Clinical Trials
Clinical Trials in Horizon 2020

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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
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:
  • Normally “Per patient” basis, allowing 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
- ECRIN network - http://www.ecrin.org/
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…
Squaring the circle

RIA template vs. Typical Clinical Protocol structure

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 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
  • Define sub-populations if subgroup analysis is planned
• **Statistic analysis planning and power calculation**
• **Cumulative safety information**
  • Pre-clinical data from in-vitro or in-vivo studies; data from previous clinical studies; data from (pharmaco-)vigilance systems
• **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
  • 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**
The European Medicines Agency (EMA) is the European Union agency for **the evaluation of medicinal products**.

Under the call for “New therapies for rare diseases”, applicants need to show a granted **orphan designation** and 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
Squaring the circle

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
Squaring the circle

H2020 funding vs. Clinical Trial payment structure

In H2020:
• Each beneficiary is paid once in each reporting period
• 2-4 payments/periods throughout the project
Squaring the circle

H2020 funding vs. Clinical Trial payment structure

The motivation: Pay Per Patient

\[
\text{Sample size} = \frac{\text{Anticipated Recruitment Rate}}{\text{Number of Medical Centers}}
\]

Fixed MC set

Dynamic MC set

Beneficiary

Ad-Hoc

Actual cost

Unit cost

Competitive cost

Per patient

Sub-Contracting

*Best value for money
Squaring the circle

H2020 funding vs. Clinical Trial payment structure

H2020 Unit cost ≠ Typical clinical trial per-patient payment

H2020 Unit cost = \{A\} \times \{B\}

- Reference unit: 1 hour of MD, 1 blood test, etc.
- Cost of unit in accounting year N-1 (according to documented evidence)

- Once defined and approved – no need to justify
- The N-1 problem
- Lack of flexibility: \{A\} and \{B\} cannot be modified during the project
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 Trial is welcome for:
  - CRO
  - Clinical sites
- Best value for money must be proven
- It allows to include profit

- Plan with care
Squaring the circle

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  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:

Coordinator | Development | Research Site | Research Site | Research Site
---|---|---|---|---
Consortium | Sub-contractors | Optional | Site | Site

Coordinator/Sponsor | CRO | Research Site | Research | Development
---|---|---|---|---
Consortium | Sub-contractors | Optional | Site | Site

Many people are involved

Around 20 sites

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

2,900,000 Euro
Squaring the circle

Typical and strict RIA duration vs. variable clinical trial timeframes

~8 Months

Deadline

GA signed

3-5 Years

Funded

No retroactive funding

Your Clinical Trial
Your Clinical Trial
Your Clinical Trial I
Your Clinical Trial

Your Clinical Trial II
Your Clinical Trial

Your Clinical Trial
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**

<table>
<thead>
<tr>
<th>Humans</th>
<th>Data Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Which humans are involved?</td>
<td>• Which data?</td>
</tr>
<tr>
<td>- vulnerable persons</td>
<td>- genetic data</td>
</tr>
<tr>
<td>- persons unable to give consent</td>
<td>- sensitive data (health, political or religious opinions, sexual orientation, etc.)</td>
</tr>
<tr>
<td>- Children</td>
<td></td>
</tr>
<tr>
<td>• Are some interventions on the body foreseen?</td>
<td>• Which procedure?</td>
</tr>
<tr>
<td>- invasive techniques (biopsy, EEG, fMRI)</td>
<td>- procedure for collection – how, by whom, information on rights, info and consent forms, anonymisation</td>
</tr>
<tr>
<td>- Patients? Healthy volunteers?</td>
<td>- procedure for protection of data – how it is protected, encrypted, where, for how long?</td>
</tr>
<tr>
<td>• Which are the procedures for recruitment and consent?</td>
<td>• Documents to provide</td>
</tr>
<tr>
<td>• Documents to provide</td>
<td>- data protection officer/authority authorisations</td>
</tr>
<tr>
<td>- ethics authorisations</td>
<td>- information and consent forms</td>
</tr>
<tr>
<td>- information and consent forms</td>
<td>- security measures</td>
</tr>
</tbody>
</table>
### 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:
# 2016 submitted proposals

In topics directly related to clinical trials

<table>
<thead>
<tr>
<th>Topic</th>
<th>Submitted proposals</th>
<th>Allocated budget</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC1-PM-01-2016</td>
<td>Multi omics for personalised therapies addressing diseases of the immune system</td>
<td>16</td>
</tr>
<tr>
<td>SC1-PM-06-2016</td>
<td>Vaccine development for malaria and/or neglected infectious diseases</td>
<td>42</td>
</tr>
<tr>
<td>SC1-PM-09-2016</td>
<td>New therapies for chronic diseases</td>
<td>138</td>
</tr>
<tr>
<td>SC1-PM-11-2016-2017</td>
<td>Clinical research on regenerative medicine</td>
<td>32</td>
</tr>
</tbody>
</table>
Health, demographic change and well-being

Treating And Managing Diseases

Clinical Trial-focused topics for 2017
SC1-PM-08–2017: New therapies for rare diseases

- **EC Orphan designation** should be in place by the deadline (2nd stage), and recommendations from **protocol assistance** given by EMA should be implemented in the trial design.

- Clinical trials may focus on a range of interventions from small molecule to gene or cell therapy.

- Can include novel interventions and/or repurposing of existing and known interventions.

- May also include limited elements of late stage preclinical research and/or experimental evaluation of potential risks.

- Should provide a clear patient recruitment strategy.

Deadline: 04 Oct 2016 (First stage), 11 Apr 2017 (Second stage)

Budget per topic: 60 M€, per project: 4-6 M€
European Medicines Agency - EMA

COMP timeline:

<table>
<thead>
<tr>
<th>Deadline for submission of applications</th>
<th>Start of procedure - day 1 (for validated applications)</th>
<th>COMP* meeting (see note below)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 May 2016</td>
<td>13 June 2016</td>
<td>6-8 September 2016</td>
</tr>
<tr>
<td>24 June 2016</td>
<td>18 July 2016</td>
<td>4-6 October 2016</td>
</tr>
<tr>
<td>20 July 2016</td>
<td>15 August 2016</td>
<td>3-4 November 2016</td>
</tr>
<tr>
<td>30 August 2016</td>
<td>12 September 2016</td>
<td>6-8 December 2016</td>
</tr>
</tbody>
</table>

SAWP timeline:

<table>
<thead>
<tr>
<th>Start of procedure SAWP meeting</th>
<th>Presubmission meeting</th>
<th>SAWP 1 start of procedure</th>
<th>SAWP 2 reports discussed</th>
<th>Finalisation day 40 adoption at CHMP</th>
<th>SAWP 3 if needed meeting with applicant</th>
<th>Finalisation day 70 adoption at CHMP</th>
<th>Finalisation for PASS procedures only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 – 29 Sep 16</td>
<td>08 Sep 16</td>
<td>08 Sep 16</td>
<td>23 Oct 16</td>
<td>26 – 29 Sep 16</td>
<td>24 – 27 Oct 16</td>
<td>07 – 10 Nov 16</td>
<td>09 – 12 Dec 16</td>
</tr>
<tr>
<td>28 Nov – 01 Dec 16</td>
<td>03 Oct 16</td>
<td>10 Oct 16</td>
<td>07 Nov 16</td>
<td>28 Nov – 01 Dec 16</td>
<td>09 – 12 Jan 17</td>
<td>06 – 09 Feb 17</td>
<td>06 – 09 Mar 17</td>
</tr>
</tbody>
</table>

Source: EMA website
SC1-PM-10–2017: Comparing the effectiveness of existing healthcare interventions in the adult population

• Compare the use of currently available preventative or therapeutic (pharmacological as well as non-pharmacological) healthcare interventions in adults
• Preference will be given to interventions with high public health relevance and socio-economic impact
• Contribute to improve interventions, and provide recommendations on the most effective and cost-effective approaches
• Outcomes such as quality of life, patient mortality, morbidity, costs and performance of the health systems should be assessed

Deadline: 04 Oct 2016 (First stage), 11 Apr 2017 (Second stage)
Budget per topic: 40 M€, per project: 4-6 M€
SC1-PM-11–2016-2017: Clinical research on regenerative medicine

- Regenerative medicine therapies which are ready for clinical (in-patient) research
- Any stage of clinical work (e.g., first in man, late stage trial, observational study) may be proposed though later stages are preferred
- Appropriate preliminary data should be presented according to the clinical phase proposed (e.g. preclinical evidence for phase I proposals).
- Ethical approvals (IRB) should be in place for clinical work to start.
- Proposals should justify why the therapy proposed is regenerative and how it represents a new approach compared to any existing treatment.

Deadline: to be published (full proposal)
Budget per topic (2017): 30 M€, per project: 4-6 M€
Health, demographic change and well-being

Additional relevant topics (2017)
SC1-PM-02-2017: New concepts in patient stratification

- Deliver novel concepts for disease-mechanism based patient stratification to address the needs for stratified or personalised therapeutic interventions.
- Integrate multidimensional and longitudinal data and harness the power of -omics, including pharmacogenomics, systems biomedicine approaches, network analysis and of computational modelling.
- The new concepts of stratification should be validated in pre-clinical and clinical studies taking into account sex and gender differences.
- Focus on complex diseases having high prevalence and high economic impact.

Deadline: 04 Oct 2016 (First stage), 11 Apr 2017 (Second stage)
Budget per topic: 40 M€, per project: 4-6 M€
SC1-PM-07-2017: Promoting mental health and well-being in the young

• Population-oriented primary prevention interventions to promote mental well-being of young people (up to 25) and assess them for their effectiveness

• Build on existing state-of-the art knowledge (and go beyond it) on biological, psychological and social determinants of mental well-being (societal, cultural, work life, lifestyle, epidemiological, economic and environmental perspectives).

• Research design should involve the young themselves, gathering their input through innovative approaches.

• Interventions should reflect the diversity of the different countries and regions in Europe and should take gender and health inequality aspects into account

Deadline: 04 Oct 2016 (First stage), 11 Apr 2017 (Second stage)
Budget per topic: 20 M€, per project: 4-6 M€
Food security, sustainable agriculture and forestry, marine and maritime and inland water research and the bioeconomy

Healthy and safe foods and diets for all

Additional relevant topics
SFS-39-2017: How to tackle the childhood obesity epidemic?

- Aim at innovative and efficient strategies, tools and/or programmes for promoting sustainable and healthy dietary behaviours and lifestyles.

- Focus on specific target groups in the young (e.g., during pregnancy and foetal development, in infants, toddlers, adolescents).

- Combine different disciplines (e.g. (epi)genetics, molecular biology, microbiome, gut-brain signalling, physiology, nutrition, physical activity sciences, information and communication technology, social sciences and humanities, education, environment, architectural and urban design, psychology).

- Partners from US, Australia, New Zealand and Canada are encouraged

**Deadline:** 14 Feb 2017 (First stage) 13 Sep 2017 (Second stage)

**Budget per topic:** 20 M€, **per project:** up to 10 M€
SFS-40-2017: Sweeteners and sweetness enhancers

• Focus on health, obesity and safety aspects (including combined/prolonged use, metabolic effects and gut brain signalling, neuro-behaviour, and effects on the microbiota) associated with S&Ses
• Investigate consumer perceptions and preferences giving proper considering the underlying physiological, psychological and socio-economic drivers
• Include stakeholders from the food industry, including SMEs

Deadline: 14 Feb 2017 (First stage) 13 Sep 2017 (Second stage)
Budget per topic 9M€, per project: up to 9M€
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

* In Clinical Trial focused projects
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.

* Lessons learnt*  
* Could be topic-specific
• 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