3.11 Meeting minutes

1. The meeting minutes will 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 an expert;

    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 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 amendment, 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.

3.12 Site suitability

1. Applicants must provide the NREC with a completed Site-Specific Assessment form or a Site Suitability form signed by lead investigator for each site. The lead investigator is the chief authorised health care professional responsible for the conduct of a clinical trial / investigation at a site.

2. The lead 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 NRECs 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.

3.13 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 Applicants 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 must 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 research study.

4.0 CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS (CTIMP)-SPECIFIC PROCEDURES

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. The NREC-CT will accept the NREC-CT application form available through the NREC website or the Clinical Trials Application Form currently used by the local RECs, for a limited period.

2. If not captured within the application form, 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 CLINICAL INVESTIGATIONS OF MEDICAL DEVICES SPECIFIC PROCEDURES

5.1 Scope of the NREC-MD

1. The scope of the remit of the NREC-MD is determined by its Terms of Reference and S.I. 260/2021.

2. For operational reference purposes, the NREC-MD will only accept applications for review related to clinical investigations involving:

    a. Non-CE marked devices being used in a clinical investigation for one or more of the purposes specified in MDR Article 62:

        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. CE-marked medical devices being used in a clinical investigation outside the scope of its intended purpose. MDR Article 74(2).

    c. 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. MDR Article 74(1).

    d. 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. MDR Article 75.

    e. Clinical investigations not performed pursuant to any of the purposes listed in Article 62(1). MDR Article 82.

3. Applicants are requested to state in the application cover letter to which Article of the MDR their application relates.

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 under the MDR.

6. The timelines for NREC decisions will be consistent with those required by the regulation for medical devices (EU No 2017/745 and S.I. 260/2021). In the first instance, the NREC-MD will review clinical investigations of medical devices monthly. Applicants submitting to the NREC-MD may expect a decision on a valid new application within 55 days and on substantial amendment within 45 days.

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 SI252/1994 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), can continue, but after this 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 as of the 26th May 2021 notify the NREC-MD on all aspects of:

- reporting, including annual and safety reports and device deficiencies;
- any other matter that requires an ethical decision, such as substantial, amendments; or
- any other matter that requires notification, such as non-substantial amendments.

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 the local REC system to the National Office for the records of the NREC-MD.

5.3 Substantial amendments

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

5.4 Documentation requirements

1. Applicants must complete an the designated NREC-MD Application Form as part of the application for ethics review of a clinical investigation of a medical device. The NREC-MD will accept the NREC-MD application form available through the National Office website or the 'Standard Application Form – Adapted Version (August 2018) for the Ethical Review of Health-Research Studies, which are not Clinical Trials of Medicinal Products for Human Use as defined in S.I. 190/2004' until January 2022. Where applications are supported by the latter, they must include an Application Appendix, which includes supplementary questions required by the NREC-MD.
2. In addition to the application form, Applicants must provide the following information, if relevant to their clinical investigation:
    a. Validation Checklist
    b. Evidence of payment of the relevant fee
    c. Cover letter on headed paper
    d. Summary CV for the Principal Investigator
    e. Research participant information leaflet
    f. Research participant consent form
    g. Insurance / Indemnity certificate for each investigation site
    h. Site suitability form or site-specific assessment form (for each site)
    i. Data protection impact assessment (or statement why not required) signed by the DPO

j. Details of any data monitoring committee

k. Signed statement of conformity to safety and performance requirements

l. Letter from sponsor confirming outsourcing of duties and functions

m. Case report form

n. Copies of advertisement material for research participants, e.g. posters, newspaper adverts, website. For video or audio recordings, printed scripts are required.

o. Clinical Investigation Plan

p. Investigator Brochure

Additional Documentation (if available)

q. Letter of invitation for participant

r. Next-of-Kin information leaflet and assent form

s. Diary card /participant card

t. Validated questionnaire

u. Non-validated questionnaire

v. Medical device implant card (if applicable)

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.

5.5 Notification of conclusion or early termination

1. Applicants must inform the NREC-MD of the completion of the clinical investigation within 90 calendar days of the completion date. A definition of conclusion should be included in the study protocol.

2. If an investigation is discontinued prematurely, notification must be submitted within seven calendar days to the NREC-MD. The notification must specify the reasons for discontinuing the investigation prematurely.

3. When the Applicant halts a clinical investigation temporarily, the NREC-MD should be notified within seven 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. The Applicants must submit an End-of-Study Report to the NREC-MD within one year after completion of the clinical investigation

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

5.6 Urgent safety measure

1. The 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 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

1. It is the primary obligation of the Applicant to monitor the ongoing safety of a clinical investigation, for which he or she is responsible.

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

3. The Applicants are responsible for submitting annual safety reports in connection with investigations each year to the NREC. The annual safety reports will consist of an itemised analysis of safety information related to the concerned clinical investigation, highlighting the main points for ethical consideration.

4. The NREC-MD will be notified of annual safety reports. The NREC-MD, NREC-MD subcommittee or NREC-MD Chairperson may:

a. Assess the continued safety of the concerned clinical investigation;

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.

5. Where an NREC has concerns about any of the above, the Chairperson or Deputy-Chairperson should express these in writing to the investigation's Principal Investigator. The Principal Investigator 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.

6. 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.

7. 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.

8. 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.

5.8 Payment of fees for NREC-MD

1. The procedure for payment of fees for review outlined in the "National Office for Research Ethics Committees – Payment of Fees[3]" guidance document.

5.9 Appeals process

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

1. The appeals process is currently only available for opinions of the NREC-MD. While the NREC-CTs are running concurrently with the local ‘recognised RECs’ for a defined transition period, an appeals process will not be available for NREC-CT decisions.

2. Following NREC-MD decision, Applicants will be asked to notify the Committee in writing whether they a) accept the decision; b) intend to resubmit the application; c) plan to appeal the decision within 10 days of receipt of the NREC-MD opinion.

3. Where an Applicant is unsatisfied with an unfavourable opinion, in the first instance the Applicant is strongly advised to speak with the National Office.

4. The Applicant may be given the option to resubmit a new application addressing the concerns of the NREC or to resubmit the original application with a statement clearly outlining why the original application should be re-reviewed by the NREC. It will be a matter for the Chairperson of the NREC to decide if more than one opportunity for re-review is appropriate.

5. Only when the Applicant has fully engaged with the NREC through the National Office and exhausted all avenues at NREC level, should they approach the National Office about initiating an appeal.

6. A request for appeal of an NREC decision should be submitted by the Applicant to the National Office within 28 days from the date of notification of the NREC’s final decision. The Applicant should clearly state the grounds for appeal in addition to submitting all original documentation reviewed by the NREC.

7. 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 external experts to inform their deliberations.