Clinical Studies in Horizon 2020 - EC perspective

International Programmes for research and innovation fundinng: opportunities for health, translational and clinical research
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HORIZON 2020

European Commission

Applicability/Definition

1 A 'clinical study' … 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. It includes but is not limited to clinical studies and clinical trials in the sense of the EU Clinical Trials Directive (2001/20/EC) and the Regulation (EU 536/2014).

- Broad, inclusive definition!

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EU-funded clinical studies - Why?

- Bringing innovations to patients and markets
- Providing evidence to impact clinical practice and improve patient care
- Critical mass (e.g. rare diseases, stratified approaches)
- Maximise recruitment through EU or international collaboration
- Increase robustness of data
- Multidisciplinary expertise

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EU-funded clinical studies - What?

Scope, methodology, nature of the intervention, disease and target group

- Adults
- Children
- Elderly
- Gender

- Phase I
- Phase II
- Phase III
- Observational studies

- Regenerative therapies
- Rare diseases
- Non-communicable diseases
- Infectious diseases
- Quality of life interventions
- Palliative care

- Off-patent trials
- Repurposing trials
- Paediatric trials
- Drug, surgery, radiotherapy, QoL trials
- Medical devices and companion diagnostics trials
- Comparative effectiveness trials

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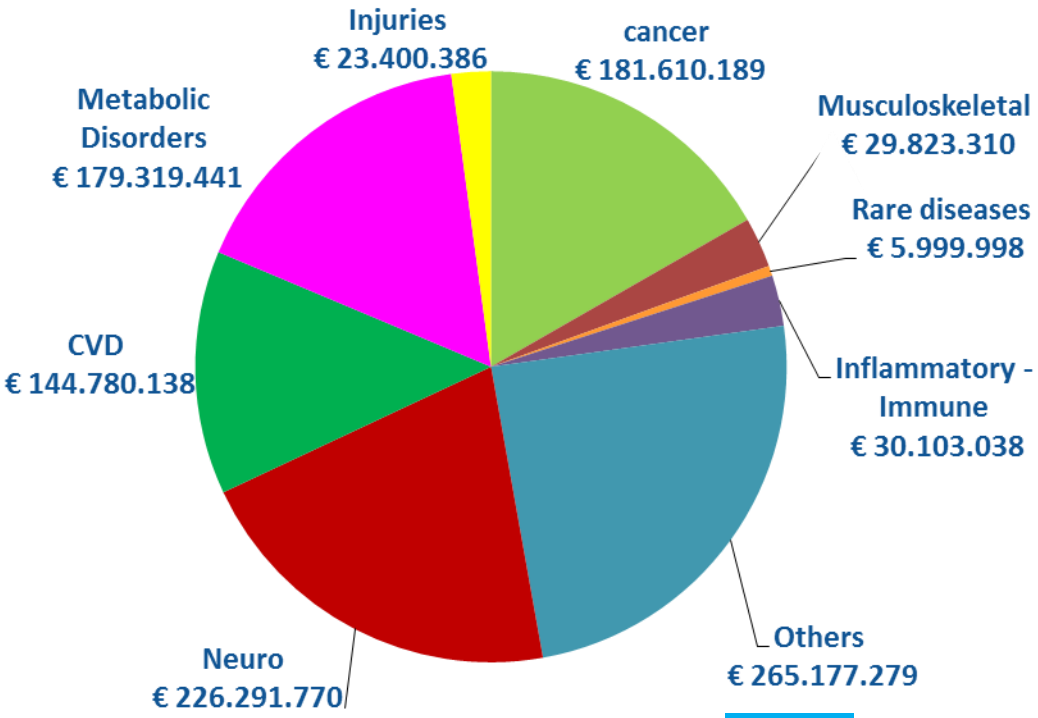
SEVENTH FRAMEWORK PROGRAMME

Clinical studies - What?

> 340,000 patients recruited
165 Projects, 286 CTs , € 1.1 billion



Phase I : 16%
Phase I/II : 23 %
Phase II : 21%
Phase II/III : 5 %
Phase III : 6 %
Phase IV : 1 %

Horizon 2020: around 75% of SC1 projects include clinical studies!

Research and Innovation

Agenda

I. Horizon 2020 application form and reimbursement issues
   - Template 'Essential information about clinical studies’
   - (Unit) costs, subcontracting and status of recruitment sites
   - Mandatory deliverables

II. Do's and don'ts – key issues for evaluation and implementation

III. Additional support and funding opportunities

Template[1]

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Essential information about clinical studies

Purpose/Applicability

- providing structured information to experts for evaluation
- giving applicants the chance to provide detailed information about clinical studies **without page limitations**
- providing necessary information to request 'unit costs'
- mandatory for certain single-stage and second-stage topics (listed in the template itself), if a clinical study is included
  - But: no eligibility criterion, no disadvantage when information provided in other part of proposal
  - Rather: more and more appreciated (applicants, evaluators) as an opportunity for structured information

[1] http://ec.europa.eu/research/participants/data/ref/h2020/other/legal/templ/h2020_tmpl-clinical-studies_2018-2020_en.pdf

Template

Essential information about clinical studies

1 Clinical study No. 1

1.1 Identifier

1.2.1 Study design

1.2.2 Primary and secondary endpoint(s)

1.2.3 Relevant guidance documents

1.3 Regulatory status and activities

1.3.1 Regulatory/ethics status

1.3.2 Scientific advice/protocol assistance

1.3.2 Qualification advice

1.4 Subjects/populations

1.5 Statistical analysis plan(ning) and power calculation

1.6 Cumulative safety and efficacy information

1.6.1 Cumulative safety information

1.6.2 Cumulative efficacy information

1.7 Conduct

1.7.1 Schedule for study conduct including timelines for key study milestones

1.7.2 Description of recruitment strategy

1.7.3 Description and assignment of intervention

1.7.4 Study management, study monitoring, data and sample management

1.7.5 Sponsor, coordinating centre(s) and committees

1.7.6 Study medication

1.7.7 Clinical centres

1.8 Orphan designation

1.9 ‚Unit costs per patient'

2 Clinical Study No. 2

etc.

Scope

- Ethical considerations have to be addressed in the respective separate section.
- Risks and contingency plans have to be addressed in the respective section of the proposal (part B.3.2 and table 3.2.a) … If contingency plans are not outlined in the proposal (and the grant agreement), your grant agreement might be terminated and/or the EU contribution significantly reduced if a study cannot proceed as planned.

"Extensions of project duration can generally not be granted in H2020. Significantly delayed key study milestones (e.g. 'first patient/first visit') might lead to the termination of the grant agreement."

Unit Costs
Conditions

- requested in the proposal (and evaluated)
- fixed methodology[1] (not beneficiary's own methodology!)
- resources (e.g. personnel time – identical for all beneficiaries) multiplied with costs (identified in the last closed accounts of each beneficiary)
- fixed for the entire duration of the project. No adjustments for inflation or wage increases during the time course of an action.
- can be combined with direct costs
- no need for time sheets and detailed actual costs for each patients
- only items that are audited: Number of patients enrolled and correctness of historical costs listed.
- more detailed explanations and calculation table in the template[2]
- *Possibly simpler alternative in some cases: internally invoiced costs (Art. 6.2.D5 MGA)*

[1] Commission Decision C(2016) 7553 final (http://ec.europa.eu/research/participants/data/ref/h2020/other/legal/unit_costs/unit%20costs_clinical_studies.pdf)
[2] http://ec.europa.eu/research/participants/data/ref/h2020/other/legal/templ/h2020_tmpl-clinical-studies_2018-2020_en.pdf

Status of
Recruitment sites

Clinical centres whose contribution is limited to subject recruitment or treatment may have status of:

- Full beneficiary –> always preferred!

But: if obstacles for centres to become beneficiary (or linked third party), two other options remain:

- Use of in-kind contributions provided by third parties against payment (Art. 11 MGA) – patient data are considered as in-kind contribution.
- Subcontractor (Art. 13 MGA)
- Please note: It is not possible to reimburse recruitment sites based on Article 10 MGA (Purchase of goods, works or services)

Status of
Recruitment sites

Use of in-kind contributions provided by third parties against payment (Art. 11 MGA)

- Third parties must be identified in DoA
- No profit, reimbursement of unit / actual costs (!)
- Requires prior agreement with beneficiary – prior to start of work, not necessarily prior to signature of GA
- Agreement might be 'ad-hoc'/specific to project
- 25% indirect costs can be claimed (by the 3rd party itself, not by the beneficiary!) when actual or unit costs are used

Status of
Recruitment sites

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Subcontractor (Art. 13, MGA)

- **Only task (!)** must be identified in DoA
- agreed 'price per patient/subject', profit possible
- best price/quality ratio, transparency and equal treatment
- public bodies: internal rules and applicable legislation related to public procurement
- No indirect costs for beneficiary! But in case of 100% reimbursement rate of direct costs, no more "shortfall" for linked beneficiary

Contract Research Organisations (CROs)

- Commercial CROs usually work 'for profit' and may not intend to join a consortium as beneficiary → In those cases the commission will consider accepting subcontracting
- Please note: It is not possible to reimburse CROs based on Article 10 MGA (Purchase of goods, works or services)
- **Academic CROs** exist (e.g. ECRIN network) – might be willing to become beneficiary!
- Only **limited part of the action** can be sub-contracted (Art. 13 MGA)

Subcontracting

Rule of thumb for subcontracting:

- If clinical study is the main activity of the project:
  - ➢ Core study expertise cannot be subcontracted, but certain parts (GMP manufacturing, monitoring etc.) might be subcontracted as long as general regulatory expertise is available and the study design, high-level study management and oversight remain as tasks within the consortium (budget share: not essential criterion!)
- If clinical study is just a small part of the project, i.e. most of the project is preclinical activity:
  - ➢ Study might be subcontracted in its entirety

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Mandatory deliverables

1) **'First study subject approvals package'**, for each included CS (prior to enrolment of first study subject):
   a. Final version of study protocol as submitted to regulators / ethics committee(s)(no need to change deliverable if later amendments)
   b. Registration number of clinical study in a WHO- or ICMJE- approved registry
      (Please note: Result posting for the study must be possible)
   c. Approvals (ethics committees and national competent authority if applicable) required for invitation / enrolment of **first** subject in at least one clinical centre

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Mandatory deliverables

2) **'Midterm recruitment report'**, for each included CS: Deliverable to be scheduled for the time point when 50% of the study population is expected to have been recruited. The report shall include an overview of recruited subjects by study site, potential recruiting problems and, if applicable, a detailed description of implemented and planned measures to compensate delays in the study subject recruitment.

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Mandatory deliverables

3) Report on status of posting results in the study registry(s), for <u>each</u> included CS:
Report on the status of the result posting including timelines when final posting of results is scheduled after end of funding period.

„Please note the obligation to post results in the registry within 12 months of primary study completion in line with the WHO ‚Joint Statement on public disclosure of results from clinical trials"

Do's and Don'ts

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Based on most commonly observed problems of H2020 studies:

Detailed and **realistic** planning impresses evaluators and helps implementation; overoptimistic planning and lack of evidence → **decreased scores** in evaluation/failure of study.

- „Regulatory intelligence" and clinical trial project management expertise - **if not available in-house, consider in-sourcing**!
  - → does not come with regular medical training! H2020 (or any other…) study cannot be the training ground to learn/acquire that expertise!
- Expertise and planning for document requirements: Study protocol, IPMD, statistical analysis plan, data input, data warehousing…
- Study drug supply (GMP production, but also placebos, labelling etc.): Consider all pitfalls, plan for contingencies, early contracting, close monitoring!

Do's and Don'ts

European Commission

- If FIM / FIH (First in HuMan): descriptions of the *'FIM / FIH package'* (safety pharmacology / toxicology) has to be exhaustive, allowing experts to evaluate the risk of the project to (not) achieve the required ethics and regulatory approvals
- Patient recruitment:
  - **Realistic** calculation based on documented numbers (patients presenting/being followed per centre, competing e.g. industry-financed studies (!), patients' willingness to participate), consider feasibility study!
  - Early contracting with recruitment sites (time-consuming), consider different models (see „status of recruitment sites"), if subcontracting → plan tender!
  - Contingency plans, close monitoring!

Do's and Don'ts

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- Realistic time planning!
  - Grant period is fixed, extensions can generally **not** be granted in H2020. (Request appropriate duration!)
  - Significantly delayed key study milestones (e.g. 'first patient/first visit') might lead to the termination of the grant agreement
- (Registration and) reporting of study results is **mandatory** within 12 months of study completion!
  - EU trials tracker (https://eu.trialstracker.net) names and shames…
- Impact!
  - Are regulatory pathways considered? Are the data fit to support a marketing authorisation/label change?
  - Is the MAH/manufacturer on board?

Additional support

European Commission

„STARS"

The STARS project: Strengthening training of academia in regulatory sciences & supporting regulatory scientific advice

*The STARS proposal was selected under the **SC1-HCO-05-2018 topic**: Strengthening regulatory sciences & supporting regulatory scientific advice*

designed to strengthen regulatory knowledge among academic clinical researchers to ensure that innovations reach the patients in a timely and efficient manner.

STARS
STRENGTHENING REGULATORY SCIENCE

- **Budget:** ~EUR 2M
- **Duration:** 01/01/2019 - 31/12/2021 (36 months)
- **Type of action:** coordination and support action (CSA)
- **Co-ordinator:** BfArM (Germany) - Prof. Dr. med. Julia C. Stingl
- **Portuguese participant:** INFARMED - Autoridade Nacional do Medicamento e Produtos de Saude IP

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Additional support

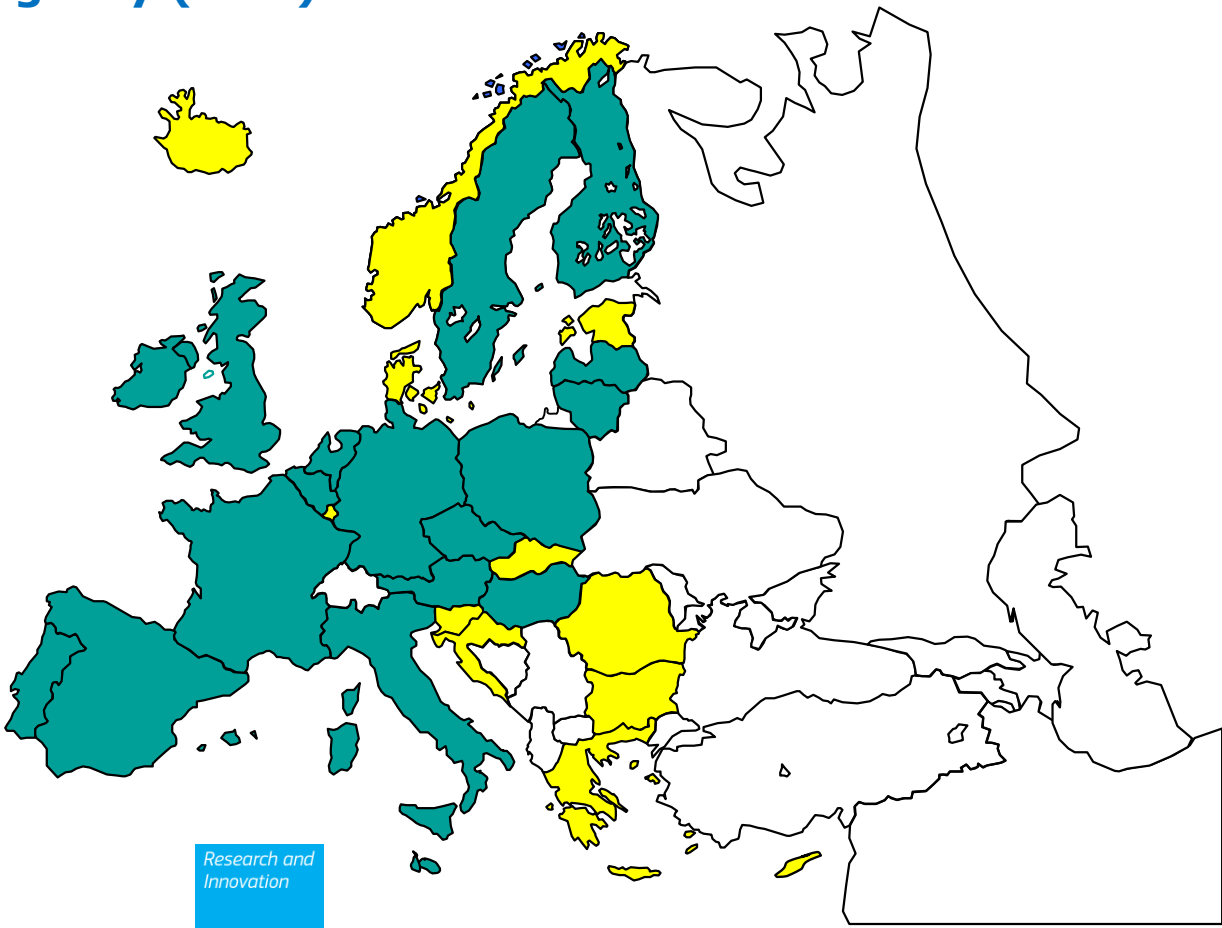
„STARS"

European Commission

STARS
STRENGTHENING REGULATORY SCIENCE

Consortium partners

National Competent Authorities (NCAs) of 18 EU Member States & the European Medicines Agency (EMA)



Research and Innovation

Additional support

„STARS"

Aims/objectives

Overall aims:

- to improve the direct regulatory impact of results obtained in medical research.
- to reach academic researchers very early in the planning of relevant grant applications.
- to strengthen regulatory knowledge in general by reaching clinical scientists during professional training and qualification

Objectives:

- To deliver consensual recommendations ensuring sustainable support of academic research.
- To propose additional support mechanisms based on a comprehensive analysis of needs.
- To complement, coordinate and harmonise regulatory efforts among Member States and at European level to support academic health research for the benefit of patients.

Additional support

„STARS"

Expected outcomes:

- ✓ **Comprehensive inventory of existing support activities for regulatory Scientific Advice and Protocol Assistance in Europe**
- ✓ **Common strategy for the sustainable implementation of the STARS objectives agreed between all STARS partners / countries**
- ✓ **Core & Comprehensive Curriculum development to strengthen regulatory knowledge of clinical scientists during professional training**
- ✓ **Pilots: (I): transfer of best-practice examples to Member State(s); (II) addressing gaps; (III) implementation of a training curriculum for academia**
- ✓ **STARS recommendations for innovative solutions on a national, European and global level**

Impact

Improving regulatory knowledge & success of academic medical research

Additional support

EMA

Specific website with advice related to H2020 projects[1]

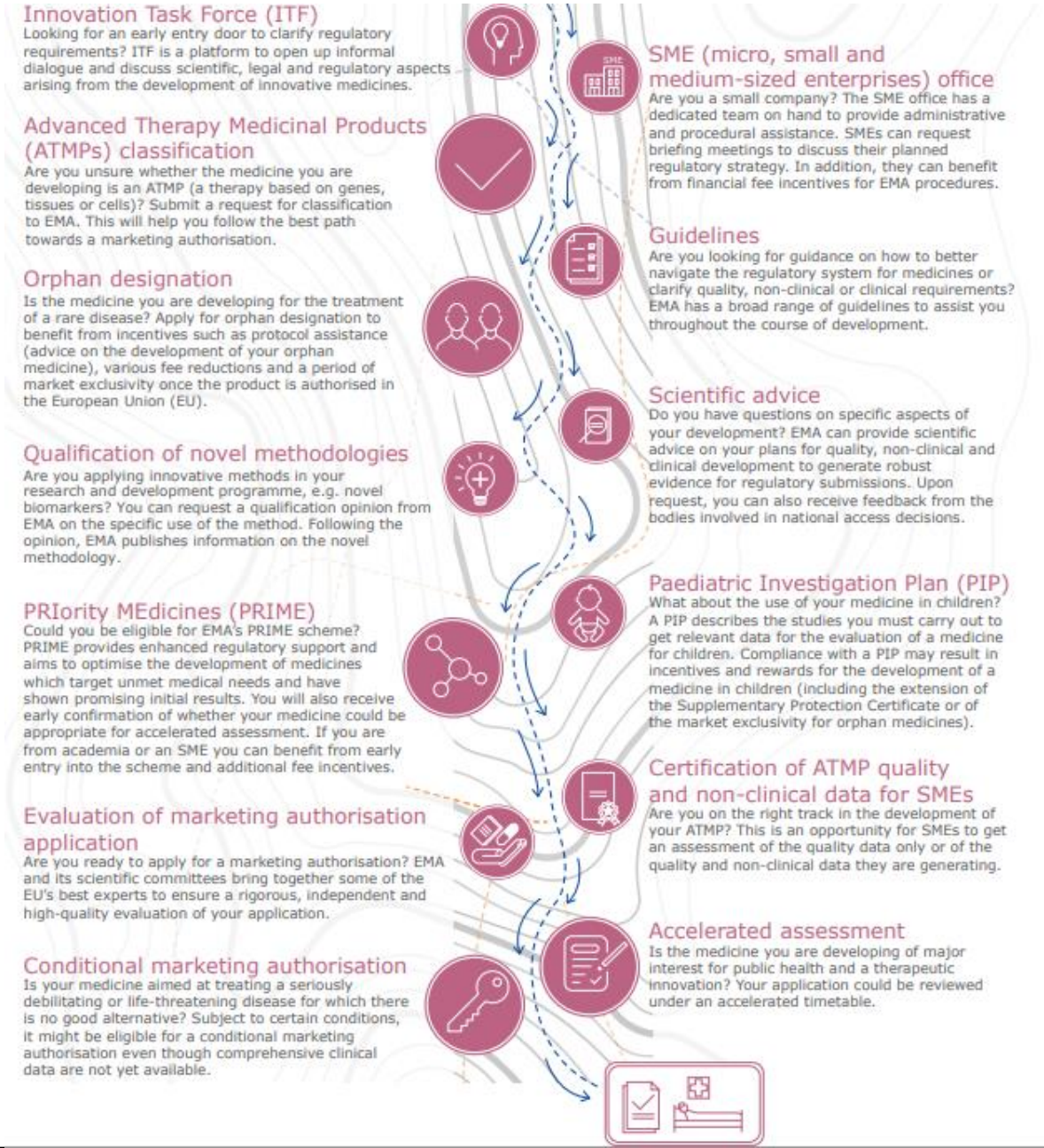
Framework for collaboration of EMA with academia (2017)[2]:

- raising awareness on the support the Agency can offer
- seeking to better understand academics' and researchers support needs
- providing education and training for these stakeholders[3]
  - training resources: videos, presentations
  - workshops and scientific events

[1] https://www.ema.europa.eu/en/partners-networks/academia/horizon-2020-research-funding
[2] https://www.ema.europa.eu/en/academia
[3] https://www.ema.europa.eu/en/partners-networks/academia/resources-academia

EMA supporting medicines developers

EUROPEAN MEDICINES AGENCY



What does the EMA SME Office do?

- *Assignment of SME status :* Enterprises have to apply for SME status before requesting financial or administrative assistance from the EMA

- *Regulatory Assistance :* direct assistance by phone, email, teleconference or through briefing meetings on regulatory aspects of the pharmaceutical legislation

- *Fee Incentives for EMA procedures :* fee exemptions and reductions for pre- and post-authorisation regulatory procedures, including scientific advice, inspections and pharmacovigilance

Procedure	Fee incentives
Scientific advice	90% fee reduction for non-orphan products
	100% fee reduction for designated orphan products
	100% fee reduction for products granted eligibility to PRIME
	90% fee reduction for veterinary medicinal products

What does the EMA SME Office do?

EUROPEAN MEDICINES AGENCY

- *Training and Awareness :* the SME office engages with SMEs and stakeholders at conferences, congresses and roundtable events. SME outreach activities include info days (regulatory training course tailored for SMEs), newsletters and targeted communications to increase the regulatory knowledge base of SMEs.

For more information : https://www.ema.europa.eu/en/human-regulatory/overview/supporting-smes

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Funding Opportunities

European Commission

SC1

- Horizon 2020 Societal Challenge 1 (‚Health, Demographic Change and Wellbeing‘) - WP 2020 (highest yearly budget so far!)
- Indicative topics with opportunities for clinical trials: e.g.
  - SC1-BHC-08-2020 : New therapies for Non Communicable Diseases
  - SC1-BHC-24-2020 : Healthcare interventions for the management of the elderly multimorbid patient
- Significantly updated work programme 2020:
- **pre-publication early June**, official adoption: end of June
- indicative deadlines:
  - 1st stage: September/October 2019,
  - 2nd stage: April 2020

Research and Innovation

Funding Opportunities

EIC

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European Innovation Council pilot – funding opportunities for innovators

Instrument →	SME-Instrument		FTI	FET-Open	EIC Horizon prizes
	Phase 1	Phase 2			
For whom	One or more eligible[1] SMEs		From 3 to 5 eligible[1] entities (mostly industrial[2])	At least 3 entities[3]	One or more entities (with restrictions[1] for some of the prizes)
Focus	Exploring the feasibility of a business idea (~ 6 months)	Breakthrough innovation & international growth (12-24 months)	Close-to-market innovation	Radically new technologies	6 different topics (major societal issues)
Maximum funding[4]	50,000 €	2.5 M€	3 M€	3 M€ (RIAs) 0.5 M€ (CSAs)	Varies for each prize
Total budget 2018-20	164 M€	1,425 M€	300 M€	647 M€ (RIAs) 10 M€ (CSAs)	40 M€

(1) Applicants must be established in an EU Member State or in a country associated to Horizon 2020

(2) This industry involvement implies: (a) either the allocation of at least 60% of the budget to industry participants in the consortium, or (b) the presence of a minimum number of two industry participants in a consortium of three or four partners, or of three industry participants in a consortium of five partners

(3) A FET-Open consortium must always include at least 3 participants from 3 different EU Member States or Associated Countries. In addition to these three partners, any legal entity from anywhere in the world can also be included in the consortium.

(4) Per project – with possible exceptions

Eligibility

eurostars™

EUREKA Σ!
innovation across borders

Project leader is an **R&D-performing SME** from a Eurostars country

At least 2 Participants

- Autonomous entities
- Legal entities

from at least 2 Eurostars countries

SMEs are in the **driving seat**

International balance

Project duration is max. **3 years**

Market introduction within **2 years**

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Thank you

www.ec.europa.eu/research/health

www.ec.europa.eu/research/horizon2020

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