Fit for Health 2.0

Support to SMEs & Researchers in FP7 and Horizon 2020 health-oriented projects

Clinical trials management in Horizon 2020 projects

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Clinical Studies in H2020 collaborative projects

Definition

*A '**clinical study**' in the context of **Horizon 2020** means any **clinical research** involving a **substantial amount of work** related to*

- *the observation of,*
- *data collection from,*
- *or diagnostic or therapeutic intervention*

*on **multiple or individual** patients or study subjects.*

*This includes **different types of studies** (such as observational studies, interventional studies, and other) **as well as all phases** (Phase I – IV), and is not limited to clinical studies & trials in the sense of the* EU Clinical Trials Directive (2001/20/EC) and the Regulation (EU 536/2014).

→ very comprehensive understanding of clinical studies

A ‘clinical study’ in H2020 can be…

- …the **core of** a project
- …or **part of** a project
- …included in a project designed **in response to a topic** that specifically asks for a clinical study, **or not**
- …a **highly relevant issue** for many proposals to be submitted **under Societal Challenge 1**

Why clinical studies?

The implementation of clinical studies in a collaborative, transnational approach has a **clear European added value**:

- easier to reach **sufficient patient numbers** (especially in the case of rare diseases and stratified treatment groups)
- **faster recruitment rates**
- **consolidated expertise**

In addition, clinical studies are the **ultimate validation step for any innovation in clinical Health Research**, bringing innovations to markets and patients – one of the main objectives of Horizon 2020.

Characteristics of these clinical studies

- work with patients
- collect samples and/or data from patients
- special part of your project with certain characteristics that are different from rest of your project / ‚classical' collaborative project

Typical challenges

Even among ‘regular’ FP7 projects:

- ~ 50% of grants were not completed in time & had to be extended through an amendment

Clinical studies

- are known to be particularly complex
- literature: up to 85% of clinical studies in general are not completed in time
- delay often leading to cost increase

Typical challenges

BUT

declared goal under Horizon 2020 **timely completion** of projects & **quick translation** of research results into application is a

→ **project extension not generally granted**

- maximum EC contribution per project is fixed

Non-compliance with expected timelines and recruitment estimates (significantly delayed key study milestones) might lead to **reduced EU contribution** or the **termination of the grant agreement**.

Typical challenges

To help overcome these challenges, the European Commission provides clear guidance on how to optimally plan and describe your study in the proposal phase, and has adapted their financial rules in appreciation of the special requirements of clinical trials (→ “Unit Costs”).

Typical challenges

There are many parallel and competing factors/challenges when preparing for and conducting clinical studies:

- …around coordination of manufacturing activities (timely availability of study medication,…)
- ...around site involvement/initiation, patient recruitment and management (study protocol, ethics/ regulatory reviews,…)
- …around financial management
- ...around data collection and management
- …integration into rest of the H2020 project

…within fixed project time frame

Management issues

1. **Before start of study**
   - Protocol development
   - Ethical approval
2. **During study implementation:**
   - **Working with patients**
     - Patient availability / recruitment delays
     - Financial issues
   - **Data collection**
     - Case Report Forms (CRFs)
     - Data entry/integration, QC
3. **Conclusions & useful links and reference documents**

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Management issues: site initiation

Protocol development

- Only outline of protocol required in proposal… development of final protocol may take some time, esp. if initiated after start of the project as part of the work plan
- Harmonized study protocol across sites needed, to start the work

Ethical approval

- Not required for proposal submission, but indispensable for uptake of activities
- H2020: very short time to grant!

If not in place already: Designate one person in charge who will drive protocol development and ethics applications.

Note: costs for related activities can only be reimbursed if they occur during project duration.

Final protocol & ethics approval = mandatory deliverables

Mandatory deliverables for H2020 clinical trials

1. **'First study subject approvals package'**
   a. Final version of the study protocol
   b. Registration number of clinical study
   c. Regulatory and/or ethics approvals

2. **'Midterm recruitment report'**
   to be scheduled for the time point when 50% of the study population is expected to have been recruited

3. **'Report on status of posting results' in the study registry(s)**

Ethics in H2020 collaborative projects

- When preparing a proposal, it is required to complete an **Ethics Issues Table** (Part A) & to conduct an **Ethics Self-assessment** (Part B).

- **Ethics Review Procedure:** All proposals above threshold and considered for funding will undergo an **Ethics Review** carried out by independent ethics experts and/or qualified staff working in a panel. The review starts with an **Ethics Screening** and if appropriate a further in-depth analysis called **Ethics Assessment** (e.g. in case of severe intervention on humans) is conducted.

- The **Ethics Assessment**
  - might provide 'ethics recommendations'
  - will provide an 'ethics opinion' ('additional info needed', 'ethical clearance', 'conditional clearance' i.e. clearance is subject to conditions, i.e. ethics requirements)

Ethics in H2020 collaborative projects

- **Ethics Requirements:** the Ethics Assessment will provide information on the requirements the consortium will have to comply with – there are **two types of ethics requirements**, those that you need to comply with
  i) during grant preparation and
  ii) during the ongoing project

- **Ethics deliverables**: All ethics requirements *due after project* start are **automatically included in the grant agreement** in the form of deliverables. These deliverables are known as '**ethics deliverables**' and will be placed in an automatically generated work package called '**ethics requirements**'.

Ethics in H2020 collaborative projects

Selected examples of ethics requirements included for clinical trials (to be available before start of related activities):

- Detailed information must be provided on the informed consent procedures that will be implemented for the participation of humans in the context of reuse of their personal data and samples. (Copies of examples of Informed Consent Forms and Information Sheets must be included)

- Copies of ethics approvals by the competent legal local/national Ethics Boards/Bodies/administrations must be kept on file and produced upon request to the European Commission

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Management issues: working with patients

Patient availability / recruitment delays

- Estimates based on thorough feasibility analyses
- Common challenges: higher than expected drop-outs, new competing studies, changes in legislation, changes related to personnel conducting the work..
- Upcoming challenges MUST be reported quickly and fully

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Management issues: working with patients

- **Patient availability / recruitment delays**
  - Estimates based on thorough feasibility analyses
  - Common challenges: higher drop-outs than expected, new competing studies, changes in legislation, changes related to personnel conducting the work…
  - Upcoming challenges **MUST** be reported quickly and fully

- **Management**
  - must **establish a trustful and close relationship with each site**
  - must **know and optimize workflows**, and reduce admin challenges to a minimum
  - should be ready and able to react promptly
  - should ensure a **close monitoring** of recruitment numbers at all sites
  - must have **strategies in place** to compensate for lower than expected patient numbers, reaching the original targets in the original timeframe with the fixed budget

Management issues: working with patients

Financial issues

- sites may not be aware of/ experienced with the principle of reimbursement/instalments/negative cash flow
- high workload, large number of individuals involved per site, continuity must be ensured
- shifting of activities related to patient recruitment is common
- if patient numbers significantly lower than expected in one site: prepayment exceeding max. funding
- unit costs or subcontract option were created to increase flexibility

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- high workload, large number of individuals involved per site, continuity must be ensured
- shifting of activities related to patient recruitment is common
- if patient numbers significantly lower than expected in one site: prepayment exceeding max funding? **Reduce risk by opting for instalment option in CA**
- unit costs or subcontract option were created to increase flexibility
- **know the system and typical challenges to minimize risk & optimize your project**
- **provide close support to recruiting centers**

Budget

Unit Costs

Based on Commission Decision C(2016) 7553[1] Unit costs are:

- a fixed reimbursement amount
- for each study subject enrolled
- in a given centre
- calculated according to a defined methodology[2]
- based on historical costs of the beneficiary/third party in last closed accounts
- for the entire funding period of an action

MUST READ!

[1]http://ec.europa.eu/research/participants/data/ref/h2020/other/legal/unit costs/unit_costs_clinical_studies.pdf

[2]*Described in detail in Annex 1 of the Clinical Study Template „Method to determine the unit costs" (= the only valid method!)*

Budget

Unit Costs

Advantages

- Ex-ante acceptance of unit costs = No need for time sheets and detailed tracking of resources used!

  Items audited: no. of patients enrolled & correctness of historical costs listed

- Consortia more realistic estimate their budget and time management for CSs.

Disadvantage

- NOT a flexible tool, amount of unit costs per patient is fixed in the GA.

  Unit cost modification only if: protocol change & change of estimation of resourced needed; error in cost identification for year N-1

Budget - How to calculate Unit Costs?

Per clinical study subject: Estimation of the resources:

- per task on the basis of the protocol,
- the same for all beneficiaries involved (applying unit costs).

Per beneficiary/third party: Calculation of costs based on its historical costs:

- recorded in its certified or auditable profit and loss accounts,
- for last closed financial year at the time of submission of the proposal.
- costs can vary between partners

Unit Costs - the component ‘personnel costs’

3 unique and exclusive personnel categories:

- Doctors
- Other medical personnel
- Technical personnel

No other personal category / calculation base for personal costs possible

(e.g. separate categories for 'nurses‘, 'study nurses' or 'pharmacists' do not exist)

Budget

Unit Costs – practical tips to minimize risks

- **Underestimation of costs involved**

Have an **experienced clinician** together with an experienced project manager set up your unit cost system. Plan **enough time** for several rounds of circulation and of feedback to the elements involved by all sites.

- **Loss of funds due to drop-outs**

Possible to divide into steps (e.g. recruitment + intervention one, intervention two, follow-up) → **establish sequential unit costs**

- **Loss of funds after audit**

Pay utmost attention that beneficiary/third party has used the accounting data of year N-1. **No cost estimates!** Mistakes in this step of the planning process may result in significant loss of funds for the respective site.

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Management issues: data management

Data collection/CRFs

- paper and/or electronic version (PC vs mobile devices)
- 'mainly established' vs 'new system'
- changes during the project difficult/impossible

Data entry/integration, QC

- key to secure generated data and ensure their usability
- only data that are in the database can be processed → bottleneck
- option: dedicated data entry clerk

DMP: rules and procedures for data generation & data management, for clinical and other data

Management issues: data management

Data collection/CRFs

- paper and/or electronic version (PC vs mobile devices)
- 'mainly established' vs 'new system'
- changes during the project difficult/impossible
- **ensure sufficient training of personnel** who will be filling out the CRFs

Data entry/integration, QC

- key to secure generated data and ensure their usability
- only data that are in the database can be processed → bottleneck
- option: dedicated data entry clerk
- **ensure sufficient training of personnel** who will be entering the data
- **implement continuous monitoring/control mechanisms**
- **keep an eye on the time needed for completion of following tasks to determine data entry deadlines**

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Concluding remarks

Timely completing of planned work is particularly challenging in clinical studies

Tips for Minimizing Delays

1. **Start work immediately** to ensure timely site initiation
2. **Revisit site assessment regularly** – Review/obtain key operational criteria and information on administrative capacity to optimize calculations of expected patient distribution (continuous process)
3. **Adapt your project management approach** - Structures and activities need to acknowledge the inherent variability of the process and allow for quick identification of difficulties, and prompt changes/adaptations during implementation
4. **Build relationships** – the responsible project management team must create an authentic, responsive relationship with each of the sites. Site visits early on often pay off in the course of the project.

Info and support

Sources of advice and support:

- National Contact Points
- FAQs concerning the H2020 SC1 *Health, demographic change and wellbeing* http://ec.europa.eu/research/participants/portal/doc/call/h2020/sc1-hco-07-2017/1730125-faqs_v5_august2016_en.pdf
- EU IPR helpdesk: www.iprhelpdesk.eu
- ECRIN: http://www.ecrin.org/ helpful info and tools on website, and diverse trial support services to their member countries
- FFH 2.0 support (FFH 2.0 CT factsheet, FAQs on CT, etc.)

Thank you!

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