

## Guidance on proposals with clinical trials

The purpose of this document is to provide applicants with additional guidance for the preparation of proposals that include clinical trials, and thus to provide proposal evaluators with the information needed to judge them properly. This structured approach should facilitate the negotiation, implementation and follow-up of successful projects.

Clinical trial proposals submitted in response to a call for proposals are subject to the same formal and legal requirements (including e.g. the mandatory information in part A and the structure and page limitations of part B of the proposal) as any other proposal. This also applies to the electronic submission format. For information on these issues, please consult the other documents contained or referred to in the "information package" on the call website, which take precedence over this guidance.

**Given that trials vary in methodology and design, the following should be used according to the particular study type proposed and only those issues pertinent to the trial(s) in question need to be addressed.** For example, a first-in-human trial of a new therapy or a device will require different considerations and a different selection of issues mentioned below than a comparative effectiveness trial of two known drugs used within their approved indication. Proposals where the clinical trial starts only later in the project, after preliminary work has been carried out, should address the issues as far as is realistic; however, in addition, they should set out the milestones that need to be achieved and describe the decision points that are necessary for the clinical trial to go ahead.

### 1. Minimum information to be provided in stage-1 proposals:

The following issues should be considered for each trial envisaged and addressed – if applicable – in part B of the stage 1 proposal **within the given page limitation**:

- background evidence and need for the trial (sections 1.1, 1.2 and 2.1):
  - scientific rationale and primary hypothesis of the trial
  - epidemiology of the underlying disease/disorder
  - magnitude of expected benefits over currently available therapeutic options
  - preclinical and/or preliminary clinical evidence; systematic review evidence
- description and justification of trial design and methodology (Section 1.3)
  - study type<sup>1</sup>: classification by objective (e.g. human pharmacology, therapeutic exploratory, therapeutic confirmatory, therapeutic use), by phase (I-IV), by methodology: randomised/non-randomised, type of masking (none, single, double, observer blind), type of controls (active, placebo), parallel group/cross-over, prognostic, diagnostic etc.
  - proposed setting: number, location and type of centres
  - precise description of intervention(s): experimental, control, duration of intervention and duration of follow-up
  - key inclusion and exclusion criteria
  - outcome measures/endpoints: primary/secondary, efficacy/safety etc.
  - bias protection: feasibility of randomisation, allocation methods, feasibility of blinding etc.

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<sup>1</sup> cf. European Medicines Agency's (EMA) 1998 note on ICH topic E 6: <http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf>

- statistical justification of proposed sample size/power calculations: number of patients to be assessed for eligibility, to be allocated to trial, to be analysed etc. (including subgroups if applicable)
- feasibility of recruitment: provide the evidence that the intended recruitment rate is achievable!
- trial duration and timing: recruitment period, first-patient-in to last-patient out, duration of the entire trial

## **2. Minimum information to be provided in stage-2 proposals:**

**Part B of the stage-2 proposal should specify the above-mentioned issues in significantly more detail and in particular provide more in-depth justifications, evidence and references.** Please note that if an issue is addressed in a specific section, the same issue doesn't need to be addressed again in another (just the reference to the pertinent section).

*In addition* the stage-2 proposal needs to address the following issues – if applicable – in its part B:

- trial management: distribution of roles (sponsor, principal/coordinating investigator, trial statistician), evidence of trials expertise, specific trials facilities and resources, quality assurance and monitoring strategy (section 2)
- trials expertise of individual investigators/sites (section 2.2)
- plans for data and database management, including location, access and regulatory implications (section 1.3).
- statistical analysis: strategy for (multiple) primary outcome(s), interim/subgroup analyses etc. (section 1.3)<sup>2</sup>.
- monitoring of recruitment and contingency planning for recruitment problems (section 1.3)
- pharmacy issues: planning for the good manufacturing practice (GMP) batch production: timeline, facilities, testing, approval; planning for drug dispensing and accountability (section 1.3)
- plans for management and retention of biological samples, cooperation with existing or creation of new bio-banks (section 1.3)
- plans for reimbursement and contractual involvement of patient recruitment sites and trial management, including contract/clinical research organisations (CRO) if applicable: full beneficiaries, "third parties making available their resources", subcontractors (see below) (section 2.3)
- financial plan (section 2.4): trial (data, clinical) management, case payments/hospitalisation costs, trial drug(s) or device (including GMP batch production), additional diagnostic procedures, co-financing by industry or other third parties, the distribution of costs between health insurer, hospital and trial sponsor, statistical analysis, insurance, submission fees for regulatory dossiers, data and safety monitoring boards (DSMB) etc.

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<sup>2</sup> The justification of the proposed sample size/power calculations (see section on information to be provided in stage 1) and the statistical analysis are essential elements of the proposal. Proposals without a proper statistical methodology are likely to fail with a below-threshold score for "S+T Quality".

- provisions and timelines for approval by (which?) ethics committees and (which?) national competent authorities: which regulatory requirements have to be fulfilled, which have already been achieved and what is the status of the others, results of prior discussions with authorities (section 1.3)
- overall timeline of the trial, including preparation time (section 1.3.ii – include in Gantt chart of WPs or provide separate Gantt chart)
- independent trial oversight (section 1.3): e.g. DSMB, clinical event committee, scientific advisory or steering committee, ethical advisory board
- involvement and specific contribution of patients' organisations
- ethics (section 4): risks/benefits, protection of research participants, informed consent process and forms, participants' compensation, confidentiality, data protection, conflict of interests/commercial interests etc.

### 3. Financing clinical trials under FP7 rules:

#### 3.1. Clinical centres, whose contribution to the project is limited to the recruitment and inclusion of patients into the trial.

Integration into the consortium as *beneficiary*, which is the preferred option for any entity contributing to FP7 projects, might not be practical or feasible in some clinical trial projects because the large number of such centres might make the management of the project cumbersome and/or because these centres themselves consider the responsibilities linked to full beneficiary status not as proportionate to their involvement. In these cases the status of *"third party making available its resources"* or the status of *subcontractor* might offer acceptable alternatives. Please read carefully the sections in the FP7 "[Guide to Financial Issues](#)" referring to the respective Articles II.14.2 and II.7 of the [grant agreement](#) and Annex VI of the [Negotiation Guidance Notes](#) (on subcontracting), which describe the conditions under which these options are applicable and related costs are considered eligible.

- A *"third party making available its resources"* (based on Article II.14.2 of the grant agreement) charges its costs to the linked beneficiary, who reimburses them fully and is in turn reimbursed by the Commission according to the applicable funding rate. Third parties need to be described in section B.2.3 of the Technical Annex (Annex I) to the grant agreement. Third parties are also required to have a *prior* agreement with the beneficiary that defines the frame in which these resources are made available. This can be a longstanding agreement covering a large range of areas of cooperation, but may also be specific to the project and the resources in question. The reimbursement to the third party covers only costs, and there will not be a profit for the third party.
- A *subcontractor* charges an agreed price to the linked beneficiary. Tasks to be subcontracted need to be described in section B.2.3 of the Technical Annex. Any subcontract must be awarded to the bid offering best value for money (best price-quality ratio), under conditions of transparency and equal treatment. Participants that are public bodies are reminded that the selection of subcontractors has to follow their internal rules and applicable legislation related to public procurement in order for the related costs to be eligible.

In cases where it is difficult for beneficiaries or third parties to substantiate each of the actual costs involved for each individual test, the beneficiary or third party may opt to charge an

average cost per patient or per test or type of test, calculated with a methodology based on its actual costs and that is auditable.

### **3.2. Performance of certain tasks in the clinical trial by a clinical/contract research organisation (CRO).**

Because of their specialised expertise, CROs are often entrusted with clinical trial tasks, such as GMP production, pharmacokinetic studies, data management or the submission of regulatory dossiers. While the core expertise related to the performance of clinical trials needs to be available in the consortium itself, there might be certain services for which the specialised expertise of CROs is required. CROs are usually for-profit service providers and generally have no intellectual property or other direct interest in the performance of the trial. They might not be able to join the consortium on the basis of a partial reimbursement or co-funding and, as for-profit entities might even be unable to participate as a third party on the basis of a cost reimbursement only.

In view of this situation, the Commission will consider accepting subcontracting for the performance of specialised clinical trials services. The tasks to be subcontracted need to be well described and the reason for subcontracting well justified in section 2.3 of the Technical Annex. The award of subcontracts needs to be carried out under the conditions specified above.