Clinical Trials in Horizon 2020

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Clinical trials in H2020

In the past:
- No public funding for Clinical Trials until 2008-2009 (FP7)
- It used to ‘belong’ to the pharma industry
- The pharma industry used to set the research agenda
- Resulted in unattended diseases and unexploited knowledge
- The need for public funding emerged, via FP7/H2020:
  - Less structured in FP7
  - More structured in H2020

In Horizon 2020:
- Dedicated topics for clinical trials
- Additional topics in which clinical trials are an option
- US partners are welcome and can be funded
Clinical trials in H2020

Which clinical trials can be funded in Horizon 2020?

- **Methodology:**
  - Observational
  - Interventional
  - Randomized
  - Longitudinal

- **Type of intervention**
  - Medicinal products
  - Medical devices
  - Advanced therapies
  - Surgery
  - Education/Training
  - Psychotherapy

- **Phases**
  - ‘Phase 0’ to ‘Phase 4’

Must correspond to a specific topic
Clinical Trial basics

- Protocol driven
- Single center vs. multi-center
- Inclusion / Exclusion criteria
- Patient recruitment plan
  - Recruitment rate (no. of patients / month) – given or estimated
  - “Power analysis” to reach statistical significance
  - Expected no. of patients per site (medical center)
  - Flexibility in recruitment and overall duration
  - Drop outs and recruitment problems are always an issue
Clinical Trial basics

• Payments structure:
  – In industry-initiated, “Per patient” basis is common
  – Allows competitive recruitment
  – Profit might be included

• Many people are involved

• Clinical Trial monitoring is essential - CRO

• Data analysis

• Sponsorship and insurance
Clinical Research Organization

• Typical roles of CRO:
  – Patient recruitment management
  – Clinical Trial monitoring
  – Regulatory affairs / support (e.g. IRB, communication with competent authorities)
  – Data analysis and statistics

• Represent core expertise in managing Clinical Trials
• “For profit” companies and “Academic” CROs
The H2020 RIA basics

• Clinical Trials are implemented in H2020 by the RIA instrument
• RIA (Research and Innovation Action) is one of the main H2020 funding instruments
• Addresses a specific topic in the H2020 Health work program
• Concrete deadlines
• Working in a consortium (minimum of 3 partner from 3 member states or associated countries)
• Can run for 3-5 years
• No flexibility in duration, once set
• Funding rate: 100% of all actual direct costs
• Overheads : 25% flat-rate on top of all actual direct costs (except for sub-contracting costs)
• Strict payment structure (in terms of timing and budget)
The challenge: Squaring the circle

- Inherent “conflicts”:
  - RIA template vs. Clinical Protocol structure
  - H2020 funding vs. Clinical trial payment structure
  - Fixed consortium structure vs. Competitive recruitment of patients
  - Typical and strict RIA duration vs. variable clinical trial timeframes
  - Legal and Ethical issues and conflicts
  - More...
RIA template vs. Typical Clinical Protocol structure

1. EXCELLENCE ..............................................................
   1.1 OBJECTIVES ......................................................
   1.2 RELATION TO THE WORK PROGRAMME ......................
   1.3 CONCEPT AND APPROACH ......................................
   1.4 AMBITION ..........................................................

2. IMPACT ...........................................................................
   2.1 EXPECTED IMPACTS ..............................................
   2.2 MEASURES TO MAXIMISE IMPACT .............................
      a) Dissemination and exploitation of results ..................
      b) Communication activities ....................................

3. IMPLEMENTATION ...........................................................
   3.1 WORK PLAN — WORK PACKAGES, DELIVERABLES AND MILESTONES ....
   3.2 MANAGEMENT STRUCTURE AND PROCEDURES ................
   3.3 CONSORTIUM AS A WHOLE .....................................
   3.4 RESOURCES TO BE COMMITTED .................................

Discrepancies:
Structure
Content
Length
Squaring the circle

Essential Information

- Respect the template!
  - Do not add information which is not requested (e.g. the full protocol)
  - Do not add chapters, annexes or change headings

- Identifier

- Study design and endpoints:
  - Study design
  - Primary and secondary endpoints, and how these are measured
  - Relevant guidance documents (e.g. guidelines from scientific societies, Health Technology Assessment agencies or regulatory bodies)
  - Scientific advice / protocol assistance / communication with regulatory / competent authorities / ethics committees
    - Full text answer / comprehensive summary of communication with the authority (e.g. EMA). Clearly define the regulatory / ethical status and requirements for the study according to the national and EU regulations
Essential Information

• Subjects / Population
  – Inclusion and exclusion criteria. Discuss inclusion of women and special populations.
  – Define sub-populations if subgroup analysis is planned
• Statistic analysis planning and power calculation – get your CRO involved here!
• Cumulative safety and efficacy information
  – Pre-clinical data from in-vitro or in-vivo studies; data from previous clinical studies; data from (pharmaco-)vigilance systems
  – Safety and tolerability of study interventions as well as efficacy of study interventions
• Conduct:
  – Schedule for study conduct including timelines for key study milestones
  – Description of recruitment strategy – realistic recruitment rate (subjects per month/per centre)
  – Assignment of intervention for controlled trial (randomization, blinding)
  – Study management, study monitoring, data and sample management, AE reporting etc.
  – Sponsor, coordinating centre(s) and committees
  – Study medication
  – Clinical centres
• Orphan Designation, if relevant to topic/proposal
• ‘Unit cost’ per patient break-down, if relevant
Mandatory Deliverables

- Note the following mandatory deliverables to be implemented in section 3 of the proposal:
  - First study subject approvals package
  - All approvals package (for clinical studies including more than one study site)
  - Midterm recruitment report
  - Report on status of posting results
H2020 funding vs. Clinical Trial payment structure

A typical Clinical Trial:

- Medical Centers can be pre-defined or recruited Ad-Hoc
- Competitive recruitment of patients
- Pay per patient = Ongoing payment
In H2020:
• Each beneficiary is paid once in each reporting period (12 or 18 months)
• 2-4 payments/periods throughout the project

Clinical trial in H2020
H2020 funding vs. Clinical Trial payment structure

The motivation: Pay Per Patient

Sample size

Anticipated Recruitment per Medical Center

Number of Medical Centers

Fixed MC set

Dynamic MC set

Beneficiary

Ad-Hoc

Actual cost

Unit cost

Competitive cost

Per patient

Sub-Contracting

*Best value for money

Orchestrating the MC funding

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H2020 funding vs. Clinical Trial payment structure

- H2020 Unit cost ≠ Typical clinical trial per-patient payment

\[
\text{H2020 Unit cost} = \{A1\} \times \{B1\} + \{A2\} \times \{B2\} + \ldots + \{An\} \times \{Bn\}
\]

- \{Ax\} (item of reference) can be any of the following items, per patient participating in the trial:
  - Estimated number of hours of Personnel (Medical Doctors, Other medical personnel and Technical personnel)
  - Consumables
  - Medical equipment (based on depreciation cost)
  - Other specific services

- \{Bx\} is the historical cost of the item in each medical centre according to last closed financial year at the time of submission of the grant proposal

- The list of reference units \{A\} is identical to all beneficiaries per clinical trial

- Costs \{B\} are specific to each Medical center
The recent “Unit Cost” update

- Decision C(2016) 7553 from Nov 2016 allows more flexibility and clarity to the way Unit Costs are implemented in Clinical Trials.

  - The ability to combine different reimbursement methods (actual or unit costs) was enhanced.
  - All personnel, assigned to horizontal tasks (e.g. study monitoring or study coordination tasks), can be calculated as actual cost, unit cost or a combination of the two.
  - Personnel directly assigned to the clinical trial, should be calculated as either actual or unit costs, but not a combination of both.
  - In case of multiple clinical trials under a single project, it is possible to have different sets of cost calculations, per trial, for each beneficiary.
  - Unit Cost can now be corrected and modified during the project execution under certain conditions.
Unit cost – good or bad?

• Advantages:
  • Easier budget estimation per beneficiary
  • Resembles per-patient reimbursement as done in industry-initiated trials
  • Easier and well justified budget transfer between beneficiaries (in the case of recruitment difficulties)
  • No need to document actual costs, e.g. timesheet management
  • Audit is easier

• Disadvantages:
  • The N-1 problem
  • Lack of flexibility: {A} and {B} can be modified through amendment to the GA only in two cases, while not increasing the requested contribution:
    • Change in the clinical protocol
    • Errors in calculation
Sub-contracting in Clinical Trials

• Sub-contracting is known to be unwelcome in Horizon 2020
• The big exception is in Clinical Trials
• Sub-contracting in Clinical Trials is welcome for:
  – CROs
  – Clinical sites
• Best value for money must be proven
• It allows to include profit (common issue with CROs)

• Plan with care
Fixed consortium structure vs. Competitive recruitment of patients

Fixed Medical Centers and consortium set:

- Coordinator
- Development
- CRO
- Patient Group

Clinical Site

4 Clinical Sites (as beneficiaries)

- Coordinator
- Site
- CRO
- Admin, data and financial mgmt

Clinical Site

7 Clinical Sites (as beneficiaries)
Squaring the circle

Fixed consortium structure vs. Competitive recruitment of patients

Dynamic Medical Centers set:

Many people are involved

Around 20 sites

Optional. Unknown number of sites to meet target, if needed at all

2,500,000 Euro

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Typical and strict RIA duration vs. variable clinical trial timeframes
Legal and Ethical aspects

• The Clinical Trial must conform to the EU Clinical Trial Regulation No. 536/2014, Declaration of Helsinki and the principles enshrined in the Oviedo Bioethics Convention

• Potential issues to consider:
  – Liability (Insurance)
  – Non-EU sponsor
  – Regulation conflicts with the US (Indemnity)

• Ethical annex
  – IRB approvals – note call-specific requirements
  – Make sure no ethical issue was left unattended
Ethical Issues

• All proposals above threshold and considered for funding will undergo an Ethics Review
• The grant agreement cannot be signed until the review is complete and all conditions are met.
• Better be “Ethics ready”

A-Form
Ethics Issues Table

Complete questionnaire

Prepare Ethics Self-assessment (Ethical Annex)
Ethical Issues

Ethical self-assessment – examples

Humans

• Which humans are involved?
  – vulnerable persons
  – persons unable to give consent
  – Children

• Are some interventions on the body foreseen?
  – invasive techniques (biopsy, EEG, fMRI)
  – Patients? Healthy volunteers?

• Which are the procedures for recruitment and consent?

• Documents to provide
  – ethics authorisations
  – information and consent forms

Data Protection

• Which data?
  – genetic data
  – sensitive data (health, political or religious opinions, sexual orientation, etc.)

• Which procedure?
  – procedure for collection – how, by whom, information on rights, info and consent forms, anonymisation
  – procedure for protection of data – how it is protected, encrypted, where, for how long?

• Documents to provide
  – data protection officer/authority authorisations
  – information and consent forms
  – security measures
Ethical self-assessment – examples

Cells and Tissues

• What type?
  – hESCs
  – foetal cells/tissues
  – use or creation of cells/cells lines

• What for?
  – justification of use
  – origin: direct collection/ biobanks /secondary use

• Documents to provide
  – ethics authorisations
  – information and consent forms
  – justification of right for secondary use

Animals

• Which animals are involved?
  – vertebrates
  – GMOs
  – Primates
  – wild / protected animals

• For what use?
  – Justification for choice of species
  – 3Rs, precise evaluation of number
  – Description of procedure, husbandry, anaesthesia, euthanasia
  – Applicable legislation

• Documents to provide
  – Ethics authorisations / project license
  – personal and laboratory licenses
The main thing to remember:

\[ r = 1 \]

\[ \sqrt{\pi} \]
Clinical trial topics – what to expect?

- Recurring topics:
  - Rare diseases
  - Chronic diseases
  - Regenerative medicine
  - Mental health
  - Infections diseases
• The European Medicines Agency (EMA) is the European Union agency for the evaluation of medicinal products
• In calls addressing rare diseases, applicants typically need to show a granted orphan designation and might be asked to implement recommendations from protocol assistance provided by EMA in the clinical protocol.
• Orphan Drug designation applications are reviewed by the Committee for Orphan Medicinal Products (COMP)
• Protocol assistance is a form of scientific advice provided for development of orphan medicines by the Scientific Advice Working Party (SAWP)
• Both COMP and SAWP meet once a month, on predefined dates
• SAWP follows COMP, they are not parallel
To qualify for orphan designation, a medicine must meet the following criteria:

- Targeting a disease that is life-threatening or chronically debilitating
- Prevalence not more than 5 in 10,000 (rare disease)
- There is no satisfactory method of diagnosis, prevention or treatment of the condition OR the medicine is of significant benefit to those affected by the condition.

Consult EMA!
• Timeline:

**COMP**: Committee for Orphan Medicinal Products

**SAWP**: Scientific Advice Working Party

Source: EMA website
Lessons learnt*

• Commercial impact should be expected
  – Provide a clear business plan, marketing strategy, market analysis and time-to-market estimation.
  – Involve SME/industrial partner to take the product ahead beyond the project’s end.
• Show clear advantage over existing treatment (both medically and commercially).
• Build a strong and complementary consortium, including partners with good track record and experience in clinical trials.
• Involve patient advocacy groups
• Provide a good and clear trial design, specifically statistical analysis and sample size calculation.
• The project should be focused and any deviation or additional activity (e.g. secondary trials) should be strongly justified and appropriate to the topic.

* Could be topic-specific
Lessons learnt*

• Patient safety: provide risk/benefit considerations, stopping criteria, explain how you will deal with adverse events, etc.
• Provide a realistic timeline for regulatory approvals.
• Show that you are able to produce results which will be advantageous even if outcomes of trial are negative (e.g. databases, new biomarkers of recovery)
• Show relation and continuity from FP7/other past projects when relevant.
• Shipping cells/tissue samples between centres/partners is a complicated issue – plan adequately, consider budget, logistics and regulatory issues.

* Could be topic-specific