NATIONAL OFFICE FOR RESEARCH ETHICS COMMITTEES

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Clinical Trials Regulation

National Collaboration Project Guide for industry and academic volunteer applicants

March 2021

1.0 PROJECT SCOPE

The way clinical trials are conducted across the European Union will undergo major changes under the Clinical Trials Regulation (CTR) – due to be applied in early 2022. The CTR will harmonise the assessment and supervision processes for clinical trials throughout the EU, via a Clinical Trials Information System (CTIS). This in turn will harmonise submission and assessment processes, improve collaboration and information-sharing, increase transparency, and further improve standards of safety for research participants – collectively fostering an environment that is more favourable for conducting clinical trials across the EU.

The CTR represents significant change to the way sponsors submit clinical trial documentation, and how the Health Products Regulatory Authority (HPRA) and the newly launched National Research Ethics Committees (NRECs) review and approve clinical trials in Ireland. The scope of the NREC for review of Clinical Trials of Medicinal Products (NREC-CT) will be based on the requirements of the EU CTR.

The National Collaboration Project is jointly run by the HPRA and the National Office for Research Ethics Committees (hereafter the 'National Office') over a six-month period. It aims to enable national readiness for and facilitate a smooth national transition to, the CTR by replicating in so far as possible the coordinated processes necessary to deliver a 'single national opinion' from the two authorities.

As part the collaborative project, the HPRA and the NREC-CT, supported by the National Office, will work closely with a small group of volunteer academic and industry sponsors conducting trials in Ireland. Together, we will work through the CTR timelines and processes for review of a select number of clinical trials ahead of the application of the CTR later in 2021.

In addition to testing the coordination of processes of the HPRA and the NREC-CT to simulate the 'real CTR environment', applicants also have much to gain from participating in the project:

- Acquire a comprehensive understanding of the requirements of the CTR;
- Obtain experience in the submission of CTR-relevant documentation;
- Submit single set of documentation to both authorities for review;
- Receive ethics and national competent authority decisions simultaneously;
- Have opportunity to feedback on regulatory and ethics review processes ahead of the application of the CTR.

This project is due to commence in May 2021 and will run until December 2021.

2.0 PROCEDURE

2.1 General

Sponsors and applicants will participate in the project on a voluntary basis. As part of participating in the project, the sponsor must consent to the relevant documentation being

sent to the NREC-CT for review. Fees are paid to the HPRA, and the National Office, respectively in the usual way.

It is important to note that CTIMPs submitted for review under the CTR-National Collaboration Project will be authorised under current legislation. This means that the project's processes reflect those required by the CTR, while also being in compliance with current national and European legislation.

2.1 Submission

1. To participate in the project, the sponsor must submit the relevant documentation within 7 calendar days of the HPRA cut-off deadline at the very latest.
2. Applications should be submitted to the HPRA. The HPRA will then share the relevant documentation from Part I and all of Part II with the NREC-CT via the National Office
3. The sponsor must include the following statement in the subject line of the cover letter submitted with the Clinical Trial Application (CTA) to the HPRA: **CTR -National Collaboration Project – Request to participate**.
4. The cover letter should also include a list of the documents submitted in Part I and Part II. (Please see Section 3.0 for an outline of the documentation required under Part I and Part II).

2.2 Validation

1. The HPRA will undertake the validation of Part I documentation and the National Office will undertake the validation of Part II documentation
2. Notification of validation of both Parts will be sent to the sponsor jointly by the HPRA and the National Office on or before the general HPRA cut-off deadline (or within 7 calendars days of the date of the deadline for receipt of the project documentation) along with a timetable of the assessment process.
3. If the application is deemed 'invalid', for any reason, the sponsor has up until the HPRA cut-off deadline to rectify any issues with the documentation (or within 7 calendars days of the date of the deadline for receipt of the project documentation).
4. If submissions cannot be validated before the HPRA cut-off deadline, they will be validated at the next monthly cut-off date.

2.3 Assessment

1. The HPRA will assess Part I jointly with the NREC-CT, while Part II will be independently assessed by the NREC-CT.
2. Requests for further information on Part I documentation will be sent to the sponsor by the HPRA within 25 calendar days of validation.
3. Requests for further information on Part II documentation will be sent to the sponsor by the National Office on behalf of the NREC-CT within 25 calendar days of validation.

4. The sponsor should submit the requested information as a single response to both the HPRA and the NREC-CT within 14 calendar days.

2.4 Approval

1. The sponsor's response to the request for further information will be reviewed by the HPRA and the NREC-CT.
2. The HPRA and the NREC-CT will jointly agree on an opinion for Part I, while the NREC will independently come to an opinion on Part II.
3. Under the CTR, a single national opinion would be provided. To mimic this system, the HPRA and the NREC-CT will issue their opinions within 60 calendar days of the validation date.

2.5 Substantial amendments

1. Substantial amendments (modifications) to clinical trials that were approved via the Clinical Trial Regulation-National Collaboration Project should be submitted to the HPRA for approval through the Clinical Trial Regulation-National Collaboration Project. A substantial amendment may consist of amendments to Part I documents only, amendments to Part II documents only, or amendments to both Parts I and II.
2. The HPRA and the NREC-CT will jointly review substantial amendments to Part I documents, while the NREC-CT will independently review substantial amendments to Part II documents
3. When submitting a substantial amendment as part of the National Collaboration Project, the sponsor will need to include a cover letter with the following statement in the subject line: **Clinical Trial Regulation-National Collaboration Project – substantial amendment to <Part 1> or <Part I & Part II> or <Part II>.** They will also need to provide a list of the documents submitted in Part I and/or Part II, highlighting the documents in Part I that cannot be shared with EC.
4. The HPRA will validate amendments related to Part I and the National Office will validate amendments related to Part II. Notification of validation will be sent within 5 calendar days of receipt of the substantial amendment.
5. If the amendment application is invalid or documentation is missing, the applicant has 10 calendar days to correct deficiencies or omissions. Again, notification of validation from the HPRA and / or the National Office will be sent within 5 calendar days of receipt of the amended or corrected substantial amendment.
6. A substantial amendment may be directly approved, or grounds for non-acceptance/requests for further information may be issued by the HPRA, and/or by the National Office on behalf of the NREC-CT.
7. The applicant will have 9 calendar days to respond to requests for further information.
8. The HPRA and the NREC-CT will jointly agree on an opinion for substantial amendments to Part I documentation, while the NREC-CT will independently come to an opinion on substantial amendments to Part II documentation. Final opinions will be issued within 35 calendar days of the validation date.

3.0 Document requirements

The tables below are to assist applicants and / or sponsors in identifying and differentiating the documents required for Part I and Part II assessment. The documents covered by Part I of the assessment report for a clinical trial are listed in Table I. The documents covered by Part II of the assessment report are listed in Table II.

The content of the documents fulfil the requirements of the current legislation.

Table I: Part I documentation requirements

Part I documents	
A	Cover Letter
B	EU application form
C	Clinical trial protocol
D	Investigator's brochure (or SmPC)
E	Documentation relating to compliance with good manufacturing practice (GMP) for the investigational medicinal product
F	Investigational Medicinal Product Dossier (IMPD) for investigational medicinal products and placebos – this may be simplified for authorised
G	Auxillary Medicinal Product Dossier
H	Scientific Advice and Paediatric Investigation Plan
I	Content of the labelling of the investigational medicinal products
J	Proof of payment of fee per Member State concerned

Table II: Part II documentation requirements

Part II documents	
K	Recruitment arrangement information per Member State concerned • *Completed 'Recruitment and informed consent procedure template'* • *All relevant materials such as advertisements or invitation letters*
L	Subject information, informed consent form and informed consent procedure per Member State concerned. • *Completed 'Recruitment and informed consent procedure template'* • *Consent / assent forms* • *Participant information leaflet*
M	Suitability of the investigator per Member State concerned • *CV of Principal Investigator*
N	Suitability of facilities per Member State concerned • *Completed 'Site-specific assessment form' signed by site Principal Investigator and site CEO or person on behalf of CEO.*

	• *CV of Principal Investigator at each site*
O	Proof of insurance cover or indemnification per Member State concerned
P	Financial and other arrangement per Member State concerned • *Statement confirming source of funding* • *Completed 'Compensation for trial participants' template* • *Signed 'Declaration of interest'*
Q	Proof of payment of fee per Member State concerned • *Or fee waiver request if relevant*
R	Proof that data will be processed in compliance with union law on data protection • *Statement outlining measures in place to comply with both Irish national legislation (e.g. Health Research Regulations 2018) and European legislation (e.g. General Data Protection Regulations 2018).* • *Data Protection Impact Assessment reviewed by Data Protection Officer (or statement stating why DPIA not necessary*).