Montage et conduite de projets de recherche clinique multinationaux Européens
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Focus sur les infrastructures de recherche Européennes et les règlements

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European regulatory context for clinical trials

- European Regulations
  - Clinical Trial Regulation 536/2014
  - Medical Device Regulation 737/2017
  - General Data Protection Regulation 2016/679

- European Directives
  - Directives 2001/20/EC (Main)
  - 2005/28/EC (GCP, Monitoring)
  - 2001/83/EC
  - 95/46/CE and 2002/58/EC (Data protection)
  - 2003/94/CE (Manufacturing and authorization)

- European Member States National Laws

- Competent Authority Rules
  - Ethical guidelines
  - ICH GCP
  - FDA / EMA rules
  - Declaration of Helsinki

- Quality System set up by each sponsor
European legislation on clinical trials: 2001/20/EC
Directive for clinical trials on medicinal products

Competent Authority (# FDA)

Sponsor

Investigator

Patient

Ethics Committee (# IRB)
Sponsor, investigator, patients
## National regulatory requirements

<table>
<thead>
<tr>
<th>EC</th>
<th>CA</th>
<th>Sponsor</th>
<th>Insurance</th>
<th>AER</th>
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### 1 - CT on MP
- phase 1
- phase 2
- phase 3
- phase 4
- tissue eng
- cell therapy
- gene therapy
- blood-derived
- MAB, prot, pep,
- oligonucleotides
- vaccines
- fixed combination
- multimodal

### 2 - CT on MDevice
- authorised
- non authorised
- authorised
- non authorised

### 3 - Other TTT trials
- radiotherapy
- surgery
- transplantation
- transfusion
- physical therapy
- psychotherapy

### 4 - Diagnostic studies
- in vivo
- in vitro
- imaging

### 5 - Nutrition
- nutritional
- nutr. Supplements

### 6 - Other clin. research
- CAM
- biobanks
- physiology
- pathophysiology
- psychology

### 7 - Epidemiology
- pharmacoepidemiology
- interventional
- non interventional
- epidemiology
- interventional
- non interventional
- registries of patients
Major changes under Clinical Trial Regulation 536/2014

- Regulation NOT a Directive
- Risk-based approach of clinical trials
- Single application dossier via a EU portal with tacit approval if no response within 60 days
- Transparency of clinical trial results
- New Rules on Informed Consent of Subjects
- Introduce the concept of co-sponsorship
- Simplified safety reporting system
EU clinical trial Regulation 536/2014
EU clinical trial Regulation 536/2014

✓ “Regulation”: no transposition into national legislation

✓ Focus on clinical trials on medicinal products
✓ Definition of “intervention” and of “clinical trial” (!)

✓ Provisions for “low intervention trials”: trials on authorized products, used either within their licensed indication, or off-label if this represents the established standard treatment.

✓ Co-sponsor, sponsor’s representative in the EU
✓ Possible insurance/indemnity by public health systems (for “low intervention”): country decision
EU clinical trial Regulation 536/2014

✓ Clinical trial application through a single portal (operated by EMA) with a reporting Member State coordinating the authorisation process

✓ Single, electronic dossier
  - Part 1: product and protocol: coordinated
  - Part 2: “ethical” review (information, consent, site): national
  
Each country has its own organisation (CA vs. EC) to provide authorization

✓ Sponsor proposes the reporting MS
EU clinical trial Regulation 536/2014

- Limited possibility to opt-out
- Timelines: 60 days for authorisation, tacit approval
- Transparency: publication of results
- Trials in emergency situation
- Need for adaptation of national legislation: procedure for approval (CA vs. EC), clinical research without medicinal products
2017/745 Regulation (starting May 2020)

Clinical investigation (1)

- Access to market based on \( \mathbb{C} \mathbb{E} \) closer to FDA approval
- Provided by notified bodies, expert groups
- Clinical « investigation » required for implantable class III, and active class IIb delivering drugs
- Objective : assess safety and performance (efficacy ?)
- No guidance on level of evidence, « robustness of data »
- Possible scientific advice / expert groups
- Single sponsor in the EU (or legal representative)
- Provisions for vulnerable populations
2017/745 Regulation (starting May 2020)

Clinical investigation (2)

- Coordinated clinical trial autorisation / rapporteur country (voluntary until May 2027), opt-out, timelines (45 + 50)
- No coordination for ethical review
- Compliance with ISO 14155:2011 and with Declaration of Helsinki
- Insurance / indemnification (national rules)
- Registration, interoperable / EUdraCT, reporting, lay summary
- Single electronic portal
- Central adverse event reporting system
- EUDAMED database, MD identifier (IUD) : transparency, traceability
- After CE label : repurposing -> autorisation, if not -> notification
Data protection and transparency in clinical trials

- **EU General Data Protection Regulation**
  - National provisions
  - Broad consent for reuse?
  - Withdrawal of consent

- **Transparency**
  - 2004: registration of clinical trials (ICMJE)
    - [www.clinicaltrials.gov](http://www.clinicaltrials.gov), EUDraCT, WHO ICTRP
  - 2014/536 and 2017/745 Regulations: aggregated data
  - 2017: data sharing plan, FAIR access
    - Access to individual patient data
    - Re-analyses, secondary analyses, meta-analyses