Transposition of the Clinical Trial Regulation
CTR N° 56/2014 in Belgian law

The Belgian legislative proposal

BAREC meeting : 15/12/2016

EU Clinical Trial Regulation

• MS organises at the national level a joint assessment between
  — the local competent authority (FAMPH)
  — the ethical reviewer
• MS opinion should be a "consolidated" evaluation of both the ethical reviewer (part I & II) at a Belgian level and the FAMPH (part I)
• The persons / the « only » EC assessing the application should be independent of the sponsor, the clinical trial site, and the investigators involved, as well as free from any other undue influence (preliminary mark n° 18).

Transposition of the CTR in Belgian law

• Drafting a new law incorporating the main provision of the CTR N° 56/2014 whose scope is strictly limited to CTA on drugs
  — Main stakeholders
    • FPS of health & safety of the food chain + FAMPH
    • CHAR + BAREC
    • Sponsors
    • Patients associations
  — CTA on drugs will therefore be out of the scope of the Belgian law of May 2004 that remains of use for all other experiments on the human persons
Ethical body according to BAREC

EC's College
- Coordinating structure composed of one member from each CEC
- Administrative structure
  - Accredited ECs are in charge of the CTA evaluation
  - Concerned EC = Local EC / EC of the sites involved in the clinical trial
  - Accredited EC established within the FPS Health
  - Composition (members and alternates) similar to that of a local Ethics Committee
  - Ethics College establishes its internal regulations which lays down the rules of organization and operation (to be approved by the King)
  - In the CTA evaluation process, the Ethics College seeks the advice of a competent EC and / or expert(s) external(s) on aspects that "He" determines

Ethical body according to the first law project (1)

Ethics College
- Is the ethics committee within the meaning of Article 2, § 2, 11° of EU Regulation
- Ethics College established within the FPS Health
- Ethics College secretariat provided by the general official appointed by the Minister responsible for FPS Health
- Composition (members and alternates) similar to that of a local Ethics Committee (qualification of members, most doctors, ...)
- Ethics College establishes its internal regulations which lays down the rules of organization and operation (to be approved by the King)
Ethical body according to the first law project (2)

- Ethics College is responsible of the ethics assessment & the ethics decision
  - Choose the accredited EC (or external experts if needed) whose opinion is requested (but non-binding)
    - Accredited EC not concerned by the assessment of phase I CTA
    - The proposal is to create within the Ethics College a subgroup for the evaluation of Phase I trials and FIM. Justification: the expertise requested is not specific to a disease or particular therapeutic area.
  - Ask advice on pre-defined scientific & ethical domains of the CTA
  - Liaise with the FANPH for the assessment report consolidation
  - Accredited EC (or external expert) provide advice as needed on request of the College

Ethical body according to the first law project (3)

Ethics College is the ethics committee within the meaning of Article 2, § 2, 11° of EU Regulation

Danger

- removed: 1/10 to the CTA & 1/10 to the RECs amendments / yr
- full voting for random
- 2000 members / yr
- independent
- independent
- independent

- REM must be independent and demonstrably able to make decisions without undue influence, pressure, or financial or market influence. This collective must be able to make independent and impartial decisions. The independent collective must be able to impartially evaluate professional or financial related interests.
- REM must, when evaluating applications for funding, have no conflict of interest. The REMs, when evaluating applications for EC-Membership, and in the procedures for dealing with potential conflicts of interest (members must declare potential conflicts of interests and in the course of funding of REMs)

"Guide for Research Ethics Committee Members" adopted by the Steering Committee on Bioethics on 12 December 2010 - © Council of Europe. Revised version of April 2012

Agenda July and August

- Presentation of the main lines of the preliminary law project to sponsors representatives & ethics committees current may 2016
- Presentation of the draft explanatory statement & preliminary law (FPS of health, end of June 2016)
- Multiple meetings to explain BAREC & CHAB-RUZB reluctance to this preliminary draft law (minister’s office, Absym-Bevas) current July 2016
- Publication of an open letter / white card in various newspapers
- Writing a cons-proposal with the help of a lawyer funded by the CHAB-RUZB
- Presentation of the revised explanatory statement & draft law (FPS of health)
Alarme dans les comités d'éthique hospitaliers

De saurion en les De Wever, respective el les secretaires va les ateliers centraux va les CSU de l'agence de l'oie.

De evaluation de genesmiddelen toekennen aan een centraal "college", zet de veiligheid van patiënten op de beddeng.

Vincent Sautin en Les De Wever, respective el les secretaries va les ateliers centraal va les CSU de l'agence de l'oie.

Estudes éthiques de médicaments sur patients et volontaires : "Un projet de loi inacceptable"
Ethical body according to the revised law project (1)

- Creation of a Federal College, independent, within the FPS of health & safety of the food chain
- Composition, organization, and relations with FAMHP & accredited ECs defined in law, Royal Decrees & internal regulations
  - Will not act as evaluating body, but as administrative structure in charge of coordination, harmonization and quality surveillance
  - Acting as single contact point for FAMHP (contact point, evaluation team) & the competent ECs along the whole process
  - Attribution of CTA application according pre-established rules to the competent EC

Ethical body according to the revised law project (2)

- Accredited ECs are in charge of the CTA evaluation:
  - part I (protocol, IB, ...) & part II
    - Reduced number (n = 8 to 10/80) compared to the current number of ethics committees with full agreement (n = 24/80)
    - Voluntary commitment of the EC to evaluate clinical trials in accordance with the requirements of European Regulation & of the related local operational frame
  - Local EC = EC of the sites involved in the clinical trial (n = ± 80)
    - LEC will receive the submission file for information
    - No role in the evaluation process by the Belgium Member State
    - May object to the local implementation of the Protocol if provided by the internal regulations of the institution

Ethical body according to the revised law project (3)

Accredited ECs
- The King determines the conditions for agreement of EC's empowered to provide an advice to the College in the CTA evaluation process.
  - Composition of the EC in conformity of the last regulation (Circulaire 613, Nov. 7th, 2014 = one representative of a patient association)
    - Specific conditions for EC’s agreement entitled to assess phase I CTA : representative of healthy volunteers in phase I studies (to be confirmed)
  - Facilities : adequate administrative staff / support
  - Standard operation procedure & quality system
  - Public agenda, regular meetings (once a week), web site
  - Current experience: statistics of CTA assessment during a period to be defined
  - Etc.,
- Reduced number (n ≤ 10/80) compared to the current number of ethics committees with full agreement (n = 24/80)
Evaluation process (1)

- FAMPH = Belgian contact point for all interactions with the EU portal
- 2 bodies in charge of a coordinated assessment
  - FAMPH: part I
  - EC: some elements of part I related to recruitment and risk/benefit balance for the participant and part II
- Assessment templates
- Application of the timelines (defined in calendar days) of the CTR for the initial CTA submission dossier and for the amendments
  - Sponsor: Submission file through the EU portal
  - Process in 3 phases: validation, assessment, decision (slides 40 to 49)
- Possibility of fixing shorter deadlines through Royal Decree and Law, among others for Phase I trials and "Proof of Concept" (15 days)

Evaluation process (2)

- Receives the submission file through the EU portal
- Transmits the file to the FAMP evaluation team & the College
- Validates the submission file
- Manages the timing of the evaluation process
- Chooses the EC in charge of the evaluation process
- Transmits the file to the chosen EC & the LECs concerned by the CTA
- Acts as single point of contact between ECs & the FAMHP
- Must be independent of any sites concerned by the CTA
- Evaluates predefined scientific & ethical issues
- Transmits its assessment report to the College
- Gives an advice on request of the EC in charge of the assessment

Evaluation process (3)

Timelines for an initial submission file:
- Deposit to the portal = D0
- Validation phase: D0 → D10 / D0 → D5 (phase I)
  - Extra timelines for submission dossier invalid: + 15 days (10 for sponsor answer + 5 for validator)
- Assessment phase (Ethical body & FAMPH): D11 → D55 / D6 → D15
  - Assessment & consolidation process under the King's decision
  - Report Templates
    - Part I: Independent assessment by the FAMPH & the EC with priority roles for each instance for the protocol evaluation (EU assessment report mandatory)
    - Part II: assessment by the EC (EU assessment report not mandatory)
  - Interaction between FAMPH & EC through the College
  - Extra timelines for conditional approbation (Q&A): 31 days (12 for sponsor answer + 12 for answer assessment + 7 for final assessment report)
- Decision phase: D56 → D60 (Ethical body & FAMPH)
### Part I

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<tr>
<th>Proposal – to be confirmed</th>
<th>EC</th>
<th>FAMP</th>
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<tr>
<td>1. The primary objective and public health benefits versus the risks and inconveniences for the subjects involved in the proposed intervention have been determined by the FAMP and in the related document.</td>
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<td>2. The compliance with the CT-protocol, including monitoring procedures, has been defined and outlined in the protocol.</td>
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<td>3. The investigator’s specific characteristics, including the adequateness of his/her knowledge and experience, have been assessed.</td>
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### Evaluation process (4)

- The Minister or his delegate takes the decision on the CTA under art. 8 of the regulations.
- CTA may be allowed if the FAMP and the Ethics College both have a favorable opinion.
- CTA may be authorized under certain conditions if FAMP and the Ethics College have suggested one or the other, one or more conditions.
- Assuming the conditions issued respectively by FAMP and the Ethics College are incompatible with each other, the CTA can not be allowed. The Minister shall not derogate.

- **What is the place of the concerned local sites ECs?**
  - None during the evaluation process.
  - May deny the involvement of the local site in the CTA (… if the site regulations provides that a CTA must have the approval of the local EC to be conducted)

### Actions

- Workshop on work process flow (FAMP – College - ECs)
- Workshop on assessment Part 1 (FAMP – College - ECs)
- Workshop on assessment report Part 2 (College - ECs)
- Creation of the College, drafting of its internal regulations, drafting of harmonized EC’s SOPs,…
- Designation of the ECs authorized to evaluate CTA
- Preparation of Royal Decrees (RD) for application of the new law "clinical trials"
- Preparation of the RD on assessment fees
- …
- Organization of pilot projects
Organisation of the CTR pilot (1)

Why?

• Fundamental differences between Law 2004 process and CTR process:
  – Single approval per member state
  – Independency of the EC (LECs non concerned by the evaluation process)
  – Short timelines and tacit approval for the entire process
• Important to obtain experience with this new way of working

Organisation of the CTR pilot (2)

Legal aspects

• The new law will include a section where it is stated that, in view of the pilots, article 11 of the law of 7 May 2004 can be considered as not applicable anymore.
  – Start of the first step of the pilot process after publication of the new law (best case scenario: Mid March 2017)
  – Timelines of the Law 7 May 2004 prevail
  – Independent ethics committee to be selected by College for running the pilot evaluations and LECs no more involved in assessment (modification of article 11 of law May 2004)
  – No additional fees for running the pilots
Organisation of the CTR pilot (3)

Scope

• First step (Mid March 2017 ?)
  — Limited scope of 10 trials
  — If possible with at least these kind of trials included in the pilot process but purpose to remain flexible :
    • CTA Phase I First in Human (FIH) mono-national
    • CTA Phase I FIH multi-national
    • CTA with an investigational medicinal product (IMP) with pre-existing critical issues
• Second step
  — Extension of the pilot trials with multinational applications (VHP) after publication of the RD (Best case scenario : Mid June 2017)

Organisation of the CTR pilot (4)

In practice from sponsor side

• On voluntary basis
  — Intention to participate to the pilot process with planned submission date to be submitted to FAMHP (February 2017)
• Without additional costs
• Substantial amendments for trials approved in pilot process will also go in the pilot process
• Safety reporting as usual

Organisation of the CTR pilot (5)

In practice from FAMHP side

• FAMHP will be the single point of contact (national contact point) => dossier provided to EC by College
• Collaboration with the College via assigned project manager
• No assessment according to the Directive (Law May 2004) performed in parallel but room for a certain flexibility (learning by doing process)
Organisation of the CTR pilot (6)

In practice from EC side

• On voluntary basis
  – Intention to participate to the pilot process to be submitted to FAMHP (End of January 2017)
• Criteria for the choice of the independent EC to be defined (College – EC’s – FAMPH)
• Collaboration with the College via assigned project manager
• No assessment according to the Directive (Law May 2004) performed in parallel but place for a certain flexibility (learning by doing process)
• EC’s Retribution equivalent to the actual retribution

Ethical body according to the BAREC proposition
College of Ethics Committees (1)

• Coordinating structure specifically dedicated to the evaluation by EC’s of drugs CTAs in the context of the Regulation
  • acting as contact with FAMHP along the whole process
  • attributing applications following pre-established system
  • acting as support to the competent ECs
    – facilitating assessment and reporting by ECs
    – facilitating consolidation process (part I) between competent EC & FAMPH
• Should be independent from
  • Competent authorities
  • Sponsor
  • Trial sites (hospital directions, investigators)
  • Any other undue influence

College of Ethics Committees (2)

• Composition: one representative from each selected EC allowed to give opinion on EudraCT application (competent EC).
• Alternate presidency / vice-presidency
• President / vice president chosen by the effective members among the effective members
• Weekly meetings
• Will not act as evaluating body, but as coordinating, supporting, facilitating and surveillance body

College of Ethics Committees (3)

• Administrative unit
  – Administrative staff dedicated to the function (number and competence to ensure the quality of work, timelines and consistency of service)
    • various job profiles to cover the different aspects of a CTA (scientific, ethical, regulatory & judicial aspects) but also computer skills (data base conception & developments)
    • some of this staff should be highly qualified
    • bilingual staff (Fr, Nl, Eng)
  – Working at central office for administrative availability and meeting facilities
  – Tasks
    • Administrative support for the College (database, website, meetings, contacts, etc.) and for the evaluating ECs
    • Attribution of CTA applications according pre-established rules (see further) & under supervision by the President
    • Primary administrative review: checking of the regulatory requirements (privacy protection, trial coverage with no-fault insurance, compliance of the clinical trial agreement to Belgian legal context, etc.)
    • Contact point for the FAMHP & the competent EC
  – should be done through an IT based facilitating the contact with the different parties in the different steps of the evaluation process & making the positions and decisions transparent for all concerned.
College of Ethics Committees (4)

**College’s tasks**
- Harmonisation
  - Will harmonise SOP of competent EC on the following points: composition, appointment and renewal process of EC; roles & activities of competent EC under other EC’s regulations, management of conflicts of interest, etc.
  - Will prepare standard forms & document annexes (REC, CTA, clinical trial agreement), etc. to be used in the national application decision of a clinical trial.

- Coordination, facilitation, support
  - will represent the EC’s of the related local and national ECs, such as, for instance, the related European system (EudraCT database).
  - will facilitate the work of the designated competent EC (e.g. administration support, network of experts under the responsibility of the College in part of the supporting services).
  - will facilitate the decision between designated competent EC and FAMPH (validation of report, evaluation of agreement) for a specific application, an unique contact point with EudraCT.

- Surveillance
  - The College should ensure adherence to the principles of the European Regulation and related local (Belgian) regulations: a perspective meeting of “relevant stakeholders”.
  - The College should ensure the integrity and independency of the assessment work.
  - The College should be entitled to implement (in collaboration with FAMPH) corrective measures to ensure the CTA assessment quality by all competent EC.

Accredited ECs (1)

**ECs allowed to assess CTA-Part 1 & 2**
- Selection out of EC with fully agreement (n = 22 / 80) based on:
  - Voluntary commitment of the EC to evaluate clinical trials in accordance with the requirements of European Regulation & of the related local operational frame
  - Voluntary commitment to delegate one EC’s member to the EC’s College
  - Composition confirm to the requirement of the FAMPH Circular n° 613 dated November 7, 2014 & the requirements of the EU regulation (laypersons representing the interest / perspective of patients)
  - Facilities, public agenda, web site, quality system, audit, regular meetings
  - Current expertise: number of EudraCT evaluation on yearly basis: 1 ≤ CTA or (continued)
  - (may 2004)

  - Reduced number justified by statistics of single opinions provided by year:
    - Academic EC (n = 7) are responsible for 87% of all single opinions
    - ECs providing ≥ 10 single opinions /year (n = 9) are responsible for 95% of all single opinions

- Note:
  - Role of ECs, not recognized as “competent EC” is still essential and very valuable in making specific expertise available
  - Essential role to be played by network of experts under the responsibility of the College

Accredited ECs (2)

“Research ECs must be independent and demonstrably able to make decisions without undue political, professional, institutional or market influence.
This crucial requirement should be duly reflected in the procedures for appointing REC members, in the requirements for REC membership, and in the procedures for dealing with potential conflicts of interest (members must declare potential conflicts of interests) and in the sources of funding of RECs.”

Guide for Research Ethics Committee Members (page 17)
Steering Committee on Bioethics
http://www.coe.int/t/dg3/healthbioethic/activities/03_biomedical_research_en/Guide/Gui
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Accredited ECs (3)

Guarantees of independence

- Structural independence
  - not concerned by the CTA
- Functional independence
  - Multidisciplinarity of members
  - Membership voluntary based
  - Some members non affiliated with the institution
  - Policies and procedures to identify and manage conflicts of interests, financials or other
    - Declaration of financial conflict of interest (at least annually)
      - Members directly or indirectly concerned by a file submission are excluded from the evaluation process

Accredited ECs (4)

- Accredited EC’s tasks
  - Participation in the initial assessment of a CTA (phase I to 4)
    - see evaluation process: slides 21 to 27
  - Part I of the CTA (slide 19)
    - scientific & ethic’s assessment & drafting of a report (slide 23) on its acceptability with or without comments
    - participation in the consolidation process to issue the single national opinion
      - E & FAMHP share their own final report
      - divergences, if any, are discussed between the concerned assessors at the level of FAMHP and reporting EC through the COLLEGE
      - assessment report is consolidated
  - Part II (slide 20) of the CTA
    - ethic’s assessment & drafting of a report on its acceptability with or without any comments
  - Continuing review of the evaluated CTA
    - Assessment of amendments when concerned (protocol in part I, all elements of part II)
**EU REGULATION (1)**

- One submission dossier (part I) for EU & one national dossier (part II) through one single IT portal
- One Reporting Member State [RMS] & some Concerned Member States [CMS]
- For each MS, one contact point
  For all interactions with the portal (validation, evaluation, decision …)
- Sponsor chooses RMS (must be concerned). Other CMS can take over if mutually agreed (validation process)
  → therefore, the sponsor doesn’t choose anymore the national EC in charge of the CTA assessment

**Application dossier**

- **Part I (art. 6)** – CTA common file submission : coordinated advice leaded by RMS with input from CMS
  - Protocol, IB (Risks / benefits, …), GMP files, …
- **Part II (art. 7)** – CTA national specific file submission : national advice by each MS
  - PIL/ICF, Recruitment procedure, Compensation (hospitals / subjects), CTA, Facilities, etc.
- Simultaneous evaluation of part I & part II or sequential evaluation of part I & part II possible
- For more details on part I & II, see slide 16 & 17

**Aspects covered by Part I**

- **Benefits / Risks balance**
  - Anticipated therapeutic & public health benefits taking account of
    - characteristics of and knowledge about the IMP
    - relevance of the clinical trial,
    - current state of scientific knowledge
    - participating population / population to be treated
    - reliability and robustness of the data
  - **Risks & Inconveniences** for the subject taking account of
    - characteristics of and knowledge about IMP & AMP
    - characteristics of the intervention compared to normal clinical practice
    - safety measures, risk minimisation measures, monitoring,
- Compliance with GMP of IMP & AMP, labelling requirements
- Completeness and adequateness of the IB
Aspects covered by Part II

- Patient information leaflet & informed consent form (PIL/ICF)
- Arrangements for rewarding or compensating
  - subjects
  - hospitals / investigators
- Arrangements for recruitment of subjects
- Protection of individuals confidentiality with regard to the processing of personal data (Directive 95/46/EC)
- Suitability of individuals involved in conducting the clinical trial
  - CV, GCP, previous experience in CTA, COI
- Suitability of clinical trial sites
  - Written statement on the suitability of the clinical trial sites including a description of the suitability of facilities, equipment, human resources and description of expertise, issued by the head of the clinic/institution at the clinical trial site.
- Damage compensation
- Compliance with the applicable rules for the collection, storage and future use of biological samples of the subject.

EU REGULATION (3)

- CTA evaluation process: Maximal timelines defined in calendar days
  Submission file deposit to the portal = D0
  - Validation phase: D0 → D10 (contact point = FAMPH)
  - Assessment phase: D11 → D55 (Ethical body & FAMPH)
  - Decision phase: D56 → D60 (Ethical body & FAMPH)
- To ask for additional information (through the contact point)
  - validation phase: 15 days (10 for sponsor answer + 5 for validation)
  - assessment phase: 31 days (12 for sponsor answer + 12 for answer assessment + 7 for final assessment report)

Evaluation process (1)

- Promotor
  - submits CTA folder
  - proposes RMS
- Validation
  - CMS wishing to be RMS submits it within 2 days
  - RMS selected within 3 days (J+4)
- Final Validation of the submission file by the RMS within 4 days (J+10)
- Maximum time for sponsor to submit required additional information is 10 days, followed by a review of 5 days.
Evaluation process (2a)

Part I Assessment for a multinational CTA

Initial assessment by RMS: 26 days

- 20 days
- 12 days
- 7 days

Independent assessment by Ethical body & CA

CMS submit additional comments to RMs

Questions & answers
- Sponsor’s answers within 12 days
- CMS complete its assessment within 19 days

Writing of final consolidated report by RMS

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Evaluation process (2b)

Part II Assessment for a multinational CTA

Each CMS shall assess for its own territory, the application

- 26 days
- 12 days
- 7 days

Questions & answers
- Sponsor’s answers within maximum 12 days
- CMS complete its assessment within 19 days

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Evaluation process (3)

Decision on the clinical trial

• Each CMS notify his decision (trial authorized with or without conditions which by their nature cannot be fulfilled at the time of that authorisation / trial refused)
  – CMS may disagree
    • with the RMS (Part I) on specific grounds (to be motivated)
    • with sponsor’s answers to the request of his Part II assessment report (to be motivated)
  – if an EC has issued a negative opinion which is valid for that entire MS, appeal procedure in respect of such refusal to be provided by CMS.
• Without decision’s notification by a CMS within time frame, trial is considered “authorized” for this CMS
• Without subject inclusion in a CMS within 2 years, trial authorization expires in that CMS