

Guide to **Clinical Trials Regulation-National Collaboration Project (CTR-NCP)**

Health Products Regulatory Authority and National Office for Research Ethics Committee Joint Project for the Authorisation of Clinical Trials on Medicinal Products for Human Use

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DISCLAIMER

This guideline may be modified during the pilot project, due to ongoing discussions at European and national level on the implementation of the Clinical Trial Regulation.

This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.



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1 GLOSSARY

AR: Assessment Report – the EU-agreed assessment report templates for Part I and Part II (see below) will be used in the collaboration project.

Clinical Trial: Clinical trial as defined in European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004.

CTA: Clinical Trial Application.

CTIS: Clinical Trial Information System, set up under the CTR, will contain the centralised EU portal and database for clinical trials in Europe overseen by the Regulation.

CTR: 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, and repealing Directive 2001/20/EC.

CTR-National Collaboration Project: A collaboration project for assessment of clinical trial applications and subsequent substantial amendment submissions in Ireland established by the HPRA, in conjunction with ethics committees and sponsors to prepare for implementation of the Regulation.

EC: Ethics committee as defined in European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004. Only ethics committees that are formally 'recognised' by the Department of Health under the current legislation can review clinical trials.

HPRA: The Health Products Regulatory Authority, the national competent authority for clinical trials of medicinal products in Ireland.

National Office: The National Office for Research Ethics Committees which is established as a statutory office with an independent role within the Health Research Board.

NREC-CT: National Research Ethics Committees for the review of Clinical Trials of Investigational Medicinal Products, set up in accordance with European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 (S.I. No 190 of 2004), to return ethics decisions that are respected nationally in relation to clinical trial applications.

Part I and Part II documents (as per Articles 6 and 7 of Regulation (EU) No 536/2014): Under the CTR, assessment of CT application dossiers will be divided into two parts. Part I documents will be assessed by the competent authority (HPRA) and, potentially, the NREC-CT, while Part II documents will be assessed by the NREC-CT.

For the CTR-National Collaboration Project (Collaboration Project), the NREC-CT will assess both Part I and Part II documents. The aspects of the dossier covered by Part I and Part II of the assessment report are detailed in Annex I of the CTR (see Tables 1 and 2 below).

Submissions under the CTR will be made through the EMA Clinical Trial Information System (CTIS), which will clearly divide the dossier into Part I and Part II for assessment purposes. However, this function will not be available to stakeholders participating in the Collaboration Project. Nonetheless, applications submitted under the Collaboration Project should follow the dossier format outlined in the CTR (the HPRA and the National Office will provide a folder structure for downloading on their websites). The tables below should assist applicants on behalf of sponsors in 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 1. The documents covered by Part II of the assessment report are listed in Table 2.

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

Table 1. Application Dossier – Part I

Part I documents - Relevant to the HPRA and ethics committee	
1	Cover letter – including request for participation on the collaboration project and a list of commercially-sensitive documents that should not be circulated to the NREC-CT.
2	EU application form. (The current EudraCT form should be used during the collaboration project.)
3	Clinical Trial Protocol.
4	Investigator’s brochure (or SmPC).
5	Documentation relating to compliance with Good Manufacturing Practice (GMP) for the Investigational Medicinal Product (IMP)*. For example: Copy of the manufacturing authorisation; Certification by a Qualified Person (QP).
6	Investigational Medicinal Product Dossier (IMPD) for IMPs and placebos (can be ‘simplified’ if the medicine is authorised).
7	Auxiliary Medicinal Products*.
8	Scientific advice and Paediatric Investigation Plan*.
9	Proof of payment of HPRA fee, or fee waiver request.
10	Content of the labelling of the IMP – <i>not required at present</i> .

*may not be relevant

Table 2. Application Dossier – Part II

Part II documents - Relevant to ethics committee only	
1	Recruitment arrangement information – 1) Completed ‘Recruitment and informed consent procedure template’; 2) All relevant materials such as advertisements or invitation letters.
2	Subject information, informed consent form, and informed consent procedure per Member State concerned – 1) Completed ‘Recruitment and informed consent procedure template’; 2) Consent/assent forms; 3) Participant information leaflets.
3	Suitability of the investigator per Member State concerned – 1) CV of Principal Investigator in Member State.
4	Suitability of the facilities per Member State concerned – 1) Completed ‘Site suitability template’ signed by site Principal Investigator; 2) CV of Principal Investigator at each site.
5	Proof of insurance cover or indemnification per Member State concerned.
6	Financial and other arrangements – 1) statement confirming source of funding; 2) completed ‘Compensation for trial participants’ template; 3) signed ‘Declaration of interest’.
7	Proof of payment of NREC fee.
8	Proof that data will be processed in compliance with Union law on data protection – 1) completed Data Protection Impact Assessment (DPIA) or statement why DPIA is not required; 2) 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 Regulation 2016/679).

2 SCOPE AND OBJECTIVES OF THE NATIONAL COLLABORATION PROJECT

2.1 Scope

The Clinical Trials Regulation-National Collaboration Project is a joint undertaking by the HPRA and the National Office for Research Ethics Committee (the National Office) to facilitate preparation for the implementation of the new Clinical Trials Regulation (CTR) (Regulation (EU) No 536/2014). The HPRA, the National Office, and sponsors of clinical trials will participate in the Collaboration Project to gain experience that will facilitate the implementation of the CTR in Ireland.

The CTR aims to create an environment that is favourable for conducting clinical trials, with the highest standards of patient safety, across the EU. Intrinsic to this is the simplification of current rules. The CTR will impact the way that sponsors submit clinical trial documentation, and how the competent authority (the HPRA) and the NREC-CT review and approve clinical trials.

Under current EU and national law (Directive 2001/20/EC and S.I. No. 190 of 2004, respectively), the authorisation procedures for clinical trial applications and substantial amendment submissions at the HPRA and the ECs are independent. This will change when the CTR is implemented, as one 'single decision' per Member State will have to be provided through the Clinical Trial Information System (CTIS). The assessment of the Part I documents will be performed independently by the HPRA and potentially in parallel, by the NREC-CT, and a single conclusion for Ireland reached. The assessment of Part II documents will be performed by the NREC-CT only, and an opinion provided. The positions on Part I and Part II will be consolidated as the single decision within a short timeline. Close collaboration between the HPRA, the National Office and the NREC-CTs will be required, in particular when Ireland has the role of Reporting (responsible for the assessment) Member State (RMS) for Part I assessment under the CTR.

The collaboration project provides an opportunity for learning for all stakeholders. It will facilitate the ongoing development of national procedures.

The HPRA and the National Office encourage feedback from all stakeholders on the functioning of the collaboration project.

Key points are outlined below:

- Clinical trial applications submitted to the HPRA through the collaboration project will be assessed in accordance with the current legislation.
- All time periods mentioned in the guideline are calendar days.
- Applications should be submitted by the sponsor to the HPRA, who will provide relevant documents to the National Office, via a secure IT communication platform (developed by the HPRA).

- Responses from the sponsor should be submitted to the HPRA, with the National Office in copy.
- The HPRA and NREC-CT will separately issue their respective decisions/opinions.
- The collaboration project does not apply to voluntary harmonisation procedures. It is limited to clinical trial applications and resulting substantial amendment submissions in Ireland, and will not include any interactions between Member States in relation to multinational clinical trials (multinational trials *per se* are not excluded from the collaboration project procedure; however, separate applications to NCAs and ECs in other MSs will be required, as per usual practice).
- Safety reporting is not included in the collaboration project. Safety reporting documents including suspected unexpected adverse reactions (SUSARs), and development safety update reports (DSURs) should be submitted to the HPRA and to the relevant Research Ethics Committee in the usual way.
- To facilitate the collaboration project in advance of CTIS, the HPRA and the National Office may engage in activities that will not fall within their remits under the Regulation (for example, accepting CT application dossier submissions or sharing the Part I assessment report via the communication platform).

Some differences between the key aspects of the Regulation and the collaboration project are outlined in Appendix 1.

The National Collaboration Project will run until December 2021 and it is envisioned that sponsors will transition clinical trials submitted under the Collaboration Project to the Clinical Trial Regulation once this has been implemented.

2.2 Objectives

The purposes of the collaboration project are:

- 1 to develop processes and procedures for the joint scientific and ethical assessment of CTAs and for the potential compilation of the Part I assessment report, and
- 2 to evaluate and amend current processes and procedures so that an efficient system is in place in Ireland when the Regulation is implemented.

This will be a learning opportunity for all participants. It is particularly relevant for the interactions between the National Office, the NREC-CTs and the HPRA.

2.3 Voluntary basis

Sponsors participate in the Collaboration Project on a voluntary basis and without additional costs. Participation is encouraged as this is an opportunity to test their own processes with regard to the timelines and procedures of the CTR.

Participation in the Collaboration Project is taken to mean that the sponsor consents to the release of relevant clinical trial documents to the National Office and the NREC-CT. All information, including that identified as commercially sensitive, will be treated with the strictest confidentiality.

A CTA can only proceed through the Collaboration Project if both the HPRA and the National Office validate the application and agree to its inclusion in the project.

3 LEGAL BASIS

There is no legal basis for the Collaboration Project in Ireland. CTs submitted under the Collaboration Project will be authorised under current legislation. Pilot projects are ongoing in many Member States.

The Collaboration Project may inform the drafting of national legislation.

The collaboration project will only run until the CTR is implemented. Following its implementation, the project will no longer accept applications. Depending on the number of applications submitted to the Collaboration Project per month, the number of initial clinical trial applications accepted may need to be limited.

Sponsors are encouraged to apply to have their clinical trials approved under the Clinical Trial Regulation (Regulation (EU) No 536/2014) as soon as the regulation is implemented.

4 PROCEDURE FOR APPLICANT – NEW APPLICATION (SEE APPENDIX 2, TABLE A)

4.1 Request to submit a clinical trial using the CTR-National Collaboration Project

The selected sponsor intending to submit through the Collaboration Project should include the following statement in the subject line of the cover letter submitted with the CTA to the HPRA: **CTR-National Collaboration Project-Participation submission.**

The cover letter should include a list of the documents submitted in Part I and Part II, highlighting any commercially sensitive documents that are not required to be shared with the NREC (all documents submitted under Part II will be assessed with the NREC-CT).

The CTA is made to the HPRA, no application to the National Office and the NREC-CT is required. The HPRA will provide the relevant documents to the National Office through the secure IT communication platform.

The HPRA, in collaboration with the National Office, will decide on a case-by-case basis whether a CTA can be processed in the Collaboration Project.

A decision on participation in the Collaboration Project will be sent to the sponsor by the HPRA. A decision to refuse to include a CTA in the Collaboration Project, along with the reasons for the refusal, will be communicated to the applicant.

If it is not possible to process a CTA within the Collaboration Project, the HPRA will inform the sponsor within two days of the published cut-off date for clinical trial submissions (see the [HPRA website](#) for information on cut-off dates). In this case, the CTA will be processed and assessed in accordance with the current procedures and does not need to be resubmitted. The format of the dossier, as prepared according to the requirements of the CTR, will be accepted by both the HPRA and the National Office. The NREC-CT and the HPRA will continue to carry out independent assessments, as is current practice.

4.2 Submission of the clinical trial application

CTAs intended for inclusion in the Collaboration Project can be submitted at any stage throughout the month, up until **one week before the published HPRA cut-off date**. Applications should be submitted via CESP. This is the preferred route of submission. Applications can also be made to submissions@hpra.ie.

The submission dossier (structure and content) must comply with the requirements of Annex I of the CTR (see Appendix 3 for information on the dossier structure). Part I and Part II documents must be submitted simultaneously as one CTA to the HPRA (the CTR provides the option of submitting Part I and Part II documents separately, however, this is not possible in the Collaboration Project).

The process is summarised in Figure 1.

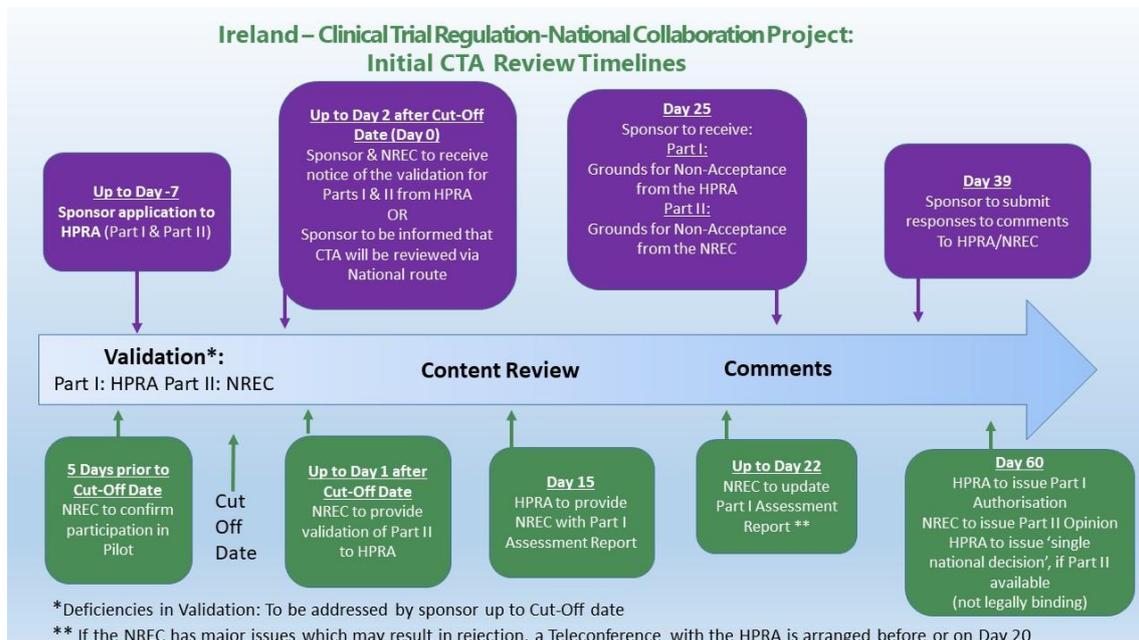


Figure 1: Ireland – CTR-National Collaboration Project: initial CTA review timelines

4.3 Payment of the fee for an initial dossier

Fees are paid separately to the HPRA and the National Office. The fee for the NREC-CT review should not be sent to the HPRA. Proof of payment of fee or request for a fee waiver, where appropriate, is required to be included with the Part I and Part II documents, respectively.

4.4 Validation phase

There are two aspects to validation of the CTA dossier: Part I of the dossier will be validated by the HPRA and Part II of the dossier will be validated by the National Office who will advise the HPRA of the status of the application, as soon as possible, and within one day after the cut-off date.

At the end of the validation phase, which will conclude **within two days after the cut-off date**, the sponsor will receive a notice of validation (beginning of assessment) from the HPRA.

If the validation process finds deficiencies in the dossier leading to the CTA being invalid, the sponsor is permitted to address the deficiencies, up to the HPRA cut-off date. Clinical trials that cannot be validated prior to the cut-off date will be validated within two days of the next monthly cut-off date.

4.5 Assessment phase

After successful validation, the CTA is assessed by the HPRA and the NREC-CT. The EU-agreed assessment report templates for Part I and Part II will be used in the collaboration project. These will be available to both the HPRA and the National Office on the secure IT communication platform.

The NREC-CT will receive the CTA in two parts (Parts I and II), but is required under the current legislation to give an opinion on the entire CTA.

The assessment of the aspects covered by Part I of the CTA is performed by the HPRA and the NREC-CT, in parallel. The HPRA will generate a draft Part I AR with the administrative sections completed and share it with the NREC-CT on the secure IT communication platform by Day 0. The HPRA will update the Part I AR on Day 15 with outcomes of assessment and any requests for further information. The NREC-CT will update the Part I AR with the aspects covered by NREC-CT assessment at any point up to Day 22. If either the NREC-CT or the HPRA have major issues which might result in a rejection of the CTA, a teleconference could be organised before, or on, Day 20.

The HPRA will send requests for additional information/grounds for non-acceptance regarding Part I to the applicant on Day 25. The applicant should submit the requested information as a single response **within 14 days to the HPRA, copying in the National Office**, in order to comply with the deadlines specified in the current legislation.

The aspects covered by Part II are assessed, in parallel, by the NREC-CT. The National Office on behalf of the NREC-CT will issue grounds for non-acceptance/requests for further information to the applicant by Day 25. The applicant should submit the requested information as a single response **within 14 days to the HPRA, copying in the National Office**, in order to comply with the deadlines specified in the current legislation.

4.6 Approval

After evaluation of the sponsor's response to grounds for non-acceptance/requests for further information in relation to Part I, the HPRA and NREC-CT will agree their position on Part I. Under the current legislation, the HPRA is required to issue a decision on the CTA and will continue do so under the Collaboration Project.

The National Office on behalf of the NREC-CT will issue their opinion on the CTA to the applicant, as per current practice, and will also notify the HPRA of their opinion.

If the HPRA decision and the NREC-CT opinion are positive, the clinical trial can commence.

Under the CTR, a 'notification' will be provided to the applicant through the CTIS of the 'single national decision' for Ireland. In order to mimic this situation, the HPRA and the National Office

on behalf of the NREC-CT will endeavour to issue a 'single national decision' comprising the HPRA decision and the NREC-CT opinion. This 'single national decision' is not a legal document and is not required for the commencement of a trial.

5 PROCEDURE FOR APPLICANTS SUBSTANTIAL AMENDMENTS – (MODIFICATIONS) (SEE APPENDIX 2, TABLE B)

5.1 Submission of a substantial amendment regarding a clinical trial approved in the CTR-national collaboration project

Substantial amendments (modifications) to clinical trials that were approved via the Collaboration Project should be submitted to the HPRA. 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.

Substantial amendments to clinical trials approved under the CTR-NCP may only be submitted for review under the CTR-NCP, provided that they occur within the envisioned lifespan of the Collaboration Project.

The cover letter should include the following statement in the subject line: **CTR-national collaboration project – substantial amendment to <Part 1> or <Part I & Part II> or <Part II>** and should include a list of the documents submitted in Part I and/or Part II, highlighting any commercially sensitive documents in Part I that are not required to be shared with the NREC.

The submission dossier must comply with the requirements of Annex II of the CTR (see Appendix 3).

The HPRA will provide the relevant documents to the National Office.

The process is summarised in Figure 2 and Table 3.

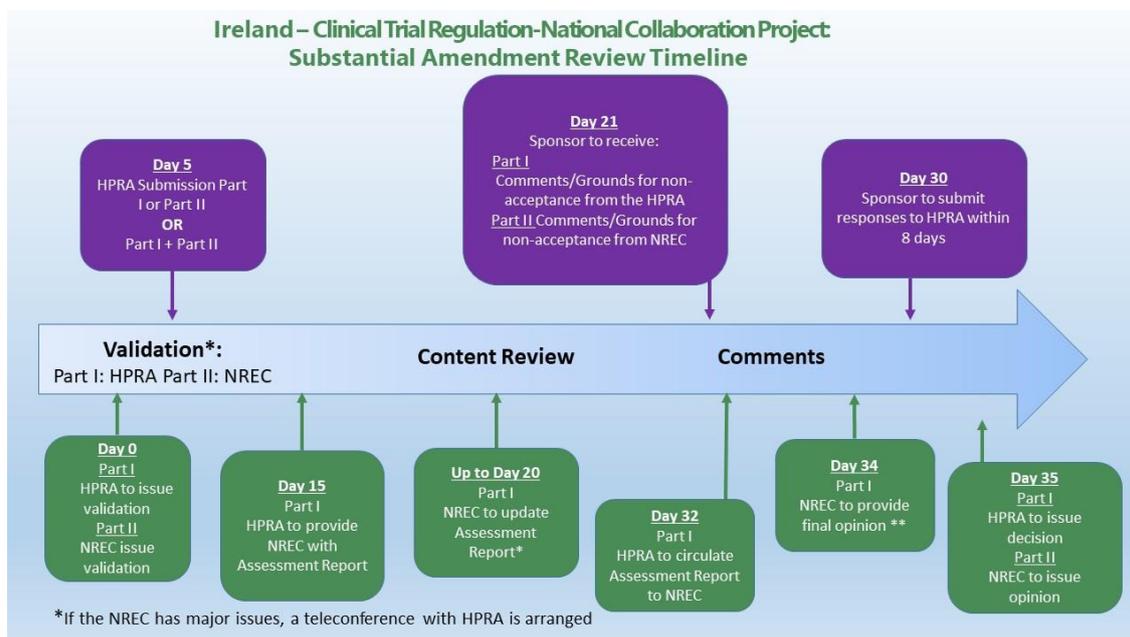


Figure 2: Ireland – CTR-National Collaboration Project: substantial amendment review timeline

Table 3. Substantial amendments – procedure for submission, validation, assessment and approval

	Part I only	Part I and II (linked)	Part II only
Submission	HPRA	HPRA	HPRA
Validation	HPRA	HPRA (Part I) and National Office (Part II) Single validation notice and timeline	National Office issue validation and timeline
Assessment	HPRA, and NREC-CT if amendment affects aspects relevant to NREC-CT	Part I - HPRA and NREC-CT if amendment affects aspects relevant to NREC-CT Part II – NREC-CT	National Office on behalf of the NREC-CT issue requests for further information
Responses	HPRA (copy to the National Office)	HPRA (copy to the National Office)	HPRA (copy to the National Office)
Approval/Opinion	HPRA	HPRA and NREC-CT	National Office on behalf of the NREC-CT issues approval and notifies HPRA

5.2 Payment of the fee for a substantial amendments

Fees are paid separately to the HPRA and/or the National Office, depending on which type of substantial amendments are submitted. The fee for the National Office should not be sent to the HPRA.

Proof of payment of fee or request for a fee waiver, where relevant, is required to be included with the Part I and Part II documents, respectively.

5.3 Validation phase

The validation of substantial amendments to Part I of the dossier will be performed by the HPRA.

At the end of the validation phase, which will last a maximum of **five days**, the applicant will receive a notice of validation (beginning of assessment).

For substantial amendments to Part I of the dossier, a notice of validation will also be sent to the National Office.

If the validation shows that deficiencies are present or that relevant documentation is missing, the applicant is granted a **ten-day period** to correct deficiencies.

The HPRA evaluates the supplemented documentation within **five days** after receipt of the applicant's comments or the amended dossier.

For amendments to Part II of the dossier only, the National Office will conduct the validation and will issue the validation notice and timeline.

For amendments that include changes to Parts I and II of the dossier, the applicant should outline this in the subject line of the cover letter. The validation will be performed by the HPRA and the National Office, in accordance with the Part I only substantial amendment timelines.

5.4 Assessment phase

The assessment regarding the aspects covered by Part I of the amendment is performed in parallel by the HPRA and the NREC-CT while the aspects covered by Part II are assessed by the NREC-CT.

A substantial amendment may be directly approved, or grounds for non-acceptance/requests for further information may be issued by the HPRA, and/or the NREC-CT.

Where grounds for non-acceptance/requests for further information are issued, the applicant is required to respond within **nine days** to the HPRA, copying in the National Office, in order to comply with the deadlines specified in the current legislation. A clock-stop is permitted.

5.5 Approval

After evaluation of the applicant's response to grounds for non-acceptance/requests for further information in relation to Part I, the HPRA and NREC-CT will agree on the decision for Part I. As per current legislation, a decision will be issued by the HPRA.

The National Office on behalf of the NREC-CT will issue the conclusion on substantial amendments in relation to Part II to the applicant and will also notify the HPRA of the conclusion. Where a substantial amendment covers changes to Part II aspects only, the National Office on behalf of the NREC-CT will issue the decision for the substantial amendment.

6 REVIEW

The HPRA and the National Office encourage ongoing feedback on the operation of the CTR-National Collaboration Project to improve the process, and progress towards an efficient implementation of the Regulation.

APPENDIX 1 DIFFERENCES BETWEEN THE KEY ASPECTS OF THE REGULATION AND THE CTR-NATIONAL COLLABORATION PROJECT

Regulation (EU) No 536/2014	CTR-National Collaboration Project
<p>Application Dossier in Part I and Part II format</p>	<p>Application Dossier in Part I and Part II format (template folders will be provided on the HPRA website).</p> <p>Individual documents should fulfil the requirements of current legislation.</p>
<p>A streamlined application procedure via a single-entry point - the CTIS. Registration via the CTIS will be a prerequisite for the assessment of any application; the portal and database will be hosted by the European Medicines Agency (EMA); the HPRA and the National Office will access the clinical trial application dossier through the portal.</p>	<p>The HPRA will provide a single-entry point for a CTA (no application to the NREC-CT or the National Office is required). The application should be submitted as two dossiers containing Part I and Part II documents, respectively (see Table 1 and 2). Documents relevant to the NREC-CT will be made available to the National Office. Note: The Part I and II documents must be submitted simultaneously in one application.</p>
<p>All necessary documents will be required to be uploaded to the CTIS to allow submission to proceed.</p> <p>The Reporting Member State (RMS) will validate the submission within ten days. The sponsor is given 15 days to address any issues that arise with validation.</p>	<p>The deadline for submission of CTAs for participation in the collaboration project is one week in advance of the HPRA monthly cut-off date. The HPRA will validate the Part I dossier within two days of the cut-off date.</p> <p>The National Office will validate the Part II dossier within one day of the cut-off date.</p> <p>If the application is not considered to be valid, the applicant will be given an opportunity to respond up to the cut-off date. Applications that cannot be validated by the cut-off date can be withdrawn and re-submitted or held over until the next month's meeting.</p>
<p>A single authorisation procedure for all multinational clinical trial applications and substantial modifications, allowing a simultaneous assessment of an application by all Member States (MS) concerned, and ensuring one single assessment outcome and authorisation per MS.</p>	<p>The collaboration project will aim to deliver a single assessment and decision for Ireland (HPRA and NREC-CT) on the Part I and II documents. However, as the HPRA decision and the NREC-CT opinion are separate under current legislation, separate approval notifications will be issued by each authority,</p>

Regulation (EU) No 536/2014	CTR-National Collaboration Project
	<p>to allow the sponsor to commence clinical trial activities.</p> <p>In practice, Ireland will treat applications submitted through the collaboration procedure as mono-national applications.</p>
<p>Notifications of validation, assessment conclusions and decisions will be issued through the CTIS.</p>	<p>Notices of validation, opinions and approvals will be issued by the HPRA and/or the National Office, as appropriate.</p>
<p>The National Office in Ireland will interact directly with the CTIS.</p>	<p>The National Office will interact with the HPRA.</p>
<p>Single fee per MS, with proof of payment submitted through the CTIS.</p>	<p>Fees should be paid to the HPRA and the National Office, separately. Fee documents to be included in the relevant folder of the dossier.</p>
<p>Timelines</p> <p>Applications can be submitted at any time.</p> <p>Conclusion of Part I and Part II assessment within 45 days of validation, with up to 31 days' extension where requests for further information are made. Single decision within five days of conclusion of Part I or Part II (whichever is later).</p>	<p>HPRA CT cut-off dates will apply.</p> <p>Timelines as per current legislation will apply (60 days from validation date including requests for further information and response from sponsor).</p> <p>Note: HPRA and the NREC-CT will aim to deliver a single decision for Ireland covering all aspects of the CT application dossier within 60 days of submission.</p> <p>There will be no clock-stops for new applications.</p>
<p>Requests for additional information will be made within 45 days of the validation date. The sponsor will have 12 days to respond.</p>	<p>'Requests for additional information' will continue to be referred to as 'grounds for non-acceptance/requests for further information' and will be sent to the sponsor 25 days after the validation date.</p> <p>Responses should be sent by the sponsor to the HPRA, copying in the National Office, within 14 days.</p>
<p>Substantial modifications may include aspects covered by Part I or Part II or both Parts I and II, and will be submitted through the CTIS.</p> <p>Conclusion of Part I and Part II assessment within 38 days of validation, with up to 31</p>	<p>Substantial amendments (referred to as 'modifications' in the Regulation) to clinical trials authorised via the Collaboration Project, should be submitted to the HPRA. The cover</p>

Regulation (EU) No 536/2014

days' extension where requests for further information are made. Single decision within five days of conclusion of Part I or Part II (whichever is later).

CTR-National Collaboration Project

letter should reference participation in the Collaboration Project.
An approval or request for further information will be issued within 35 days.

APPENDIX 2 TIMETABLES FOR THE CTR – NATIONAL COLLABORATION PROJECT PROCESS

All time periods mentioned in the guideline are calendar days.

Table A. New application

Step	Timeline	Process
1	Day -7 (seven days prior to cut-off date)	Submission of CTA with request for participation in the CTR-National Collaboration Project received by the HPRA. The HPRA notifies the National Office and provides the proposed timeline. The application is reviewed by both organisations to determine if it is to be accepted into the Collaboration Project.
2	Day -5	If the application is accepted into the Collaboration Project the HPRA shares the CTA with the National Office via secure IT platform (relevant Part I documents and Part II). If the application is not accepted into the Collaboration Project, the applicant is informed and the clinical trial application is assessed as per current practices by both the HPRA and the National Office.
3	Day -1	The HPRA validates the Part I dossier. The National Office validates the Part II dossier and provides notification to the HPRA before Day -1.
4	Day 0	The HPRA sends an automatic notice of validation of the CTA (Part I and II) to the applicant. The HPRA and the National Office jointly send notification that the CTA has been accepted into the CTR-National Collaboration Project. Draft Part I AR (admin sections completed) shared with the National Office via IT platform. Draft Part II assessment report template uploaded to platform.
5	Day 14	CTA presented to the Clinical Trials Subcommittee at its monthly meeting.
6	Day 15	The HPRA shares the draft Part I AR with the NREC-CT for input (preclinical, clinical, regulatory, conclusion and the draft list of requests for additional information sections completed from HPRA perspective, and conclusion).
7	On or before Day 22	NREC-CT completes relevant sections of draft Part I AR. If there are <u>major discrepancies</u> in the opinion between the HPRA and NREC-CT, a teleconference between the National Office, Chair of the

Step	Timeline	Process
		<p>NREC-CT and the HPRA is organised to discuss the concerns. Ideally this should take place prior to Day 20.</p> <p>If no response from the NREC-CT is received within the timeline, the HPRA will proceed without the NREC-CT input.</p>
8	Day 25	<p>List of grounds for non-acceptance on Part I are sent by the HPRA to the applicant.</p> <p>The National Office, on behalf of the NREC-CT, sends the grounds for non-acceptance on Part II directly to the applicant.</p>
9	Day 39	<p>The applicant submits responses to Part I and Part II to the HPRA, copying in the National Office.</p>
10	Day 46	<p>The HPRA updates the draft Part I AR on the secure IT communications platform in light of the responses from the applicant including the proposed conclusion on Part I.</p>
11	By Day 49	<p>The NREC-CT updates the draft Part I AR on the secure IT communications platform in light of the responses from the applicant.</p> <p>If major discrepancies in the opinion between the HPRA and NREC-CT are noted, a teleconference between the National Office, Chair of the NREC-CT and the HPRA is organised to discuss the concerns. Ideally this should take place prior to Day 49.</p> <p>If no response from the NREC-CT is received within the timeline, the HPRA will proceed without the NREC-CT input.</p>
12	Day 57	<p>The HPRA Management Committee reviews the recommendation on the CTA and gives a final decision. This decision applies only to the Part I dossier.</p> <p>The National Office on behalf of the NREC-CT advises the applicant directly of their opinion on the CT (including aspects covered by the Part I AR), and provides this opinion to the HPRA.</p>
13	Day 60	<p>End of procedure.</p> <p>HPRA decision letter on the CTA is sent to the applicant.</p> <p>The National Office on behalf of the NREC-CT issues its opinion directly to the applicant.</p> <p>Final AR (Part I and Part II), HPRA decision letter, and NREC-CT opinion notification ('single national decision') are stored on the IT platform.</p>

Table B. Substantial amendment (modification)

Note: the NREC-CT will only be included in the assessment if the amendment concerns aspects relevant to the NREC-CT.

Step	Timeline	Process
1	Day -5	<p>Applicant submits the substantial amendment to the HPRA (substantial amendments are not subject to a cut-off date and can be submitted at any time).</p> <p>The HPRA validates Part I of amendment, if any.</p> <p>The National Office validates Part II of amendment, if any.</p>
2	Day 0	<p>The HPRA sends an automatic notice of validation of Part I to the applicant.</p> <p>The National Office notifies the applicant of the validation of Part II and provides timelines to the applicant.</p>
3	Day 15	<p>The HPRA shares the updated draft Part I AR with the NREC-CT through the IT platform, including draft conclusion on Part I.</p>
4	Day 20	<p>NREC-CT provides opinion on the circulated Part I AR, and a list of additional concerns, if any, which should be addressed by the applicant.</p> <p>If there are <u>major discrepancies</u> in the opinion between the HPRA and NREC-CT, a teleconference between the National Office, Chair of the NREC-CT and the HPRA is organised to discuss the concerns. Ideally this should take place prior to Day 20.</p>
5	Day 21	<p>The HPRA sends a list of grounds for non-acceptance on Part I aspects (if any) to the applicant.</p> <p>The National Office on behalf of the NREC-CT sends grounds for non-acceptance on Part II aspects (if any) directly to the applicant.</p>
6	Day 30	<p>Responses to Part I and/or Part II grounds for non-acceptance submitted by the applicant to the HPRA and the National Office.</p>
7	Day 32	<p>Part I AR prepared by the HPRA and circulated to the NREC-CT.</p>
8	Day 34	<p>NREC-CT provides final opinion on the Part I substantial amendment to the HPRA.</p> <p>If major discrepancies in the opinion between the HPRA and NREC-CT are noted, a teleconference between the National Office, chair of the NREC-CT and the HPRA needs to be organised to discuss the concerns. Ideally this should take place prior to Day 34.</p>

Step	Timeline	Process
		<p>If no response from the NREC-CT to the final Part I AR is received within the timeline, the HPRA will proceed without the NREC-CT input.</p>
9	Day 35	<p>End of procedure.</p> <p>The final HPRA decision on the substantial amendment is sent to the applicant (if relevant), and to the NREC-CT for information.</p> <p>The National Office on behalf of the NREC-CT will issue its opinion on Part II substantial amendments directly to the applicant and will copy the opinion to the HPRA for information.</p> <p>Updated AR stored on the IT platform.</p>

APPENDIX 3 DOSSIER STRUCTURE AS PER REGULATION (EU) NO. 536/2014

1 INITIAL APPLICATION

During the course of the collaboration project, Part I and Part II dossiers must be submitted in one CTA to the HPRA. A zip-file with the structured empty folders is available on our [website](#).

Documents relevant to the NREC-CT, such as site-specific assessments, can be included in the Part II dossier.

1.1 Format of application dossier

The following folder structure is required for CTAs requesting participation in the CTR - National Collaboration Project.

Application dossier for the initial application

Part I

- 1 COVER LETTER
- 2 EU APPLICATION FORM – the current EudraCT application form should be used.
- 3 PROTOCOL
- 4 INVESTIGATORS BROCHURE (IB) (or SMPC)
- 5 DOCUMENTATION RELATING TO COMPLIANCE WITH GOOD MANUFACTURING PRACTICE (GMP) FOR THE INVESTIGATIONAL MEDICINAL PRODUCT
- 6 INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD)
 - 6.1 Data relating to the investigational medicinal product
 - 6.2 Simplified IMPD by referring to other documentation, e.g. SmPC
 - 6.3 IMPD in cases of placebo
- 7 AUXILIARY MEDICINAL PRODUCT DOSSIER
- 8 SCIENTIFIC ADVICE AND PAEDIATRIC INVESTIGATION PLAN (PIP)
- 9 PROOF OF PAYMENT OF HPRA FEE, OR FEE WAIVER REQUEST

Part II

- 1 RECRUITMENT ARRANGEMENT
 - 1.1 Completed 'Recruitment and informed consent procedure template'
 - 1.2 All relevant materials such as advertisements or invitation letters
- 2 SUBJECT INFORMATION, INFORMED CONSENT FORM AND INFORMED CONSENT PROCEDURE

- 2.1 Completed 'Recruitment and informed consent procedure template'
- 2.2 Consent/assent forms
- 2.3 Participant information leaflet
- 3 SUITABILITY OF THE INVESTIGATOR
 - 3.1 CV of Principal Investigator
- 4 SUITABILITY OF THE FACILITIES
 - 4.1 Site-specific Assessment form
 - 4.2 CV of Principal Investigator at each site
- 5 PROOF OF INSURANCE COVER OR INDEMNIFICATION
- 6 FINANCIAL AND OTHER ARRANGEMENTS
 - 6.1 Statement confirming source of funding
 - 6.2 Completed 'Compensation for trial participants' template
 - 6.3 Signed 'Declaration of interest'
- 7 PROOF OF PAYMENT OF NREC FEE
- 8 PROOF THAT DATA WILL BE PROCESSED IN COMPLIANCE WITH THE UNION LAW ON DATA PROTECTION
 - 8.1 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 Regulation 2016/679)
 - 8.2 Data Protection Impact Assessment reviewed by Data Protection Officer (or statement stating why DPIA not necessary)

1.2 File format

The CTA is required to be submitted in PDF file format.

The EudraCT application form is required to be submitted in PDF format and in XML format, as per current requirements.

2. SUBSTANTIAL AMENDMENTS (MODIFICATIONS)

Substantial amendments to the Part I and Part II dossiers must be submitted to the HPRA (see Table 3).

A zip-file with the structured empty folders is available on our website.

2.1 Format of application dossier

The following folder structure is required for CTAs requesting participation in the CTR - national collaboration project.

Application dossier for substantial amendments

- 1 COVER LETTER
- 2 MODIFICATION APPLICATION FORM
- 3 DESCRIPTION OF THE MODIFICATION
- 3 SUPPORT INFORMATION
- 4 UPDATE OF EU APPLICATION FORM
- 5 PROOF OF PAYMENT OF FEE for Part I/II

2.2 File format

The substantial amendment is required to be submitted in PDF file format. The application form is required to be submitted in PDF format, as per current requirements.