CRF-C
HRB Clinical Research Facility Cork

Regulatory Requirements in Clinical Trials

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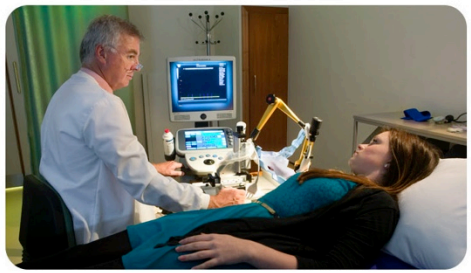

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Scope of presentation

- Interventional Clinical Trials under remit of competent authority –Health Products Regulatory Authority (HPRA)

- What is required from a regulatory point of view
  - Before starting a clinical trial
  - During a clinical trial
  - End of clinical trial

It's not always easy to determine what is an interventional clinical trial under HPRA remit and what is not, e.g consider:

- A Study with 2 marketed products – randomising patients to the 2 different treatments.
- A food study where company are making a claim for medical efficacy of the product in a particular condition.

Decision tree/ algorithm on HPRA website

If in any doubt email the HPRA and ask them

Regulatory Environment

- EU Directive 2001/20/EC - Clinical Trials Directive
- EU Directive 2005/28/EC – GCP directive
- New Regulation 536/2014 repealing Directive 2001/20/EC – scheduled to come into effect 2018
- Ireland SI 190 of 2004
  - Amendments in 2006 and 2009
- ICH E2A (Safety reporting)
- GMP for CT materials -Annex 13

POTENTIAL INVESTIGATOR

Help is at hand!

Regulatory Affairs

Before starting a HPRA regulated trial :

You need:

1. Ethical approval from one of the 12 recognised ethics committee (EC) in Ireland
2. HPRA approval
3. Approval of institution/hospital

Can do parallel applications to REC and HPRA

Getting EC Approval to run a HPRA regulated clinical trial

Application must be made by the Chief Investigator

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1 Application (to 1 REC) regardless of number of sites in Ireland

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Standard form in use for most RECS (DEPT OF HEALTH WEBSITE), CREC have their own form but will accept the standard form

REC application includes :

- Protocol
- Patient Information leaflet
- Informed Consent Form
- Any other documents seen by the patients-
  - e.g advertisments, patient ID cards, questionnaires
- CV of PI
- Site Specific Assessment form

Getting HPRA Approval to run a clinical trial

Clinical Trial Application (CTA) - See HPRA guide to CT Applications on the HPRA website

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Obtain a EudraCT number - by logging onto EudraCT website

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Complete a EudraCT application form – xml file

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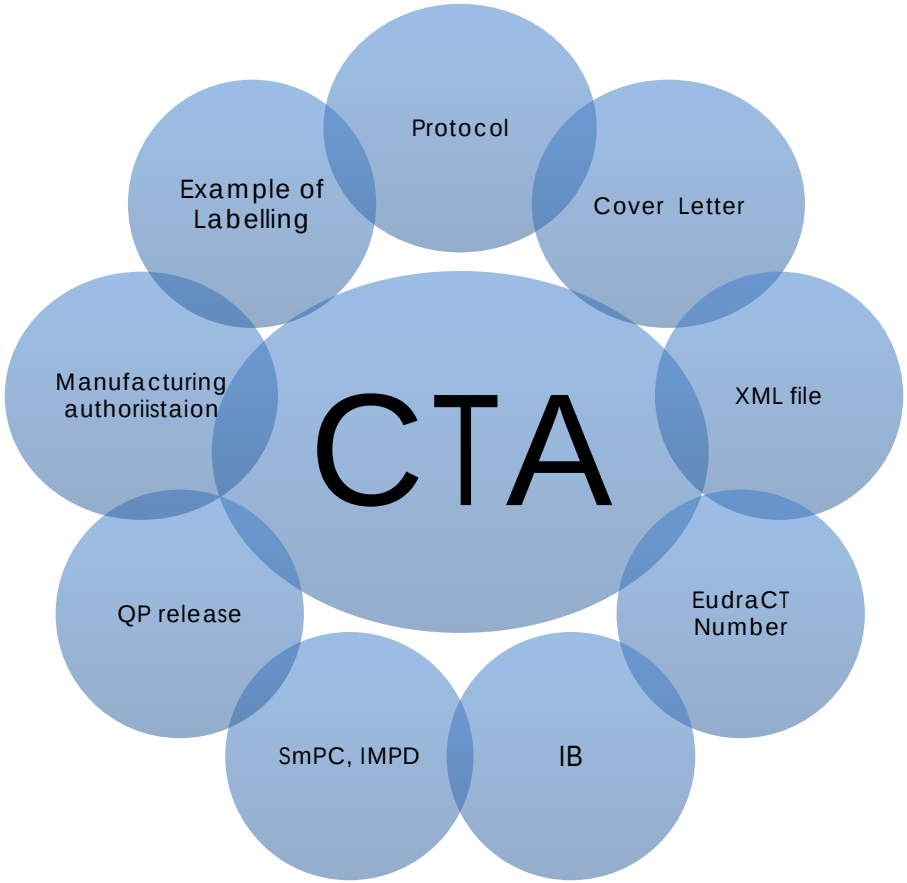
List of documents to include in the CTA -See appendix 3 of the HPRA Guide to CT applications

CTA – submission includes

HPRA Guide to CTA Appendix 3:



Clinical Trial Application (CTA) continued.

- HPRA do not ask for PIL or ICF – REC responsibility
- HPRA will check if application is valid (all documents present and correct)
- Will reply within 30 days of receipt of a **valid** application:
  - accepting request to run the trial,
  - not accepting (with reasons)
  - list of questions /requests for more information

Ongoing Communication with HPRA and REC during the study incl:

- Changes to Risk Benefit
- Amendments
- Any major issues with study -
  - It's not currently a requirement to report breaches of GCP to HPRA and EC but it will be under the new regulation
  - Best practice to do so now

Risk benefit –during trial

‘ The investigator should promptly provide written reports to the sponsor, and the EC and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects’ (ICH GCP 4.10.2)

How is risk /benefit montiored during a study?

- Noting and reporting SUSARs - Individual reports
- Development Safety Update Reports- listings and tables
- PI and Sponsor -ongoing discussions re Risk/ Benefit potential changes
    - if new treatment comes on market
    - if a lot of AEs ,
    - Lack of efficacy
    - Review of SAEs
- DSMB or IDMC may be in operation

Amendments

- Amendments to protocol,Investigator Brochure, addition of new sites, change of PI need to be submitted to the HPRA and to the EC
- Changes to the PIL, IC , advertisments etc need to be submitted to the EC only
- Substantial versus non substantial amendments
- EC and HPRA - different definitions of what consitutes substantial.....

Substantial amendments- HPRA and EC

HPRA - 'substantial'-

likely to have a significant impact on the safety, physical or mental integrity of the participants, **or** the scientific value of the trial. (HPRA Guidance document on CTA)

- It is up to the sponsor to assess what is regarded as substantial.

- Notify HPRA using 'substantial amendment notification form.' Update xml file + submit any accompanying documentation.
- RECs have substantial ammendment forms also.

Substantial amendments-

- Any change to reference safety information is seen as substantial (SI 190)
- A change of sponsor is regarded as substantial (SI190).
- A change of PI is NOT regarded as substantial by the HPRA but is regarded as substantial by EC
- Need written approval of amendment before implementing it – UNLESS it's an urgent safety measure.
- Need to reconsent patients in study if PIL/IC updated.

Non substantial amendments-HPRA and EC

- Non substantial amendments – notify the EC in writing.
- Non substantial amendments do not have to be notified to the HPRA BUT must be recorded and submitted with subsequent substantial amendment notification (HPRA CTA guidance document).
- Update the CTA form and xml file and resubmit when next substantial amendment is being done.

Substantial or non Substantial amendment?

- Change of phone number on consent form
- Change of Inclusion criterion e.g upper age limit increased from 60 to 70 years.
- Inclusion of an extra site
- Change in no. of patients to be recruited
- Change of PI at a site
- Change of study nurse at site

Urgent Safety Measures- HPRA and EC

- If sponsor and PI take an urgent safety measure to protect health or safety of subjects must notify HPRA and EC in writing no later than 3 days afterwards.
- Can notify by phone initially and send writen information within the 3 days.
- Specify what measures were taken, reasons for this and plan for further action.

Notifiction of SUSARS – HPRA and EC

- Notify EC and HPRA of SUSARs within
  - 7 days – fatal and life threatening
  - 15 days - all other 'serious' categories

  - Submit to EC, HPRA, EUDRAVIGILANCE Database

  - Academic studies –Ask if HPRA will enter SUSARs into EV.
    - NB shorter timelines (2 and 7 days)

Development Safety Update Reports (DSUR) : HPRA and EC

Sponsor required to submit a safety report (DSUR) once per year to HPRA and EC

Present a **comprehensive , thoughtful** annual review and evaluation of pertinent safety information for that period.

If IB is updated in that time period need to submit both versions of IB with the DSUR.

End of Trial: HPRA and EC

- Notify HPRA and EC using EU declaration of end of trial form.

- Within 90 days of end of trial OR within 15 days if trial ended earlier than planned.

- End of trial report to be submitted within one year of completion or cancellation of the trial.

(See EU note for Guidance on Strucure and Content of Clinical Study reports on EMA website.)

What does the future hold?

EU regulation 536/2014
Main changes:

- Single portal submission – both CA and REC
- Coordinated assessement by both CA and REC
- Single decision per Member state
- EU Portal and EU database
- Notification of start , end, first patient first visit – all via portal
- Concept of low intervention trials.

EU regulation 536/2014

- A streamlined application procedure via a single entry point, the EU portal.
- A single set of documents to be prepared and submitted for the application
- A harmonised procedure for the assessment of applications for clinical trials, which is divided in two parts.
  - Part I is jointly assessed by all Member States concerned.
  - Part II is assessed by each Member State concerned

-Sponsor will not choose EC, the EC will have applications assigned to it.

- EC will conduct part II assessment and be involved ,with HPRA in part I assessment.

EU regulation 536/2014

Potential Benefits of Portal and Database:

- One access point
- All documents in one place
- Simplification of contact
- Standard timelines for review
- Tacit approval
- Transparency
  - Public acess to info (may encourage public to look for CTs)
  - Transparency on results – even negative ones

Potential Benefits (contd)

- Rich source of data for researchers
- No duplication of trials already done
- Assessment – one decision per Member State
- No national versions of protocol
- One set of questions from CA+ REC (together)

Potential Challenges for Investigator led trials:

- New IT sytem –
  - Training for PIs, study nurses coordinators currently doing own applications – not regulatory specialists
- Ethics – lack of standardisation within the countries
- One central ethics ?
- Currently no electronic submission proceedures in RECs for Clinical Trial applications in Ireland.

EU regulation 536/2014

- Note – the Clinical trial regulation implementation is dependent on the functionality of the EU portal and database.

Table 1: Time frame for the implementation of EU portal and EU database

EU portal and EU database delivery time frame		
	Activity	**Date**
1.	Auditable Version released for audit, including implementation of auditable and non-auditable must requirements	July 2017
2.	Independent Audit commences	August 2017
3.	Development of remaining requirements commences	August 2017
4.	Independent Audit completed	November 2017
5.	Audit endorsed by EMA Management Board	December 2017
6.	European Commission notice published in *Official Journal of the European Union*	March 2018
7.	Production Version completed, including implementation of remaining should requirements	July 2018
8.	Production Version go-live	September 2018
9.	Regulation (EU) No 536/2014 becomes applicable	October 2018
10.	Further upgrade and enhancement of the system completed	Q3 2019
11.	Directive on Clinical Trials 2001/20/EC no longer applicable	October 2021

‘EU portal shall be technically advanced and user-friendly so as to avoid unnecessary work ‘ !

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EU regulation 536/2014

- Key decisions to be made before implementation in Ireland:
  - What EC will be involved? Central EC?
  - How will ECs work with HPRA on applications?
  - Who will supervise the ECs? (DOH/HIQA?)

  - 'HIQA does not yet have any remit in relation to Clinical trials. Currently waiting to hear from the DOH on the new model for implementation of the EU regulation in Ireland an whether this includes a role for HIQA as supervisory body of ECs' (HiQA Research Ethics Mansger).

EU regulation 536/2014

- ‘The DOH has commenced work to identify what changes will be necessary to imlement the new requirements and is engaging with RECs and HPRA to identify best model for Ireland.’

- ‘It is likely that secondary legislation will be required to give futher effect to the requiremements of the legislation’

DOH, Medicines , Controlled Drugs and Pharmacy legislation representative from


THE TIMES THEY ARE A-CHANGIN'
BOB DYLAN