Fit for Health 2.0

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

Clinical studies in Horizon 2020

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SEVENTH FRAMEWORK PROGRAMME

Content

1. Definition, Types and Phases
2. Rules & Regulations
3. Clinical Trials in Horizon 2020

Content

1. **Definition, Types and Phases**
2. Rules & Regulations
3. Clinical Trials in Horizon 2020

What is a Clinical Trial?

- Research study involving human subjects
  - To answer specific questions about biomedical or behavioural interventions
  - To prevent or treat disease

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

Types

- Observational study
  - Investigator observes the subjects and measures outcome
  - Investigator does not actively manage the study
    - cohort studies
    - case control studies
    - cross sectional studies
- Interventional study
  - Investigator administers a particular medicine or other intervention to research subjects
  - Investigator compares treated subjects to untreated or standard treated subjects

Types

- Prevention trials
- Screening trials
- Quality of life trials
- Diagnostic trials
- Trials with Orphan Drugs
- Pilot Studies (feasibility studies)

Phases

- Phase I
  - First in human study involving small groups of healthy volunteers (20-80) or sometimes patients
  - to determine safety and tolerance of the new drug

- Phase II
  - first clinical study of new drug in patients involving larger group of patients (100-300)
  - to confirm therapeutic effect of the drug (proof of concept) IIa
  - To further evaluate safety
  - to determine optimal dose (IIb)

Phases

- Phase III
  - Compare effects of a new treatment to standard treatment - **effectiveness**
  - Determine how well the drug works and how long the effect lasts – **efficacy**
  - Monitor side effects - **safety**
  - Mostly, randomized controlled multicenter trials on large group of volunteers/ patients (300-10,000) to provide significant clinical and statistical validity

Phases

- Phase IV
  - Determine the long term risks & benefits
  - Determine rare or long-term side effects
  - Conducted to support the marketing of a drug
  - Post-marketing Surveillance (PMS) Studies – watching drug use in public after having received a Product License for particular indications
  - May be required by regulatory authorities

Trial Design

- Controlled Trials
  - designed to compare different treatments including control group
  - Experimental treatment compared to no treatment (placebo-controlled study) or standard treatment (positive-control study)
- Randomized Controlled Trials (RCT)
  - Each study subject is randomly assigned to receive the study treatment or a placebo
  - Comparable group regarding mix of people of different ages, sex and state of health - results in different groups can be compared

Trial Design

- Blind trials
  - subjects involved in study do not know which treatment they receive (standard treatment, new treatment or placebo)
  - all patients receive identical injections or pills
  - to prevent bias
- Double-Blind trials
  - Investigators also do not know which treatment a subject receives

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1. Definition, Types and Phases
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Rules & Regulations: execution of research & protection of patients

- Declaration of Helsinki – international standard for the protection of subject's rights
- International Conference of Harmonization Guidelines for Good Clinical Practice (ICH GCP)
  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf
- The European Clinical Trials Directive 2001/20/EC
  (and Commission Directive 2005/28/EC of 8 April 2005)
- European Medicine Agency:
  - *Human medicines: regulatory information*
    http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/landing/human_medicines_regulatory.jsp&mid
  - *Clinical Trials in human medicines*
    http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000489.jsp&mid=WC0b01ac058060676f

Rules & Regulations: execution of research & protection of patients

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.**

National Medicine Regulatory Authorities ("competent authorities"): *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: execution of research & protection of patients

Clinical trials in Horizon 2020

The proposal must

- consider the relevant governance issues for clinical trials such as good clinical practice
- respect the appropriate International, European and National legislations and guidelines

ICH Guidelines E6 (R1) Guidelines for Good Clinical Practice:
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

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

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EU proposals including clinical studies - specifics

Challenges, obstacles and problems during proposal preparation or during running project

- Difficulties in controlling Patient recruitment process (e.g. delay in recruitment; requirement to shift to other study sites)
- Necessity of high number of study sites for certain research questions
- Unforeseen increase in drop-out rates or costs
- Different ethical aspects (protocol harmonization; national approvals; etc)
- *See http://www.healthncpnet.eu/jahia/Jahia/pid/26 for help*
- Missing specific expertise in monitoring, biostatistics, regulations, etc.

2015 Topics - Societal Challenge 1

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

***** *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
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 pediatric population (4-6 Mio.) *	Research & Innovation Actions	28 Mio. (+2 Mio.)	14.Oct 2014 21.Ap. 2015

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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-centered care

PHC24: Piloting personalized 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***

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

Co-ordination activities and other actions

HOA7: eHealth Sectoral inducement Prize: Food Scanner	Prize	1 Mio.	4th quarter 2015
HOA8: Inducement prize: Innovative test to reduce use of antibiotics in management of upper respiratory tract infection	Prize	1 Mio.	2nd / 3rd quarter 2016
Fast track to Innovation Topic	Fast Track to Innovation	100 Mio.	29.4.2015 1.9.2015 1.12.2015

* ***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
- Only **for full proposal** (= second stage of two stage application or single stage application)
- **Template** available in Submission Service (Participant Portal)
  - After selection of topic under topic conditions & documents: PDF for information
  - After logging on: Word doc to be filled in and submitted
- To be **uploaded as separate document** in submission system
- To be completed for **each** clinical study, but **as one single document**

Unit costs per patient

- Unit costs (UC) eligible under Horizon 2020 (Art. 28.6, 33.1)

  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
- Option for any beneficiary (alternative = actual costs!) but ***NOT*** for subcontractors
- When using unit costs: needs to be applied for **all** patients of this beneficiary

Unit costs per patient

- Alternative to the use of actual costs, on **voluntary basis**
- Unit costs per patient **set for the entire duration** of the project
- Resources and costs will be **evaluated with the proposal**
- For costs not included in unit costs: reimbursement based on actual costs
- **ex-post audits** to verify:
  - 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

- Per clinical study:
  - Estimation of the resources per patient (person-hours, consumables)
  - the same for all beneficiaries involved

- Per beneficiary:
  - Calculation of costs based on historical costs
  - Based on actual costs recorded in certified or auditable profit and loss accounts of last closed financial year (before proposal submission) of beneficiary

Unit costs per patient

Advantages

- Costs for clinical studies: Multitude of small elements, complex, extremely difficult to account for actual costs
- Hospitals = not typical beneficiaries of EU Projects: often not equipped to account for actual costs
- Greater attractiveness for participation
- Simplified reporting: no time sheets, no detailed documentation for each patient and no certificate on the financial statements (CSF) necessary
- Minimized risk of error

Disadvantages

- Based on costs of profit and loss accounts of last closed financial year
  ➔ no adjustment possible in case of increasing wages or prices

Unit costs per patient: Eligible Costs

Direct costs of clinical studies*:

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

Indirect costs of the clinical study

- 25% of direct costs (sum of unit costs components under a) – c) (see above)

* *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 included as:	advantage	disadvantage
Partner (Beneficiary)	Preferred Option for EC Clear rules, Overhead, Visiblity	Large consortium Chance of unexperienced Partners Unflexible (e.g. recruitement)
Subcontractor	Small consortium High flexibility Administration simple Profit possible	Not applicable for core tasks Procurement rules to be applied No overhead
In-kind contributions provided by third parties against payment	Small consortium	Unflexible High reporting load (same as for partners) No profit possible no unit costs per patient possible No indirect costs
Affiliated entities and third parties with a legal link to a beneficiary (Art. 14 Model Grant Agreement)	Small consortium Third Party receives overhead	Definition of „legal link“ leaves room for Interpretation, e.g., joint accountability is good indicator ???

Subcontracting to CROs

- If CT is **main activity / core task of project**:
  - ➔ Subcontracting of complete CT not recommended
  - ➔ Subcontracting of particular components possible (GMP Production, Audit, Monitoring etc.) ***WHILE*** beneficiaries are in charge of **major tasks**, e.g. design, planning, overview and intellectual efforts (independent of budget)

- If CT is **only minor part of the project**:
  - ➔ Subcontracting of entire CT possible (e.g. if major part of project is preclinical research)

Thank you!

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