ICRIN Seminar on EU Regulation of Clinical Trials

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IRISH MEDICINES BOARD
Overview

- Clinical Trial (CT) legislation in Ireland
  - CT Act 1987 - 1990
- New CT regulation proposal 2012
Regulation of Clinical Trials in Ireland

- The Control of Clinical Trials Acts 1987 – 1990
  - First system in Ireland for regulation of all studies in humans
  - Covered Phase I – IV; ADME studies
  - Issues of indemnity arose
- 1990 amendment needed to address immunity issue
- Hospital based ethics committees
- Trials approved by Minister for Health in consultation with NDAB
- Process was thorough but slow
European Directive 2001

• Commission saw a clear need to standardise the regulation of CT’s across EU
• Variable systems operated in MS
• Some MS excluded volunteer studies
• Other systems like that in Ireland were more thorough
• 10 year revision underway
European Regulation 2012

- 10 year review of progress showed a number of differences in EU system across MS
- Numbers of studies dropping in EU
  - 8000 in 2001
  - 4,400 in 2010
- Processes variable in the MS despite following same Directive
- Separate CA and ethical reviews in parallel (sequential) and different medical systems developing
- EC considers that a new Regulation (automatically applicable) was needed with tight timelines and a single national decision
Proposal for new EU Regulation on Clinical Trials July 2011

- Following 2 rounds of public consultation in 2009 and 2011, Commission published its proposal for Regulation on Clinical Trials 19/7/2011
- The proposals are being studied in Parliament (EP), Council and ECOSOC
- The intention is to maintain and enhance the protection of subjects while streamlining the processes
- Discussion in Council commenced during Cyprus Presidency and has been enhanced during the Irish Presidency
Proposal for EU Regulation (2)

- The proposal has 93 articles divided into 19 chapters (I – XIX)
- There are also 4 annexes setting out more detailed technical provisions
- Content of annexes can be amended by Commission following a Delegated Act as set out in Chapter XVII
- Will replace Directive 2001/20/EC
Chapter I of the Regulation

- Article I sets out the scope of the Regulation
- It applies to all clinical trials in humans except to non interventional studies
- Article 2 provides a number of definitions of different types of clinical studies and a range of other new definitions
  - Clinical study
  - Clinical Trial
  - Non interventional study
  - Low intervention CT
Non-interventional studies - CT Regulation

Clinical study

Clinical trial

Non-interventional studies

Low-intervention clinical trial

CT Regulation applies to clinical trials only

non-interventional study = clinical study

non-interventional study ≠ clinical trial
• Article 4 – Application to be made to the EU Portal
• Article 5 – Application process, selection of "Reporting Member State" (RMS)
  – validation of application
  – agreement on low intervention clinical trial and on who will be RMS
  – detailed timeline “within SIX days”
  – incomplete application timelines for updating or application fails (further 6 days)
  – no comment from authorities in 3 days, process is complete
• Article 6 - deals with the assessment Part I
  - public health and subject benefits vs. possible risk
  - quality and safety of the product (IMP)
  - investigators brochure
  - product labelling
• The reporting MS prepares assessment report (AR) Part I
• AR sets out draft conclusion on the trial – accept/reject
• RMS submits AR to Sponsor and other CMS
• Very short timeframes for assessment and response (10 days)
• CT is then considered approved or withdrawn
• Article 7 - deals with Part II of the assessment report
  - each MS does its own assessment
• Ethical issues include - informed consent (Chapter V)
  - selection and suitability of subjects
  - suitability of investigators and sites (Chapter VIII)
  - damage compensation and indemnification (Chapter XII)
• Part II AR completed in 10 days in parallel with Part I assessment
• Timelines challenging for the MS
• Left to MS to manage how CA’s and Ethics Committees operate and interact
Details arrangements for a substantial modification of a CT

Follows the format, approach and timelines for a new application as described in Chapter II

Revision in Part I
Supervised by RMS

Changes to Part II assessed by all concerned MS

Decisions communicated by the EU IT Portal
EC Regulation Chapter IV

- Deals with the application dossier
- Annex I sets out the details to be included in the dossier following principles and international guidance on GCP (WHO, ICH, Helsinki etc.)
- Annex II sets out the details to be included in the dossier for a substantial modification
- Trials conducted outside EU will follow same principles, to ensure data quality and validity
- Data requirements of Annexes can be amended by Commission under delegated acts (Article 27)
• Deals with protection of subjects and informed consent (IC)
• Risks to subject minimised while benefit should be anticipated
• Subjects must receive detailed information about the trial from the investigator in order to exercise IC
• Written, dated, IC supplied by a subject or his legal representative before an investigator can commence the trial
• Articles 30 and 31 makes special arrangements for incapacitated subjects and minors respectively
• Article 32 – trials in emergency situations can be initiated ahead of receipt of IC
CT Regulation Chapters VI and VIII

• Deal with supervision and monitoring of the trial
  – start and end of the trial defined
  – temporary halt, suspension, early termination and unblinding
  – Compliance with GCP and trial protocol
  – tracking, storage, return and destruction of IMP’s and auxiliary medicinal products
  – data generation, handling, storage and protection
  – sponsor shall generate a clinical trial masterfile updated and safely stored
• All safety reporting via EMA database (EudraVigilance)
• Investigator records AE’s and SAE’s
• Investigator notifies SAE’s to sponsor immediately
• **Suspected Unexpected Serious Adverse Reactions (SUSARS)** reported to EMA database without delay
• Annual safety report on each study to EMA
• MS cooperate with EMA in safety assessment
• Technical details given in Annex III
• Manufacturing of IMP's and auxiliary medicinal products (AMP’s) to be conducted under GMP
• “Manufacturing” includes importation, re-labelling, repackaging and modification to authorised products
• Exemptions for hospital pharmacies, extemporaneous preparations and radiopharmaceutical preparations
• Labelling of unauthorised IMP’s and AMP’s
• Details in Annex IV
• Authorised AMP’s and IMP’s need special labelling arrangement
• Radiopharmaceuticals used for diagnosis have exemptions
• CT must have at least one Sponsor
• Sponsor can be, or delegate to, individual, company etc.
• Sponsor can be investigator – academic investigators are facilitated by the Regulation
• Co-sponsorship permitted
• Must be a “contact person” residing in EU
• Deals with compensation for damage to subjects independently provided in accordance with liability laws in MS
• MS shall provide a national indemnification scheme (NIS) to provide for compensation needs
• Sponsor can avail of NIS to meet these obligations or can provide private insurance cover
• MS can charge Sponsor a fee for NIS
• Academic sponsors can use NIS free of charge
CT Regulation Chapter XIII - Supervision

• MS may suspend, terminate early or modify a CT where necessary
• Decisions communicated to other MS via EU Portal
• MS shall appoint GCP Inspectors to supervise CT’s in their jurisdiction
• MS to share inspection plans and results of inspection
• Inspector reports to be stored via EU Portal
• Commission to put in controls on the supervision procedures by MS and for trials outside EU
CT Regulation Chapter XIV – IT Infrastructure

- EU Portal will provide a single entry point for all CT data submissions and MS assessments
- Portal links to EU database (currently Eudra CT)
- EU database to be publicly accessible for transparency except for measures to
  - protect personal data
  - protect commercially confidential information
  - ensure effective CT supervision
- Sponsor shall update database on any changes to CT’s (except substantial modifications)
- A given subject may exercise his right to access personal information on his participation and have any inaccuracies corrected
• Designated national contact point in each MS
• Commission to support MS cooperation by ....
• CT Coordination and Advisory Group (CTAG) to be set up and chaired by Commission
• CTAG will support information exchange and MS cooperation
• MS can continue to charge fees to cover their costs
• One single fee per application assessment
• Commission with Standing Committee (Directive 2001/83/EC) will provide a decision making body
• Article 85 delegates power to Commission to amend detailed requirement, submitted to Council and EP
• If no objection within 2 months, then the Act enters into force
CT legislation will be without prejudice to medicines and other EU legislation

CT legislation is without prejudice to MS laws on cells derived from humans or animals, liabilities of sponsor or other health policy issues

CT subjects shall not bear costs for medicinal products

Directive 95/46/EC and Regulation (EC) No 45/2001 shall apply to processing of personal data by MS or EMA

CT Directive 2001/20 is repealed but a 3 year transition period will apply from date of implementation
CONCLUSION

• The new CT Regulation will replace the current Directive 2001/20 when it completes its progress through Council and the Parliament.
• The target is to complete the process in the life of the current Parliament and Commission.
• The principle aim is to have a single application and a single evaluation in each concerned MS.
• Measures for rapid assessment and simplified safety reporting through a single EU Portal are designed to encourage clinical research in Europe.
• Special provisions for non-commercial sponsor including a National Indemnity Scheme are designed to make it easier for academic researchers – worthy objectives.
• However a lot remains to be done in 2013.
### Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
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<td>ADME</td>
<td>Absorption, Distribution, Metabolism, Elimination</td>
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<td>AMP</td>
<td>Auxiliary Medicinal Product</td>
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<td>CMS</td>
<td>Concerned Member State</td>
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<td>CT</td>
<td>Clinical Trial</td>
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<td>EC</td>
<td>Commission of the European Communities</td>
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<td>ECOSOC</td>
<td>EU Economic and Social Committee</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>EP</td>
<td>European Parliament</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>IC</td>
<td>Informed Consent</td>
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<td>IMB</td>
<td>Irish Medicines Board (1996 - )</td>
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<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<td>MS</td>
<td>Member State</td>
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<td>NDAB</td>
<td>National Drugs Advisory Board (1967 – 1995)</td>
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<td>NIS</td>
<td>National Indemnification Scheme</td>
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<td>RMS</td>
<td>Reporting Member State</td>
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<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
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Thank you for your attention.
Any questions?