**777389 - c4c**

**conect4children (COllaborative Network for European Clinical Trials For Children) call for proposals for multinational clinical trials of medicinal products in children and neonates.**

**Essential information to be provided for proposals for c4c non-industry proof of viability clinical trials of medicinal products.**

**Application Template**

**Background**

**c4c** invites clinical trials of medicinal products (CTIMPs) that will answer focused research questions to improve understanding of one or more medicine used by neonates, children and young people in Europe. This grant is designed to fund studies that are “proof-of-viability” studies for the new c4c network. Applicants will need to outline how they will utilise the grant to undertake the trial using the infrastructure (e.g. clinical trials network across at least 5 countries) provided by the network (see below).

Successful applicants will be sponsored by one of the Beneficiaries of **c4c**, being a legal entity that has signed Grant Agreement No. 777389 and is bound by the terms and provisions of the Consortium Agreement for Collaborative Network for European Clinical Trials for Children (“c4c Consortium Agreement”). The principal investigator may come from other entities, formally linked with the Beneficiary (e.g. part of the national or speciality network coordinated by the Beneficiary).

Successful applications will include a clear plan for using the data beyond publication e.g. changes to the Summary of Product Characteristics (SmPC) or national/speciality guidelines to improve or change clinical practice. The study maybe be part of an existing or planned paediatric investigation plan to the Paediatric Committee (PDCO) of the European Medicines Agency (EMA). The studies should be capable of being submitted to EMA if the Marketing Authorisation Holder chooses to do so. Submission costs will not be covered by the funding. The intended use of the data beyond publication must be stated in the application with a clear plan about meeting the needs for planned submissions (data quality etc.).

Please complete this application for each clinical trial to be conducted. There are no page limitations for this application, but explanations should be as concise as possible.

Information provided that is not in the scope of this template will not be taken in to account during the evaluation of the proposal. No new or modified sections can be included. The information will be used to assess the quality and feasibility of the application. Given the

limited time available for the study, **c4c** the assessment procedure needs to conduct a detailed risk assessment of each trial underpinned by the information contained in the application. This information will also be the basis of the network’s assessment of the support needed by the trial. While this information may appear to be onerous, it should be available 18 months before a trial is due to open.

Significant funding is available for each trial. This needs to be spent on:

1. developing and implementing a high-quality trial;
2. network resources;
3. supporting staff at study sites (research nurses, data managers etc.);
4. children and young people, and/or family involvement activities throughout the lifespan of the study
5. Sponsors costs, which must be met in full.

The balance of allocations to these funding requirements will be an important part of the assessment.

Within two months of receiving notification of a successful application, it will be necessary to seek and receive advice from c4c groups about:

1. Innovative trial designs
2. Developmental pharmacology
3. Extrapolation
4. Patient involvement (e.g. eYPAGnet etc.)

The progress of trials will be closely monitored by the Trial Commissioning Committee and resource allocation will be adjusted by the Trial Commission Committee during the trials in the light of progress.

The first section of the application form reflects the H2020 template for essential information to be provided for proposals including clinical trials[[1]](#footnote-1). Subsequent sections cover information specific to this call.

Each section must be completed concisely. **If one or more issues do not apply to a particular study, please briefly explain/justify**. If information is not available, please say so.

Document 1: H2020 template

Document 2: Supplementary Information about the trial

Document 3: Additional Justification of the trial

Document 4: Network Involvement

Document 5: Costs

Document 6: Institutional Approvals (this document must be submitted with the others on January 5th 2019 although the Appendices containing “wet signatures” can be submitted until January 19th 2019.

Documents should be named as c4c application, with the code for the submitting Beneficiary and the Document Number, e.g.

c4c application ULIV Document 1

Appendices should be numbered according to which Document they refer to, e.g. the first appendix to Document 2 would be:

c4c application ULIV Appendix 2.1

**Document 1. H2020 Clinical Trials Template**

*Complete the H2020 Clinical Trials Template taking account of the following notes about specific sections in the template.*

Introduction:

“Information outside the scope of this template will not be taken in account in the proposal evaluation. No other chapters or annexes (containing e.g. complete study protocols) can be added to this template. Section headings should not be changed.”

For this call we will take account of information outside the scope of the H2020 template. This extra information is specified in the supplementary documents.

Ethics considerations will be addressed in one of the supplementary documents.

Resources for the trial will be addressed in one of the supplementary documents.

The Mandatory Deliverables mentioned in the H2020 template will be required.

Sections:

1.3.1 Regulatory / Ethics status: provide the required information. More detail should be given in Document 3, Section 7.

1.3.2 Scientific Advice from groups other than Regulatory agencies is strongly encouraged and should be summarised in Document 3, Section 2 for expertise in innovative methodologies and Document 4, Sections 1 (young people and families), 5 (clinical community) and 8 (European Reference Networks and other initiatives).

1.7.1 Study schedule. Justify why your estimates are realistic. Detailed information about the basis for your estimates is required in Document 3, Section 4.

1.7.5 Study Sponsor. Additional information about the Sponsor should be given in Document 2, Section 2.

1.9 Costs: use this if your team would like to use unit costs. Actual costs may be preferable. Detailed information about costs is required in Document 5.

**Document 2. Supplementary Information about the trial**

**1. Full title of trial and acronym**

*Descriptive title that reflects the main objective of the clinical trial and an acronym for easy reference to the trial without using its full title.*

**2. Clinical Trial Sponsor**

*a) Provide the name of the legal entity that will act as the clinical sponsor for this clinical trial. Provide details (trial registrations) of three recent paediatric clinical trials where the legal entity was the sponsor.*

*b) Supply summaries of inspection findings by national or European regulatory authorities from the past 5 years: date; nature of inspection; key findings*

*c) Describe the Sponsorship plan (elements of Sponsor’s internal processes / approvals, timelines, and costs).*

*d) Describe the issues relating to insurance of the trial (on a country by country basis) and how these will be addressed (include indicative quotes and timelines when available).*

**3. Investigational Team**

*Provide the name, employer and main professional role of key members of the study team and specify how they are related to the Sponsor and where the work will be done.*

*Team members with an asterisk \* need to submit a one page CV according to the template in Appendix 1, or description of their work*

*Chief Investigator\**

*Principal Investigators\**

*Lead Pharmacist\**

*Other Pharmacists*

*Lead Nurse\**

*Other Nurses*

*Lead advocate for parents/children and young people\**

*Other Advocates*

*Lead Data Manager\**

*Other Data Managers*

*Lead Biostatistician\**

*Other Biostatisticians*

*Lead Pharmacometrician\**

*Other Pharmacometricians*

*Clinical Pharmacology lab\* (include GLP status)*

*Other facilities (imaging, biomarker etc.)\**

*Other key members of staff as appropriate (imaging lead\*, pharmacogenomics lead\* etc.)*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| *Name* | *Lead Employer* | *Professional role* | *Relationship to Sponsor* | *Organization that will be responsible for the work* | *Number of CTIMPs the person has been involved with* |
|  |  |  |  |  |  |
|  |  |  |  |  |  |

**4. Industry involvement**

*For each industrial contributor to the application:*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| *Name of legal entity* | *Contact person (name and contact details)* | *Nature of involvement* | *For each IMP or other contributions* | | |
| *Name* | *Ownership* | *Conditions for availability* |
|  |  |  |  |  |  |
|  |  |  |  |  |  |

**5. IP**

*Summary of Background IP and who owns each part of Background*

*Outline of Agreements to be concluded & intellectual property provisions (see call text) taking account of Background, Sponsors and investigators*

**Document 3. Additional Justification of the Trial**

**1. Background to the trial**

*Why is this trial needed? (knowledge gap, priority)*

*How have children, young people and families contributed to the identification and prioritisation of the research study?*

*What is the scientific and clinical justification for the trial and its design (including all key points of the design including eligibility criteria, formulation, dosing regimen, assessments)?*

*What information supports the justification (animal, preclinical, PK, retrospective, rationale for relationship between active ingredient and its target, etc.)*

*What is the basis for prioritising this trial (give rationale in all cases, and, if possible refer to prioritisation document, e.g. WHO, EMA, other)*

**2. Trial design**

* *Use of biomarkers in screening, recruitment, assessments during the trial, and as outcome assessments. Describe how each biomarker has been validated and how each biomarker is related to clinically meaningful outcomes*
* *Innovative aspects of trial design and methodology. Describe the innovative approaches. Justify the use of the innovative methods or why you are not using innovative methods. How have the innovative approaches have been developed and adapted to your trial?*
* *Specify the collaboration(s) on innovative methods that you worked with to develop the application.*

**3. Study duration**

*Specifically, the trials will not receive any funding for costs incurred after November 30th 2023 and applications will be assessed on their ability to provide results and support the evaluation of the network before the end of 2023.*

*This will require all trial-related evaluations to be completed by November 30th 2023 and any other needs for funding (analysis etc.) to be completed by November 30th 2023. Last Patient Last Visit will need to be significantly before November 30th 2023. These realities must be reflected in the study timelines. There will be NO extensions to the study funding envelope.*

*Specify high level project milestones: Protocol final, first submission, Database locks, CSR completion.*

*Provide the total duration of the proposed clinical trial, and the estimated trial start and completion dates for each period in the trial, including:*

*setup (site contracts etc.)*

*recruitment (more detail is required in Section 5),*

*intervention,*

*follow-up.*

*TRIAL DURATION MUST BE IN LINE WITH C4C TIMELINES that is, open during 2020 and complete all study procedures that require funding from c4c by November 30th 2023. It will not be possible to submit claims for costs that are incurred ater November 30th 2023.*

*Submit Gantt chart*

**4. Preparedness**

*Supply any supporting information from feasibility studies or most relevant information from other sources, stating where the information comes from.*

*Submit a diagram to show how the proposed sample size relates to the number of participants that can be identified in collaborating sites, providing justification and data for each step*

Prevalence / Incidence of clinical diagnosis

Prevalence / Incidence of population defined by eligibility criteria

Available for recruitment

Site readiness factor (number / quality)

Consent factor

“Friction of war”

Total available for trial

**5. Recruitment and retention**

*Give details of the planned recruitment rate, including the likely rate of loss to follow-up and potential problems with compliance by addressing the following:*

* *How recruitment will be organised*
* *FPFV and LPLV and prediction on recruitment per quarter until LPFV,*
* *Evidence that the planned recruitment rate is achievable including by validated feasibility studies and estimates of screening/enrollment, screen failure rate*
* *Evidence on the likely rate of loss to follow-up*
* *Potential problems with compliance with the protocol, including evidence for the compliance figures.*

*References supporting these details should be included in the reference section at the end of this template.*

**6. Relationship to routine clinical care**

*Describe how the proposed trial relates to the care that participants will otherwise receive.*

*How much of that care will be provided by the hospitals / health authorities in each country?*

*How many assessments will be provided by hospitals / health authorities (imaging, laboratory investigations etc.)? Will special permissions be needed from hospitals / health authorities in each country? What are the timelines for any permissions that will be needed?*

**7. Ethical and regulatory approval**

*Trial selection will be based on trial not having obstacle to approval by ethics committees and competent authorities. What are the key ethical issues and how will they be handled by: a) the study team; b) countries that contribute participants?*

*What is the ethical and/or regulatory approval process for this clinical trial? Please indicate which national authorities, institution(s) or board(s) will undertake reviews and give provisional timelines. 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 in this section of the document. If the answer is not available provide explanation of current status. Please also include in this section any other relevant correspondence or minutes of meetings with regulatory authorities or ethics committees such as requested or granted approvals of clinical trial applications.*

*What are your contingency plans if regulatory or ethics approvals are delayed?*

**Document 4. Network Involvement**

**1. Involvement of children, young people and their families in the trial**

*How have children, young people and families been involved so far?*

*How will you involve children, young people and families if your application is successful in study design, setup, implementation, analysis and dissemination?*

*Specify which young people’s advisory group(s) have been / will be involved*

**2. Product(s) to be tested and arrangements for supply**

*Please describe all the products/new formulations/or a current medicine to be used in the proposed clinical trial, including controls/comparators/placebos and NIMPS (if appropriate).*

*Specify for each product whether it is still under development or whether it has been approved for use/registered in the countries where the trial will take place.*

*Specify any steps that need to be taken before the product(s) can be used in a clinical trial and your plans for those steps (include timelines and costs).*

*The trial should be supported by a plan for obtaining trial supplies (medicines / placebos) through network procedures or a similar process. Detail the arrangements for the supply of the products to be used in this trial, for both experimental and control arms, including:*

* *If applicable, whether manufacture and/or labelling of the product is required and who is responsible for manufacturing and/or labelling the product, and when this will be achieved?*
* *Guarantee of good manufacturing practice (GMP)-compliant investigational product(s)*
* *Details of any agreements made with companies or other organisations for supply of the products*

*(experimental and control). Please indicate whether signed agreements/guarantees have already been obtained for supply of the products to be tested.*

*The development of placebos may be problematic within the timescales of this funding stream. If applicants propose a placebo-controlled trial they need to provide a robust plan for obtaining placebos.*

*The use of foods or nutritional products in a CTIMP may cause challenges. If you are planning to use a food outline the challenges and how you will address them.*

***c4c*** *will provide access to advice about how to commission trial supplies to all applicants.*

**3. Risk management**

*Supply an outline risk management plan that focuses on key risks to: a) participants; b) the integrity of the trial; c) timely completion of the trial to target and budget; d) utility of the trial to c4c.*

*For example,*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *Hazard* | *Impact (1 – 5)* | *Likelihood (1 – 5)* | *Risk score (Impact x Likelihood)* | *Mitigation strategy* |
|  |  |  |  |  |
|  |  |  |  |  |

**4. Trial site selection**

***Studies must have at least 10 c4c sites (defined as sites coordinated by a c4c national hub) from at least 5 c4c national networks, with a broad spread of sites across participating countries. The trial may involve European countries that are not represented among c4c Beneficiaries. In exceptional, well-justified cases countries outside Europe may be included. More than 75% of recruitment must be done within c4c sites. For countries that are not included in c4c, c4c funding will cover the costs of research – medicinal products/data collection, according to H2020 rules. c4c funding will not cover site support in countries that are not involved with c4c.***

*Provide the rationale with supporting evidence for the selection of the trial sites, including factors such as prevalence of disease(s) being studied, the availability of appropriate study population, existing collaborations and/or established clinical trial infrastructure. References supporting these details should be included in the reference section at the end of this template.*

*Identify sites that are already involved in this application*

*Describe strategy for selecting other sites (when would you look for sites, how would you look for sites)*

*Describe processes for opening sites that are not associated with a c4c National Hub*

**5. Clinical community involvement**

*Detail the involvement by groups from the clinical community in the development of the trial design and ongoing involvement in the trial.*

**6. Pharmacovigilance**

*How will you manage pharmacovigilance?*

*Options include:*

1. *Using the c4c pharmacovigilance service hosted by INSERM (in which case describe your interactions with the c4c PV service)*
2. *Using another high-quality service (in which case describe the service, its experience and qualifications)*

*Outline costs for PV activities*

*Sponsor’s pharmacovigilance registration with EMA*

**7. Utilisation of network systems**

*Describe how you will use each of:*

1. *national hubs;*
2. *contract templates developed by the network (including CDAs, site agreements, invoicing)*
3. *patient advisory groups (Young People’s Advisory Groups and groups such as EURORDIS);*
4. *metrics for study performance*
5. *performance management of sites and investigators*
6. *data standards;*
7. *Advisory Groups*
   1. *Clinical (which will you consult with)*
   2. *Methodological (which will you consult with);*
8. *resources at study sites (nurses, data management staff, Pharmacists etc.).*

*at the following stages*

1. *between selection of the study and first patient first visit* 
   1. *to include advice about:*
      1. *innovative designs*
      2. *developmental pharmacology*
      3. *extrapolation*
   2. *to include simulation of trial procedures:*
      1. *recruitment (involving people)*
      2. *dry runs*
2. *during the trial*
3. *after the trial*
4. *how you will use network resources to extend your existing ways of working*

*Indicate how you will allocate resources to network systems.*

**8. Relationships to related initiatives**

*Are there existing initiatives in this area, e.g. European Reference Networks* [*https://ec.europa.eu/health/ern/networks\_en*](https://ec.europa.eu/health/ern/networks_en) *or learned societies or speciality networks?*

*If so, indicate which initiatives and explain relationships between this study and relevant initiatives.*

**9. Contribution to evaluation of the network**

*The network will be evaluated in several ways, including:*

1. *Time to set up sites*
2. *Time to open trials*
3. *Time to recruit patients*
4. *Benefits of working with sites that share operating procedures*
5. *Benefits of working with national hubs*
6. *Benefits of services such as pharmacovigilance and advice about commissioning trial supplies*
7. *Contributions of Advisory Groups (including nature, utility and impact of advice given)*
8. *Number and nature of protocol amendments*
9. *Education*

*Outline how your trial could contribute to these evaluations and other evaluations you would like to propose*

**10. Impact of study results**

*Outline your intentions to use the results beyond publication.*

*This could include changes to the Summary of Product Characteristics (SmPC) or national/speciality guidelines to improve or change clinical practice.*

1. *What are your intended use(s) of the results other than publication?*
2. *What are the requirements for using results in your intended uses (data quality, formatting etc.)*
3. *How will you meet those requirements?*
4. *What resources do you need to meet those requirements?*

*Costs of submission to EMA willnot be covered by the funding.*

*How do you intend to feedback to participants of the studies in a child/family friendly way?*

*Outline other impacts such as contribution to data warehouses, data sharing schemes etc.*

*Assume that the study goes to plan and yields expected results and, also, consider impact if the expected results are not available at the end of the study.*

**11. Study “Add-ons”**

*The goal of these trials is to evaluate the network, rather than study a topic exhaustively.*

*Add-ons such as mechanistic evaluations are unlikely to be funded by c4c, but describe any possible add-on studies and how you will fund them.*

*Note that if add-on studies threaten the timing, quality, recruitment or retention to the study they will stop.*

**Document 5. Costs**

**1. Outline how your trial will handle costs according to H2020 rules (actual costs vs unit costs)**

**2. Estimate costs for trial activities**

*Describe your estimates and the basis of those estimates for:*

1. *Preparation[[2]](#footnote-2)*
   1. *Protocol preparation*
   2. *Trial supplies*
   3. *Trial database*
2. *Site setup*
3. *Screening*
4. *Recruitment*
5. *Trial procedures*
   1. *Propose, and justify, your approach to paying sites for their activity*
   2. *Propose, and justify, your approach to quality control / quality assurance – data monitoring etc.)*
6. *Close down*
7. *Analysis*
8. *Publication (c4c will fund publication in Open Access journals if publication occurs before the end of the c4c IMI2 project)*

*What are your plans if study procedures are not complete by November 30th 2023? c4c will not be able to grant extensions. The Sponsor will be responsible for completing trial procedures if the trial needs funds after November 30th 2023.*

*Use a Word Document to justify all costs estimates in all these categories and other costs you envisage.*

*Use an Excel file to describe your cost estimates using one of the approaches described in the H2020 template.*

**3. Utilisation of organizations such as Contract Research Organizations**

*If CROs will be used, describe how, why and when.*

*Provide indicative costings*

*If you have selected specific CRO(s) name them (CROs may be selected after the application is successful but the overall funding for your trial will not be altered to accommodate costings that are greater than your initial specification).*

**Document 6. Institutional Approvals**

*1. Sponsor*

*Signature from person of sufficient authority to indicate that the Sponsor agrees to:*

*Sponsor the trial in full compliance with international and national legislation, regulations and standards, that is taking complete responsibility for assuring the quality of all aspects of the trial during and after the period of funding from* ***c4c****.*

*Allocate sufficient resources to the study (based on claiming costs for Sponsorship from* ***c4c****)*

*Host trial according to* ***c4c*** *rules and using* ***c4c*** *systems (including, but not limited to templates for confidentiality disclosure agreements, site agreements)*

*Allow all direct costs to be spent on the trial at the discretion of the CI, with no funds retained by the Sponsor other than declared indirect costs.*

*Follow* ***c4c*** *IP rules*

*Meet financial responsibilities, including distributing funds and reporting to IMI2 through* ***c4c***

*Make no claims for costs relating to the trial after December 2023*

*Use best endeavours to open the study in a timely way*

*Accept* ***c4c*** *decisions about suspension of component(s) of the study (e.g. add-on studies) if* ***c4c*** *judges that the component(s) threaten the ability of the trial to meet the goals of* ***c4c****.*

*Respect the Background IP that is essential for the design and conduct of the trial and have an IP agreement about Background and Results in place before the trial opens.*

*2. Chief Investigator*

*Signature from the CI to indicate that the CI agrees to:*

*Take responsibility for the study, as delegated by Sponsor*

*Devote sufficient time and effort to the study*

*Follow c4c IP rules*

*3. Lead employer of CI:*

*Signature from person of sufficient authority to indicate that the CI’s lead employer agrees to:*

*The CI leading this study*

*Allow CI sufficient time and resources to lead this study*

*4. Industry:*

*Signature from person of sufficient authority to indicate that the company agrees to:*

*Exercise every endeavour to fulfil commitments to the study, as specified (supply materials etc)*

*5. IP:*

*Indication from each organization involved in the outline of the IP that they are prepared to come to a timely agreement about IP*

Appendix 2.1. Structured CV. Do not exceed one page

Name

Age

Qualifications

Lead Employer

Duration of current contract

Involvement in CTIMPs

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Name of trial | Reference number (clinicaltrials.gov) | Role | Start | Complete | Funder | %age of planned recruitment | Comment |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |

Other skills (150 words max)

1. http://ec.europa.eu/research/participants/data/ref/h2020/other/legal/templ/h2020\_tmpl-clinical-studies\_2018-2020\_en.pdf [↑](#footnote-ref-1)
2. Money for these activities will be released as soon as contracts are in place [↑](#footnote-ref-2)