Fit for Health 2.0

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

Clinical studies in Horizon 2020

www.fitforhealth.eu

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SEVENTH FRAMEWORK PROGRAMME

Content

1. Clinical studies („clinical trials“, CT) – definition
2. Types and phases of CTs
3. Guidelines & regulations for CTs
4. Details to be known („outline“)
5. Management of CTs (in EU projects)

What are Clinical Trials?

- Clinical trial or Clinical study = Research study that involve human subjects. Each study tries to answer scientific questions to find ways to prevent and/or treat disease

- Any systematic evaluation of medicinal products or devices in human subjects whether in patients or non-patient volunteers to discover or verify the effects of and/or identify any adverse reactions to investigational products and/or to study their absorption and excretion in order to ascertain the efficacy and safety of products

Different Types of Trials

- **Observational study**

  The investigators observe the subjects and measure their outcome – 3 types

  i) cohort studies,
  ii) case control studies,
  iii) cross sectional studies

- **Interventional study**

  Research subjects given a particular medicine or other intervention. *Test experimental treatments, new combinations of drugs already on the market, or new approaches to surgery or radiation therapy*

  Compare treated subjects to those who receive no treatment or standard treatment.

Other Trials

- Prevention trials
- Screening trials
- Quality of life trials
- Orphan drug designation

  http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000034.jsp&mid=WC0b01ac058002d4eb
- Pilot Studies (feasibility studies)

  Small-scale versions of larger trials. Format same – only recruit a small number people; Useful way testing if trial design works e.g. to determine adequate number patients with adequate power – if necessary changes can be made to the design before trial starts

  Note: Often too small to say if one treatment better than the other

Phases of Studies

Clinical Trials involving new drugs are commonly classified into 4 phases – each designed to find out certain information

- Phase I - first studies in man involves small groups **healthy volunteers** or sometimes patients – to determine safety & tolerance of the new drug
- Phase II – first clinical study of new drug in **patients** conducted on small number of (hospitalised) patients, monitored closely
  - to confirm drug has therapeutic effect
  - to determine optimal dose
  - to determine correct frequency dosing

Phases of Studies cont.

- Phase III
  - compare the effects of a new treatment with standard treatment
  - Find out how well the drug works and how long the effect lasts – **efficacy**
  - Find out more about common and serious side effects or risks and about any possible longer term problems that could develop - **safety**
  - require a large number of volunteers/ patients (several hundred or thousand) to provide significant clinical and statistical power

Phases of Studies cont.

- Phase IV

= Studies conducted with a drug after it has received a Product Licence – drug marketed for particular indications. Run to find out:

- how well the drug works when it is used more widely
- the long term risks & benefits
- more about possible rare side effects

Post Marketing Surveillance (PMS) Studies

Conducted to support the marketing of a drug

Trial Design

- Controlled trials – designed to compare different treatments. Most controlled trials compare a new treatment with the standard or usual treatment (standard-of-care therapy)

  Two groups : trial group (intervention) & control group. If no standard treatment exists, patient given no treatment or placebo

- Blind trials – patient (or investigator) taking part do not know which treatment they are getting (standard treatment, new treatment or placebo) - all patients receive identical injections or tablets – blinding is to prevent bias

  Single-blind/double blind studies

Trial Design

- Randomisation

Each study subject is randomly assigned to receive the study treatment or a placebo – goal: each group has a similar mix of people of different ages, sex and state of health – treatment groups can be considered comparable and results of different treatments used in different groups can be compared

- Placebo

= An inactive substance resembling a medication given for psychological effect as a control in evaluating a medicine believed to be active. Contains harmless substance – appears same as medicine.

Placebo-controlled study – placebo compared with new drug when don't know if drug will be effective (or superior etc.)

Rules & Regulations:
How research shall be conducted & patients protected

To protect patients and to produce sound research results, treatments are carried out according to strict scientific and ethical principles.

- Declaration of Helsinki – international standard for the protection of subject's rights
- International Conference of Harmonisation Guidelines for Good Clinical Practice (ICH GCP) http://www.ich.org/products/guidelines.html
- The European Clinical Trials Directive 2001/20/EC (and Commission Directive 2005/28/EC of 8 April 2005)
- European Medicine Agency http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/landing/human_medicines_regulatory.jsp&mid= and: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000489.jsp&mid=WC0b01ac058060676f

Rules & Regulations:
How research shall be conducted & patients protected

National Legislation

Member States have transposed the requirements of the Clinical Trials directive into national laws, regulations and administrative provisions. **The approval of clinical trial applications is the responsibility of the member states.**

Find out more on national medicine regulatory authorities ("competent authorities") on http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000155.jsp&murl=menus/partners_and_networks/partners_and_networks.jsp&mid=WC0b01ac0580036d63&jsenabled=true

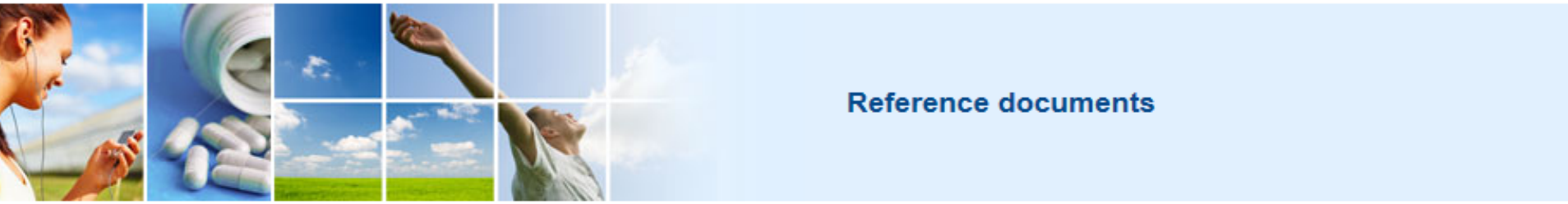
Rules & Regulations:
How research shall be conducted & patients protected

Clinical trials in Horizon 2020

The applications must consider the relevant governance issues for clinical trials such as good clinical practice… *ICH Guidelines E6 (R1) Guidelines for Good Clinical Practice:* *www.ich.org/products/guidelines.html*

…and respect of the appropriate International, European and national legislation and guidelines.

European Commission publishes guidelines in Vol10 of 'EudraLex – Rules Governing Medicinal Products in the European Union10inical Trials
http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm



Reference documents

Go back to » Reference documents » Eudralex » Vol 10: Clinical Trials

Reference documents

Archives of 'News and Updates'
Pharmaceutical Committee

Useful links

EudraLex
Community Register
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EudraLex - Volume 10 Clinical trials guidelines

Volume 10 of the publications "The rules governing medicinal products in the European Union" contains guidance documents applying to clinical trials.

General information (July 2006)

Chapter I: Application and Application Form

- Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial **(1022 KB)** (revision 3 of March 2010)
  - Annex 1 revised Pdf version **(86 KB)** Word version **(313 KB)** (revision 4 of November 2009) - EudraCT Version 8.0 uses the Revision 4 dated November 2009 of the Clinical Trials Application Form. For more information please refer to the EudraCT

Rules & Regulations:
How research shall be conducted & patients protected

Protocol

Treatment plan is described in a document called 'Protocol'

A protocol gives the reasons for doing the research and is carefully designed to safeguard the health of the participants. It should include the following information

- The background to the trial and why it should be done
- Details as to how the study will be carried out, including
  - numbers of patients needed and which patients can be included
  - Details of the procedure or treatments to be given
  - What tests the patients will have and when
  - Details about how, when and what information will be collected
  - How the results will be assessed.

Why do EU proposals including clinical studies require „extra care“?

Applicants and Beneficiaries in FP7 projects have experienced a multitude of challenges, hurdles and problems during proposal preparation and also in running projects (mainly administrative & financial), due to:

- Patient recruitment process difficult to steer/ e.g. recruitment slower than anticipated/ requires move to other study sites
- Certain research questions require high number of study sites
- Higher drop-out rates or higher costs than planned
- Many ethical aspects*– protocol harmonisations; national approvals
- Monitoring, biostatistics, regulatory, etc. require very specific expertise (not usually found in academic institutions)

See http://www.healthncpnet.eu/jahia/Jahia/pid/26 and http://cordis.europa.eu/fp7/ethics_en.html for help

Topics Societal Challenge 1 for 2015

Understanding health, ageing and disease

Topic (project size in EUR)	**Instrument**	Total budget EUR	**deadline**
PHC2: Understanding diseases: systems medicine (4-6 Mio.) *	Research & Innovation Actions	36 Mio.	14.Oct 2014 21.Ap. 2015
PHC3: Understanding common mechanisms of diseases and their relevance in co-morbidities (4-6 Mio.) *	Research & Innovation Actions	30 Mio.	14.Oct 2014 21.Ap. 2015

Effective health promotion, disease prevention, preparedness and screening

PHC4: Health promotion and disease prevention: improved inter-sector cooperation for environment and health based interventions (4-6 Mio.)	Research & Innovation Actions	18 Mio.	14.Oct 2014 21.Ap. 2015
PHC9: Vaccine development for poverty-related and neglected infectious diseases – HIV/AIDS (15-20 Mio.)	Research & Innovation Actions	21 Mio.	24.Febr. 2015

* *Additional template for clinical studies required*

Improving diagnosis

Topic (project size in EUR)	**Instrument**	Total budget EUR	**Deadline(s)**
PHC11: Development of new diagnostic tools and technologies: in vivo medical imaging technologies (4-6 Mio.) *	Research & Innovation Actions	49 Mio. *(+2 Mio.)*	14.Oct 2014 21.Ap. 2015
PHC12: Clinical validation of biomarkers and/or diagnostic medical devices	SME Instrument, 100% funding	111 Mio.	Permanently open with cut-off dates

Innovative treatments and technologies

PHC14: New therapies for rare diseases (4-6 Mio.) *	Research & Innovation Actions	62 Mio. *(+2 Mio.)*	14.Oct 2014 21.Ap. 2015
PHC15: Clinical research on regenerative medicine (4-6 Mio.) *	Research & Innovation Actions	37 Mio. *(+2 Mio.)*	24.Feb. 2015
PHC16: Tools and technologies for advanced therapies (4-6 Mio.) *	Research & Innovation Actions	36 Mio.	14.Oct 2014 21.Ap. 2015
PHC18: Establishing effectiveness of health care interventions in the paediatric population (4-6 Mio.) *	Research & Innovation Actions	28 Mio. *(+2 Mio.)*	14.Oct 2014 21.Ap. 2015

* *Additional template for clinical studies required*

Advancing active and healthy ageing

Topic (project size in EUR)	**Instrument**	Total budget EUR	**Deadline(s)**
PHC21: Advancing active and healthy ageing with ICT: Early risk detection and intervention (3-4 Mio.)	Research & Innovation Actions	20 Mio. *(-1 Mio.)*	21. Apr. 2015
PHC22: Promoting mental wellbeing: in the ageing population (4-6 Mio.) *	Research & Innovation Actions	17 Mio.	14.Oct 2014 21.Apr. 2015

Integrated, sustainable citizen-centred care

PHC24: Piloting personalised medicine in health and care systems (12-15 Mio.) *	Research & Innovation Actions	30 Mio.	14.Oct 2014 21.Apr. 2015
PHC25: Advanced ICT systems and services for Integrated Care (3-5 Mio.)	Research & Innovation Actions	20 Mio.	21.Apr. 2015
PHC27: Self-management of health and disease and patient empowerment supported by ICT (3-5 Mio.)	Pre-Commercial Procurement (PCP)	15 Mio.	21.Apr. 2015
PHC28: Self-management of health and disease and decision support systems based on predictive computer modelling used by the patient him or herself (3-5 Mio.)	Research & Innovation Actions	19,5 Mio. *(-0,5 Mio.)*	21.Apr. 2015
PHC29: Public procurement of innovative eHealth services (4-5 Mio.)	Public Procurement of Innovative Solutions (PPI)	10 Mio.	21.Apr. 2015

* *Additional template for clinical studies required*

Fit for Health 2.0

Improving Health Information, data exploitation and providing an evidence base for health policies and regulation

Topic (project size in EUR)	**Instrument**	Total budget EUR	**Deadline(s)**
PHC30: Digital representation of health data to improve disease diagnosis and treatment (3-5 Mio.)	Research & Innovation Actions	20 Mio.	21.Apr. 2015
PHC33: New approaches to improve predictive human safety testing (10-15 Mio.) *	Research & Innovation Actions	30 Mio.	24.Febr. 2015

Co-ordination activities and other actions

HCO6: Global Alliance for Chronic Diseases: Prevention and treatment of lung diseases (1-3 Mio.) *	Research & Innovation Actions	12 Mio.	24.Febr. 2015
HOA7: eHealth Sectoral inducement Prize: Food Scanner	Prize	1 Mio.	Xx 2015
HOA8: Inducement prize: Innovative test to reduce use of antibiotics in management of upper respiratory tract infection	Prize	1 Mio.	Xx 2015
Fast track to Innovation Topic	Fast Track to Innovation		Xx 2015

* *Additional template for clinical studies required*

Template 'Essential information on clinical studies'

- **Mandatory** for all clinical studies in *indicated 2015-topics: PHC-2, PHC-3, PCH-11, PHC-14, PHC-15, PHC-16, PHC-18, PHC-22, PHC-24, PHC-33, HCO-6
- Only **for full proposal** (= second stage of two stage, resp. single stage application)
- **Template** available
  - as pdf under 'call documents' on the PP and
  - as Word document in the submission system (at your topic)
- To be **uploaded as separate document** into the submission system
- To be completed for **each** clinical study, but **in one single document**

The Template for Clinical Studies

Def.: "*A 'clinical study' is defined for the purpose of this template as 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. It includes but is not limited to clinical trials in the sense of the EU Clinical Trials Directive (2001/20/EC)*"

"*Clinical studies have **a number of methodological and regulatory specificities**. Information on these issues is crucial for evaluators to assess the scientific quality of the proposal...*"

Content of Template

1.1 Identifier

Title, short title of unique identifier.

1.2 Study design and endpoints

Description of selected study design and primary and secondary objectives (endpoints/outcome measures).

1.3 Scientific advice / protocol assistance/ communication with regulatory competent authorities / ethics committees

If scientific advice / protocol assistance from a competent/regulatory authority has been requested please provide the full text answer of the authority or a comprehensive summary. If the answer is not available provide explanation of current status.

1.4 Subjects/population(s)

Definition of study population(s) by inclusion and exclusion criteria. Definition of sub-populations if subgroup analysis is intended.

1.5 Sample size

Definition and justification (power calculation) of sample size.

Content of Template

1.6 Statistical methods

Definition of statistical methods and planning of statistical analysis.

1.7 Conduct

Description of planned strategy for study management, monitoring, data management and planned schedule for study conduct (including provisions and timelines for ethics and further administrative approvals). If a study medication is required, please provide information on whether manufacturing and/or labelling of the study medication is required and which plans are in place for this.

1.8 Orphan designation

If orphan designation has been granted provide the reference of the Commission Decision. If orphan designation has been requested but not granted provide an update on the current status.

1.9 'Unit costs per patient' for clinical trials / studies / investigations

if applicable

The Template for Clinical Studies

"For proposals containing clinical studies submitted to topics **not** *listed here you may use the points listed as an orientation and provide this information in section 1.3 ('Concept and approach') or in the relevant work package in section 3.1 ('Work plan – Work packages, deliverables and milestones') of part B of the proposal.*

If required, the table provided in section 1.9 of this template on unit costs can in this case be provided in section 3.4 ('Resources to be committed') of part B of the proposal."

'Unit costs' per patient

- Unit costs (UC) eligible under Horizon 2020 (Art. 28.6, 33.1)
- Commission Decision C(2014) 1393 allows "reimbursement on the basis of unit costs for actions requiring the conduct of clinical studies under 'Societal Challenge 1: Health, Demographic Change and Wellbeing'":
  http://ec.europa.eu/research/participants/portal/doc/call/h2020/h2020-smeinst-2-2014/1605104-1602602-commission_decision_clinical_study_reimbursement_based_on_unit_costs_en.pdf
- Is ***one*** option for any beneficiary (alternative = real costs!)
- If applied, needs to be applied for **all** patients of this beneficiary

Why using unit costs for reimbursement of clinical studies?

- Costs for clinical studies: Multitude of small elements, complex, extremely difficult to track as actual costs
- Hospitals = not typical beneficiaries of EU FPs: often not equipped to track the actual costs.
- Greater attractiveness for participation
- Simplification
  - When checking at the payment stage,
  - when reporting (no CFS to be provided for those costs).
- Less risk of error.

(source: European Commission, RTD Cornelius Schmaltz)

Unit costs per patient - conditions I

- Alternative to the use of actual costs, on **voluntary basis**.
- Resources and costs will be **evaluated with the proposal**.
- Unit costs per patient fixed **for the entire duration** of the project.
- Costs of clinical studies = **amount per unit set out in Annex 2** multiplied by the number of actual units (patients or subjects).
- For costs not included in the unit cost, reimbursement based on actual cost.
- Verification and **audit ex-post** only:
  - number of patients declared = number of patients actually participating in the study
  - beneficiary has used the accounting data of year N-1.

Unit costs per patient - conditions II

- Per clinical study: Estimation of the resources
  - per task on the basis of the protocol,
  - the same for all beneficiaries involved.

- Per beneficiary: 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.

Categories of eligible costs covered by the unit cost

1) **Direct costs of clinical studies**:

- Personnel (doctors and other medical and technical personnel)
- Consumables
- Medical equipment *(depreciation and costs of service contracts necessary for their functioning)*
- Other specific service contracts necessary for the clinical study
- *

2) **Indirect costs of the clinical study** (25% of direct costs)

* Travel and subsistence costs of patients are not included *(will be reimbursed on the basis of eligible costs actually incurred under the cost category "other direct costs")*

Table X.9: Unit cost declaration for [identifier]

Task, Direct cost categories	Resource per patient	Historical Costs Benef.[a] 1 (short name)	Historical Costs Benef.[a] 2 (short name)
Task No. 1 Blood sample			
(a) Personnel costs: - Doctors			
- Other Medical Personnel	Phlebotomy (nurse), 10 minutes	8 EUR[b]	80 EUR[b]
- Technical Personnel	Sample Processing (lab technician), 15 minutes	9 EUR[b]	100 EUR[b]
(b) Costs of consumables:	Syringe		
	Cannula		
	Blood container		
(c) Costs of the medical equipment:	Use of -80° deep freezer, 60 days		
….	Use of centrifuge, 15 minutes		
(d) Services			
Task No. X …			
…			
Total amount:			

Management: How to involve study sites?

Study site	advantage	disadvantage
Partner (beneficiary)	Option #1 of EC Clear rules, Overhead visibility	Large consortium Maybe less experienced Partners Low flexibility (e.g. recruitement)
subcontractot	Small consortium High flexibility Easy administration	Not for core tasks Procurement rules to be applied No overhead
in-kind contributions provided by third parties against payment	Small consortium Overhead possible	Low flexibility High reporting load (as if partner) No profit no unit costs per patient
affiliated entities and third parties with a legal link to a beneficiary (Artikel 14 Model Grant Agreement)	Small consortium Overhead goes to Third Party	Definition of „legal link“ leaves room for Interpretation, e.g., joint accountability is good indicator

Subcontracts to CROs

Rule of thumb: 'core task':

- If CT is **main (core) activity of project**:
  → CT should not be subcontracted in total, but certain parts may (GMP Production, Auditing, Monitoring etc.), as long as design, planning, overview and intellectual efforts lie clearly with the beneficiaries (independent of total budget)

- If CT is **only minor part of the project**, e.g. project is mainly pre-clinical research:
  → CT can be subcontracted entirely

Summary:
Where to place which info?

- Details on consortium
  → Administrative Form and chapters 3 & 4 (of Part B)
- Lay-down of costs
  → Administrative Form, chapter 3.4 (of Part B) and **Template for clinical studies**
- Description of study (outline)
  → Chapter 1 and 3 (of Part B), and in **Template**
- Description of ethical and regulatory aspects
  → Administrative Form and chapter 5 (of Part B)

Note: „Template“ means Template for essential information to be provided for proposals including clinical trials / studies / investigations
Use Template only for full proposal submission

Thank you!

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