HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Clinical Trials Regulation (EU) No. 536/2014
Pilot Project - Ireland

Voluntary Pilot Project for the Processing of Applications 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.

CONTENTS

1 GLOSSARY

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

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

CTA: Clinical Trial Application.

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 Pilot Project: a pilot project for assessment of clinical trial applications and 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 current legislation can review clinical trials.

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 ethics committee (EC), while Part II documents will be assessed by the ethics committee alone. 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 Table 1 and 2 below).

Submissions under the CTR will be made through the EU Portal, 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 CTR pilot project. Nonetheless, applications submitted under the CTR pilot project should follow the dossier format outlined in the Regulation (the HPRA will provide a folder structure for downloading on the website). The HPRA has drafted the tables below to 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 I. The documents covered by Part II of the assessment report are listed in Table II.

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

Table 1. Application Dossier – Part I

	Part I documents - relevant to HPRA and ethics committee
1	Cover letter – including request for participation on the pilot project and name/contact details of EC, and a list of commercially-sensitive documents that should not be circulated to the EC.
2	EU application form (the current EudraCT Form should be used during the pilot project)
3	Protocol
4	Investigator's brochure (or EU 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	Content of the labelling of the IMP – not required at present
10	Proof that data will be processed in compliance with EU law on data protection – not required at present
11	Proof of payment of HPRA fee, or fee waiver request

*may not be relevant

Table 2. Application Dossier – Part II

	Part II documents Relevant to ethics committee only
1	Recruitment arrangements
2	Subject information, informed consent, and informed consent procedure
3	Suitability of the investigator
4	Suitability of the facilities
5	Proof of insurance cover or indemnification
6	Financial and other arrangements
7	Proof of payment of ethics committee fee, or fee waiver request.

2 SCOPE AND OBJECTIVES OF THE PILOT

2.1 Scope

This pilot project is proposed by the Health Products Regulatory Authority (HPRA) to facilitate preparation for the implementation of the new clinical trial regulation (Regulation (EU) No 536/2014). It is intended that 'recognised' ethics committees (ECs), and sponsors of clinical trials will participate in the pilot project, in order to gain experience that will facilitate implementation of the Regulation 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 EC review and approve clinical trials.

Under current EU (Directive 2001/20/EC) and national law (S.I. No. 190 of 2004), 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 EU portal. The assessment of the Part I documents will be performed independently and in parallel by the HPRA and by the EC, and a joint conclusion for Ireland reached. The assessment of Part II documents will be performed by the EC 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 and the ECs 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 pilot project provides an opportunity for learning for all stakeholders. It will facilitate the development of national procedures.

The HPRA is happy to receive feedback from all stakeholders on the functioning of the pilot project, and intends to amend this guideline, and the scope of the project, as stakeholders gain experience.

Key points are outlined below:

- Clinical trial applications submitted to the HPRA through the pilot project will be assessed in accordance with the current legislation.
- All time periods mentioned in the guideline are calendar days.
- Applications, and any responses should be submitted by the sponsor to the HPRA, who will provide relevant documents to the EC nominated by the sponsor, via a secure IT communication platform (developed by HPRA).
- The HPRA and EC will separately issue their respective decisions/opinions.

- The pilot project does not apply to voluntary harmonisation procedures. It is limited to clinical trial applications and substantial amendments 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 pilot 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 pilot 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 local EC in the usual way.
- To facilitate the pilot project in the absence of the EU Portal and Database, the HPRA may engage in activities that will not fall within its remit 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 pilot project are outlined in Appendix 1.

2.2 Objectives

The purpose of the pilot is

1 to develop processes and procedures for the joint scientific and ethical assessment of CTAs and for the 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 to the interactions between the ECs and the HPRA.

2.3 Voluntary basis

Sponsors participate in the pilot 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.

A request to participate in the pilot project is taken to mean that the sponsor consents to the release of relevant clinical trial documents to the EC, proposed by the sponsor. Information identified as commercially-sensitive by the sponsor e.g. the investigational medicinal product dossier will not be sent to the EC.

A CTA can only proceed through the pilot project if both the HPRA and EC validate the application, and agree to its inclusion in the project.

3 LEGAL BASIS

There is no legal basis for the CTR pilot project in Ireland, CTs submitted under the pilot project will be authorised under current legislation. Pilot projects are ongoing in many Member States.
The pilot project may inform the drafting of national legislation.

In the event that the EC assessment cannot be concluded during the timeline of the procedure, the HPRA assessment will proceed and the CTA will be approved, approved with conditions or rejected by Day 60.

This pilot project is limited in time, and no new CTAs will be permitted to participate after the CTR has been implemented. Substantial amendments for clinical trials authorised through the CTR pilot project will need to be submitted through the CTR pilot project, until the transition period has ended.

4 PROCEDURE FOR APPLICANT – NEW APPLICATION (SEE APPENDIX II, TABLE B)

4.1 Request to submit a clinical trial using the CTR pilot project

A sponsor intending to use the CTR pilot project should include the following statement in the subject line of the cover letter submitted with the CTA to the HPRA: **CTR pilot project– Request to participate.**

The following information should be provided in the cover letter:

- the name and validated contact point (email address) for the 'recognised' EC chosen by the sponsor
- a list of the documents submitted in Part I and Part II, highlighting the documents in Part I that cannot be shared with EC (all documents submitted under Part II will be shared with the EC).

The CTA is made to the HPRA, no application to the EC is required. The HPRA will provide the relevant documents to the EC through the IT communication platform.

The HPRA, in collaboration with the nominated EC, will decide on a case-by-case basis whether a CTA can be processed in the pilot project. The main criterion for acceptance will be whether the recognised EC, selected by the sponsor, has the capacity and competence to review the trial, this will be determined by the EC. The HPRA will contact the EC via the validated contact point, to determine their willingness to participate in the CTR pilot project, for each proposed trial.

A decision on a request to participate in the CTR pilot project will be sent to the sponsor by the HPRA. The HPRA may refuse to include a CTA in the pilot project, and will communicate the reasons for the refusal to the applicant.

If it is not possible to process a CTA within the pilot 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 EC. The ethical review will not be part of the HPRA assessment. Independent assessments will proceed, as is current practice.

4.2 Submission of the CTA

Clinical trial applications intended for inclusion in the pilot project can be submitted at any stage throughout the month, up until **one week before the published cut-off date**. This timeline is to permit time for the EC validation. Applications should be submitted via CESP, or by the submission of a dossier on CD. These are the preferred routes 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 III 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 pilot project).

The process is summarised in Figure 1.

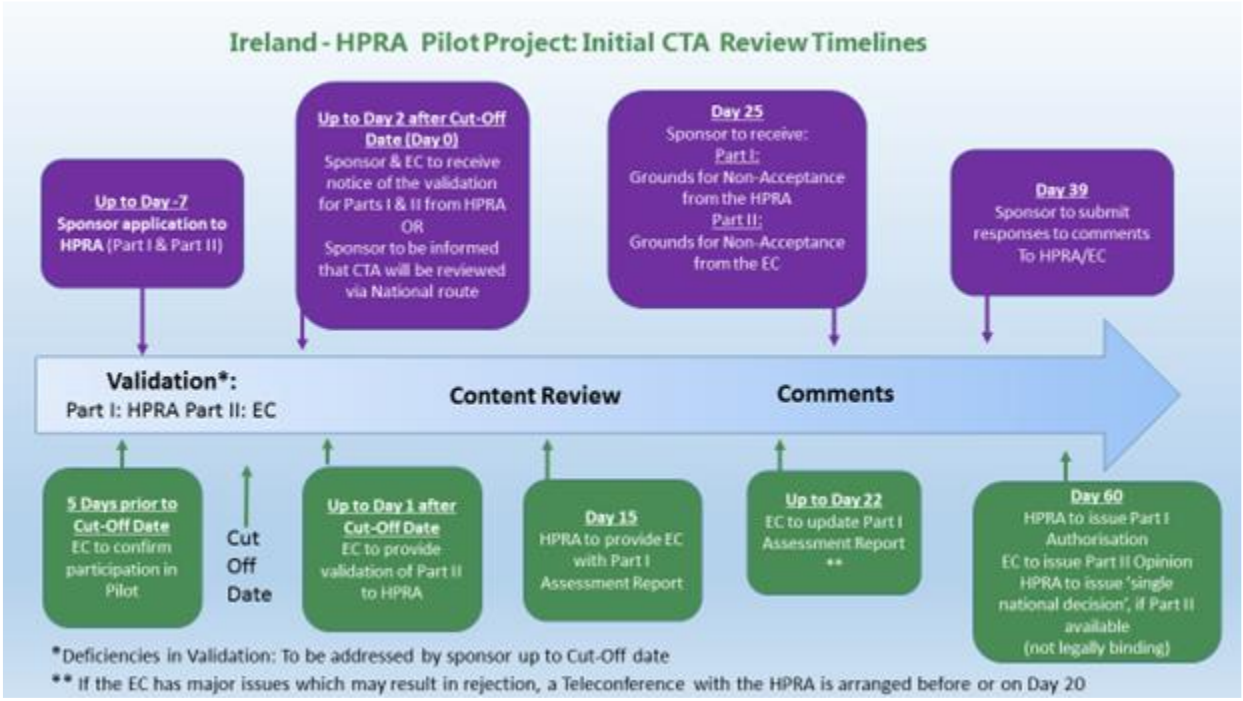

Figure 1: Ireland - HPRA pilot project: initial CTA review timelines

4.3 Payment of the fee for an initial dossier

Fees are paid to the HPRA, and EC in the usual way. The fee for the EC review should not be sent to the HPRA. Proof of payment of fee or request for a fee waiver is required to be included with the Part I and Part II documents, respectively.

4.4 Validation phase

There are two aspects to validation:

4.4.1 Validation of the CTA dossier

The validation of Part I of the dossier will be performed by the HPRA. The EC will perform the validation of the Part II of the dossier, and will advise the HPRA of the status of the application, as soon as possible, **and before one day after the cut-off date.** If no validation of Part II is received by the EC, the application cannot be accepted into the pilot project.

At the end of the validation phase, which will conclude **within two days of the cut-off date**, the sponsor will receive a notice of validation (beginning of assessment) from the HPRA. A timetable will be included in the notification to the sponsor.

Notice of validation, and the timetable (**Day 0 is set at two days after the cut-off date**) will also be sent to the EC.

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 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.

4.4.2 Validation of the request for participation in the CTR pilot project

Validation of a request to participate in the CTR pilot project can only occur if a recognised EC has been nominated, and contact details (email address) provided by the applicant.

4.5 Assessment phase

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

The EC will receive the CTA in two parts (Parts I and II), but under the current legislation, is required 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 EC, in parallel. The HPRA will generate a draft Part I AR with administrative sections completed and share it with the EC on the 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. A single individual from the EC will have access to this platform, and can update the Part I assessment report in relation to the aspects covered by EC assessment at any point up to Day 22. If the EC has major issues which might result in a rejection of the CTA, a teleconference with the HPRA should be organised before or on Day 20.

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

The aspects covered by Part II are assessed, in parallel, by the EC, who will issue grounds for non-acceptance/requests for further information directly to the applicant, by Day 25. The applicant should submit the requested information as a single response within **14 days to the HPRA** 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 EC 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 pilot project.

The EC 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 EC opinion are positive, the clinical trial can commence.

Under the CTR, a 'notification' will be provided to the applicant through the portal of the 'single national decision' for Ireland. In order to mimic this situation, the HPRA will endeavour to issue a 'single national decision' comprising the HPRA decision and the EC opinion if the EC opinion is available by Day 60. 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 II, TABLE C)

5.1 Submission of a substantial amendment regarding a clinical trial approved in the CTR pilot project

Substantial amendments (modifications) to clinical trials that were approved via the CTR pilot project should be submitted to the HPRA, via the CTR pilot 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.

The cover letter should include the following statement in the subject line: **CTR pilot project– substantial amendment to <Part 1> or <Part I & Part II> or <Part II>.**

The following information should be provided:

- the name and validated contact point (email address) for the 'recognised' EC that approved the CTA
- 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 (all documents submitted under Part II will be shared with the EC).

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

The HPRA will provide the relevant documents to the EC that assessed the initial CTA, through the IT communication platform.

The process is summarised in Figure 2 and Table 3.

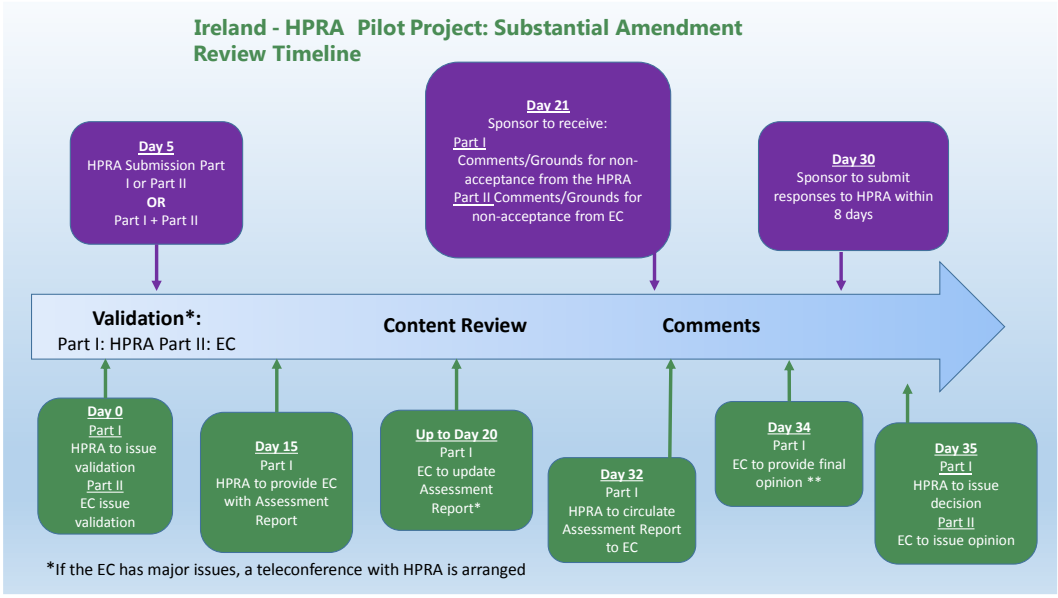

Figure 2: Ireland – HPRA pilot project: substantial amendment review timeline

Table 3: Substantial amendments - procedure for submission, validation, assessment and approval

	Part I only (highlight commercially-sensitive information, if relevant)	**Part I and II (linked) (highlight commercially-sensitive information, if relevant)**	**Part II only**
Submission	HPRA	HPRA	HPRA
Validation	HPRA	HPRA (Part I) and EC (Part II) Single validation notice and timeline	EC issue validation and timeline
Assessment	HPRA, and EC if amendment affects aspects relevant to EC.	Part I - HPRA, and EC if amendment affects aspects relevant to EC. Part II – EC	EC issue requests for further information

	Part I only (highlight commercially-sensitive information, if relevant)	Part I and II (linked) (highlight commercially-sensitive information, if relevant)	Part II only
Responses	HPRA	HPRA. Documents relevant to EC will be provided via communication platform	HPRA. Documents will be provided to EC via communication platform
Approval/Opinion	HPRA	HPRA and EC	EC issues approval, and notifies HPRA.

5.2 Payment of the fee for a substantial amendments

Fees are paid to the HPRA and/or the EC in the usual way, depending on which type of substantial amendments are submitted. The fee for the EC should not be sent to the HPRA. Proof of payment of fee or request for a fee waiver 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). A timeline will be included in this notification.

For substantial amendments to Part I of the dossier a notice of validation, and the timetable will also be sent to the EC.

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 EC 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 EC, and a single timeline for assessment will be issued, 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 EC while the aspects covered by Part II are assessed by the EC that assessed the initial CTA.

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 EC.

Where grounds for non-acceptance/requests for further information are issued, the applicant is required to respond within **nine days** to the HPRA 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 EC will agree on the decision for Part I. As per current legislation, a decision will be issued by the HPRA.

The EC 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 conclusion of the EC will be deemed the decision for the substantial amendment.

6 REVIEW

The HPRA appreciates ongoing feedback on the operation of the CTR pilot project, will review the functioning of the project with stakeholders, and will update this guideline, as appropriate, to improve the process, and progress towards an efficient implementation of the Regulation.

7 APPENDIX I

Table A Differences between the key aspects of the Regulation and the pilot project

Regulation (EU) No 536/2014	HPRA Pilot Project
Application Dossier in Part I and Part II format	Application Dossier in Part I and Part II format (template folders will be provided on the HPRA website). Individual documents should fulfil the requirements of current legislation.
A **streamlined application procedure via a single entry point** - the EU portal. Registration via the portal will be a prerequisite for the assessment of any application; the portal and database will be hosted by the European Medicines Agency (EMA); HPRA and ECs will access the clinical trial application dossier through the portal.	HPRA will provide a single entry point for a CTA (no application to the EC 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 EC will be made available to a validated contact point in the EC. Note: the Part I and II documents must be submitted simultaneously in one application.
All necessary documents will be required to be uploaded to the portal to allow submission to proceed. The RMS will validate the submission within ten days. The sponsor is given 15 days to address any issues that arise with validation.	The deadline for submission of CTAs for participation in the pilot project is **one week** in advance of the monthly cut-off date. The HPRA will validate Part I dossier within two days of the cut-off date. The EC will validate the Part II dossier within one day of the cut-off date. 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 resubmitted, or held-over until the next month's meeting.
A **single authorisation procedure for all multinational clinical trial applications and substantial modifications**, allowing a simultaneous assessment of an application by all MSs concerned, and ensuring one single assessment outcome and authorisation per MS.	The pilot project will aim to deliver a single assessment and decision for Ireland (HPRA and EC) on the Part I and II documents. However, as the HPRA decision, and the EC opinion are separate under current legislation, separate approval notifications will be issued by each authority, to allow the sponsor to commence clinical trial activities.

Regulation (EU) No 536/2014	HPRA Pilot Project
	In practice, Ireland will treat applications submitted through the pilot procedure as mono-national applications.
Notifications of validation, assessment conclusions and decisions will be issued through the portal.	Notices of validation, opinions and approvals will be issued, by the HPRA or EC, as appropriate.
The EC in Ireland will interact directly with the EU Portal.	The sponsor will nominate the EC, and include the name/contact details in CTA cover letter. The EC will interact with the HPRA.
Single fee per MS, with proof of payment submitted through the portal.	Fees should be paid to the HPRA and relevant EC, separately. Fee documents to be included in the relevant folder of the dossier
Timelines Applications can be submitted at any time. 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).	HPRA CT cut-off dates will apply. Timelines as per current legislation will apply (60 days from validation date including requests for further information and response from sponsor). Note: HPRA and the EC will aim to deliver a single decision for Ireland covering all aspects of the CT application dossier within 60 days of submission. There will be no clock-stops for new applications.
Requests for additional information will be made within 45 days of the validation date. Sponsor will have 12 days to respond.	These will continue to be referred to as 'grounds for non-acceptance'/requests for further information, and will be sent to sponsor 25 days after the validation date. Responses should be sent by the sponsor to the HPRA within 14 days.
Substantial modifications may include aspects covered by Part I or Part II or both Parts I and II, and will be submitted through the portal. Conclusion of Part I and Part II assessment within 38 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).	Substantial amendments (referred to as 'modifications' in the Regulation) to clinical trials authorised via the pilot project, should be submitted to the HPRA. The cover letter should reference participation in the pilot project. An approval or request for further information will be issued within 35 days.

8 APPENDIX II

Timetables for the CTR pilot project process (all time periods mentioned in the guideline are calendar days).

Table B New application (processes in red are relevant to ECs)

Step	Timeline	Process	Ethics committee action - Time available for action
1	**Day -7 (Seven days prior to cut-off date)**	Submission of CTA with request for the participation in CTR pilot project received by the HPRA. Applicant must have nominated a 'recognised' EC. HPRA contacts the nominated EC seeking their agreement to participate in the CTR pilot project, and provides the proposed timeline.	
2	**Day -5**	HPRA shares CTA with EC via IT platform (Part I (excluding commercially-sensitive documents) and Part II).	
3	**Day -1**	HPRA validates the Part I dossier. EC validates the Part II dossier and provides notification to the HPRA asap, and before Day -1.	Minimum time: two days
4	**Day 0**	HPRA sends automatic notice of validation of the CTA (Part I and II) sent to the applicant. HPRA send notifications that the CTA has been accepted into the CTR pilot project. Timeline provided to the sponsor and the EC. Draft Part I AR (admin sections completed) shared with EC via IT platform. Draft Part II assessment report template will be available on the platform. EC can fill in appropriate sections at any point up to Day 22.	
5	**Day 14**	CTA presented to the Clinical Trials Subcommittee at its monthly meeting.	

Step	Timeline	Process	Ethics committee action - Time available for action
6	**Day 15**	HPRA shares the draft Part I AR with the EC for input (preclinical, clinical, regulatory, conclusion and draft list of requests for additional information sections completed from HPRA perspective, and conclusion). The quality part of the AR is not provided as this may contain information that is commercially sensitive and is not relevant to the ethical aspects of the trial.	
7	**On or before Day 22**	EC completes relevant sections of draft Part I AR. If there are major discrepancies in the opinion between the HPRA and EC - a teleconference between the chair of the EC and the HPRA is organised to discuss the concerns. Ideally this should take place prior to day 20. If no response from the EC is received within the timeline, the HPRA will proceed without the EC input.	EC opinion on Part I needs to be provided **within 22 days of** the validation date (within **7 days** of the HPRA opinion)
8	**Day 25**	List of grounds for non-acceptance on Part I are sent by the HPRA to the applicant. EC sends the grounds for non-acceptance on Part II, directly to the applicant.	
9	**Day 39**	Responses to Part I and Part II are submitted by the applicant, to the HPRA. The HPRA makes the responses available to the EC through the IT communication platform. Responses relating to commercially-sensitive information will not be made available to the EC.	
10	**Day 46**	The HPRA updates the draft Part I AR on the IT platform in light of the responses from the applicant including the proposed conclusion on Part I.	
11	**By day 49**	If necessary, the EC updates the draft Part I on the IT platform in light of the responses from the applicant. If major discrepancies in the opinion between the HPRA and EC are noted - a teleconference between the chair of the EC and the HPRA is organised to	Final EC opinion on Part I needs to be provided **10 days** after responses from the applicant have been received and **3 days**

Step	Timeline	Process	Ethics committee action - Time available for action
		discuss the concerns. Ideally this should take place prior to day 49. If no response from the EC is received within the timeline, the HPRA will proceed without the EC input.	after the final AR has been circulated
12	**Day 57**	HPRA Management Committee reviews the recommendation on the CTA, and gives a final decision. This decision applies only to the Part I dossier. EC 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.	
13	**Day 60**	End of procedure. HPRA decision letter on the CTA is sent to the applicant, and to the EC for information. EC issues its opinion directly to the applicant. Final AR (Part I and Part II), HPAR decision letter, and EC opinion notification ('single national decision') are stored on the IT platform.	

Table C Substantial amendment (modification)

Note the EC will only be included in the assessment if the amendment concerns aspects relevant to the EC

Step	Timeline	Process	Ethics committee action - Time available for action
1	**Day -5**	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). HPRA validates Part I of amendment, if any. Part II of amendment, if any, forwarded to the EC for validation.	
2	**Day 0**	HPRA sends automatic notice of validation of Part I sent to the applicant. Timelines will be provided to the applicant, and the EC. EC notifies the applicant of the validation of Part II, and provides timelines to the applicant.	
3	**Day 15**	HPRA shares the updated draft Part I AR with the EC through the IT platform, including draft conclusion on Part I. The quality part of the AR is not provided to the EC as this may contain information that is commercially sensitive and is not relevant to the ethical aspects of the trial.	
4	**Day 20**	EC provides opinion on the circulated Part I AR, and a list of additional concerns, if any, which should be addressed by the applicant. If there are major discrepancies in the opinion between the HPRA and EC - a teleconference between the chair of the EC and the HPRA is organised to discuss the concerns. Ideally this should take place prior to Day 20.	EC opinion on Part I needs to be provided **20 days after** Part I documents are available and **five days** after the AR and HPRA opinion has been circulated
5	**Day 21**	List of grounds for non-acceptance on Part I aspects (if any) sent by the HPRA to the applicant.	

Step	Timeline	Process	Ethics committee action - Time available for action
		EC sends grounds for non-acceptance on Part II aspects (if any) directly to the applicant.	
6	**Day 30**	Responses to Part I and/or Part II grounds for non-acceptance submitted by the applicant to the HPRA. HPRA makes the response to the Part I and/or Part II grounds for non-acceptance available to the EC through the communication platform.	
7	**Day 32**	Part I AR prepared by the HPRA and circulated to the EC.	
8	**Day 34**	EC provides final opinion on the Part I substantial amendment to the HPRA. If major discrepancies in the opinion between the HPRA and EC are noted - a teleconference between the chair of the EC and the HPRA needs to be organised to discuss the concerns. Ideally this should take place prior to Day 34. If no response from the EC to the final Part I AR is received within the timeline, the HPRA will proceed without the EC input.	Final EC opinion needs to be provided **13 days** after responses from the applicant have been received and **one day** after the final AR has been circulated
9	**Day 35**	End of procedure. The final HPRA decision on the substantial amendment is sent to the applicant (if relevant), and to the EC for information. The EC will issue its opinion on Part II substantial amendments directly to the applicant, and provide the opinion to the HRPA for information. Updated AR stored on the IT platform.	

9 APPENDIX III - DOSSIER STRUCTURE AS PER REGULATION (EU) NO. 536/2014

1 INITIAL APPLICATION

During the course of the pilot 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 EC, 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 pilot 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)
5 DOCUMENTATION RELATING TO COMPLIANCE WITH GOOD MANUFACTURING PRACTICE (GMP) FOR THE INVESTIGATIONAL MEDICINAL PRODUCT
6 INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD)
- 1.1 Data relating to the investigational medicinal product
- 1.2 Simplified IMPD by referring to other documentation e.g. SmPC
- 1.3 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 ARRANGEMENTS
2 SUBJECT INFORMATION, INFORMED CONSENT FORM AND INFORMED CONSENT PROCEDURE
3 SUITABILITY OF THE INVESTIGATOR - CV and declaration of interest of the Investigators can be included here
4 SUITABILITY OF THE FACILITIES – the site specific assessment form can be included here.
5 PROOF OF INSURANCE COVER OR INDEMNIFICATION
6 FINANCIAL AND OTHER ARRANGEMENTS
7 PROOF OF PAYMENT OF ETHICS COMMITTEE FEE, OR FEE WAIVER REQUEST.

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 pilot 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.