

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

**Type of call: one stage evaluation with an initial expression of interest**

**Call budget: €24 million (plus indirect costs)**

**Indicative funding for each project: up to €5 million for the trial with access to up to €1 million-worth of use of the network infrastructure**

**Funding level: 100% of agreed budget (additional in-kind contributions from other organizations will be allowed)**

**Call opened: August 31<sup>st</sup> 2018**

**Expressions of interest one month after call published or sooner**

**Submissions: January 5<sup>th</sup> 2019**

**Decisions: March 5<sup>th</sup> 2019**

**Trial setup: during 2019**

**First patient first visit: during 2020**

**Final date that trial-related costs can be claimed for: November 30<sup>th</sup> 2023**

### Context

Neonates, children and young people need high quality information about new and existing medicines but have been underserved by research efforts in the past. Accordingly, there is an urgent need to improve the ability of the research community to deliver clinical trials about medicines used by neonates, children and young people. When fully developed, conect4children (**c4c**) will facilitate the development and availability of new drugs and other therapies, and the expansion of knowledge about drugs currently in practice for the entire paediatric population in Europe, <http://conect4children.org>. **c4c** will address critical problems with the design, implementation and operational conduct of paediatric clinical trials, such as the fragmented and redundant efforts between sponsors, sites and countries; the paucity of patients available for study in many paediatric indications and the need for multiple capable sites and expertise to make trials successful.

The Innovative Medicines Initiative 2 (IMI2) is a Public Private Partnership, funded jointly by the European Union (represented by the European Commission) and the European pharmaceutical industry (represented by EFPIA, the European Federation of Pharmaceutical Industries and Associations). **c4c** is one of the biggest initiatives ever funded by IMI2.

### Purpose

The purpose of this call for submitting proposals that will be conducted within the c4c project is to identify paediatric and neonatal trials that meet the highest scientific standards, which use the facilities provided by the network and, which will yield results before the end of funding from **c4c**. **The trials funded by this call will be multi-national investigator-initiated paediatric or neonatal interventional clinical trials of medicinal products that will enable the consortium to evaluate the viability and sustainability of the c4c network.** Multi-national trials (including at least five European countries) that will be setup and deliver results within the timescales of the c4c project. The

facilitation of these trials through the c4c network will be used to evaluate the network.

## Scope

**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 call for proposals 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 allocated budget to undertake the trial using the infrastructure (e.g. clinical trials network across at least 5 European countries) provided by the network (see below).

All paediatric specialties and all paediatric age-groups (neonates, children, young people) will be within the scope of this call for proposals.

The trials must be sponsored by a Beneficiary of the c4c project. With the agreement of a sponsoring Beneficiary the trial Chief Investigator may be employed by a legal entity other than the sponsoring Beneficiary. Study teams should include multiple disciplines from multiple organizations.

Successful applications shall be:

- Based around a clear unmet need that is identified by a) children, young people and families and b) clinicians across Europe
- Addressing relevant scientific questions
- Embedded in a plan for either: a) the development of a novel product; b) repurposing an existing product; c) evaluating a new formulation; d) evaluating a medicine that is used in children currently when that use is not supported by adequate information about the use of the medicine in children.
- Intended to support use of the data beyond publication e.g. changes to the Summary of Product Characteristics (SmPC) or national/speciality guidelines to improve or change clinical practice (eg). The study may 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.
- Multi-national paediatric or neonatal CTIMPS. 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. At least 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**.
- Based around clinical pharmacology study designs, or clinical exploratory, or Phase 2, or innovative designs. Phase 3, or trials based on real-world practice that will influence practice, will be considered if there is a strong case that the study will be completed within the available time.
- Without obstacle to approval by ethics committees and competent authorities (this will be assessed during the evaluation of proposals)
- Compliant with GCP and other applicable requirements (such as the Clinical Trials Directive)
- Supported by validated feasibility studies and appropriate risk assessment and risk mitigation strategies to overcome barriers to timely completion of the trial to target and budget. Specifically, the trials will not receive any funding for costs incurred after November 30<sup>th</sup> 2023

and applications will be assessed on their ability to provide results and support the evaluation of the network before the end of 2023.

- Supported by a plan for obtaining trial supplies (medicines / placebos) through network procedures or a similar process (see separate document). 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. **c4c** will provide access to advice about how to commission trial supplies to all applicants. Well justified plans for limited development and testing of a paediatric formulation, including relevant costs, will be in scope for the call. Note that funding may be withdrawn if any development and testing of formulations does not meet pre-defined timelines that allow the trial to contribute to the evaluation of the network's viability.
- Supported by a robust system for pharmacovigilance through network procedures or a similar process. Successful applications will be given support with respect to pharmacovigilance.
- 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 Chief Investigator may come from other entities, formally linked with the Beneficiary (e.g. part of the national or speciality network coordinated by the Beneficiary), in this situation the lead employer of the Chief Investigator will need to become a third party to the Consortium.
- Sponsored with the commitment to report on the trial processes and experiences with the network to facilitate dissemination and knowledge sharing within the consortium and network set up and with the commitment to follow the network's evaluation plan.

We will not consider applications under this scheme for proposals that:

- Aim to establish audits, databases and registries or are service development
- Are pharmacogenetic or pharmacovigilance studies using solely epidemiological methods. However, CTIMPs that include a genetic or safety aspect will be considered.
- Use existing infrastructure without a significant contribution from **c4c** infrastructure (e.g. processes, advisory groups, national hubs and sites).
- Have recruited any participants before September 1<sup>st</sup> 2019. Trials that have made some preparations will need to consider all advice from the network before they are finalised
- Study devices or food supplements
- Have unrealistic budgets or timeframes

We encourage the use of "innovative" methodologies, including but not limited to Bayesian approaches, extrapolation, learning and confirmation of in silico models and simulations.

We encourage the use of "innovative" designs such as multi-sponsor multi arm trials.

We strongly encourage applicants to work with existing European initiatives in innovative clinical trial methodology, including IDEAL (<https://www.ideal.rwth-aachen.de>), ASTERIX (<http://www.asterix-fp7.eu>) and INSPIRE (<https://warwick.ac.uk/fac/med/research/hscience/stats/currentprojects/inspire/>).

Applicants are encouraged to consider work being undertaken in other current/future IMI2 projects offering new methods and/or tools relating to study design.

<https://www.imi.europa.eu/projects-results/project-factsheets>

<https://www.imi.europa.eu/projects-results/catalogue-project-tools>

Other collaborations are encouraged. Proposals must take care to avoid double funding of activities.

We will consider trials that are supported by pharmaceutical companies irrespective of whether the company is a member of the **c4c** consortium. Such support could include provision of trial supplies

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(see below for agreements to be concluded & intellectual property provisions).

Applicants may consider “mechanistic” or exploratory secondary analyses but these may not be funded if **c4c** considers that the work does not meet the needs of **c4c**. **c4c** reserves the right to exclude specific trial procedures or analyses from trials if **c4c** believe that procedures or analyses pose a material risk of the trial contributing to **c4c** goals (for example if sampling of blood may reduce the likelihood of sufficient recruitment or retention of trial participants).

## Indicative budget

€3 - 5 million for each trial which will be supplemented by up to €1 million that will be allocated by **c4c** to pay for network services used by the trial and the evaluation of network services. **c4c** will allocate projected resources to the trials based on the complexity of the trial and the award may not be the same as requested by the applicants (taking account of need, benchmarking and standard algorithms). Funds will be released in stages depending on progress with trial preparation and recruitment. Budget distribution will be compliant with IMI rules. For example, reimbursement will be based solely on the reported eligible actual costs. Applicants should familiarise themselves with the IMI financial rules, especially the eligibility of the costs and process for remuneration.

## c4c support

Projects positively evaluated under the scope of this call will be required to use c4c network systems and services for the set-up and implementation of the study in all partner countries involved in the study. This will include:

- Use of the national networks
- Advice about study design and conduct from Young People’s Advisory Groups and or parent organisations
- Support services for recruitment to trial within each country
- Performance management of the trial from funding decision onwards, subject to a clear agreement about performance metrics.
- Advice about study design from clinical and methodological expert advisory groups
- Support with commissioning trial supplies
- Support with pharmacovigilance

**c4c** may require positively evaluated projects to follow recommendations from these components of the network. **c4c** will adjust study budgets in line with study and network requirements and according to reported costs.

Each selected study needs to comply with the project’s acceptance criteria and IMI2 rules and timetables for submission of ethics approvals, national Competent Authorities and other trial-related documentation. Adherence to, and utilisation of, the systems and services developed through **c4c** is a fundamental aspect of this call. For example, Sponsors and sites will commit to using the standard counterfactuals and other documents developed by **c4c**.

Trial Sponsors will be responsible for meeting all IMI2 reporting requirements relating to the trial and will be able to include reasonable costs for these activities in their applications.

Trials may use Contract Research Organizations for appropriate tasks not provided by **c4c**, as long as this is justified. Ancillary services (such as monitoring) may be consolidated across trials.

## How to apply

This call follows a single-step procedure, with an early registration of interest.

Each project team will need to register their interest within a month of the publication of the call at using the template letter of intent that will be provided with the call. This will include an abstract with a 4000 character limit.

Applications should be submitted to [trial.applications@conect4children.org](mailto:trial.applications@conect4children.org) using the template for applications that accompanies this call no later than January 5<sup>th</sup> 2019.

A summary of each proposal's evaluation will be made available to the applicant of that proposal.

## Agreements to be concluded & intellectual property provisions

Any third party investigator may propose a proof-of-viability paediatric clinical trial using the c4c network, involving off-patent or on-patent investigational medicinal products ("IMP") proprietary to either an industry party who is already a member of the c4c consortium or an industry third party who is not a c4c consortium member. The clinical trial proposed will always be sponsored by a not-for-profit member of the c4c consortium. To this end, arrangements will need to be made involving the IMP contributor, the initiating investigator and the sponsor. Further, the sponsor shall ensure that the trial is subject to appropriate clinical trial and other agreements to be concluded with the clinical sites to carry out the trial.

Any agreement the sponsor enters into in the framework of the trial shall contain provisions which, at a minimum and to the extent relevant and possible under applicable legislation, provide protection for study subjects and personal data consistent with the terms of the c4c Consortium Agreement, and shall not conflict with the terms of that Consortium Agreement or the Grant Agreement, in particular as regards (but not limited to) intellectual property rights, including ownership (and, as the case may be, transfer) of any output generated in such trial and the access rights with respect thereto. Any agreement in the framework of such trial shall be subject to prior legal review on its compliance with the terms and conditions of the Consortium Agreement and the Grant Agreement.

In particular, the applicant investigator acknowledges that the output arising from the performance of the trial will, as the case may be, be divided into:

- "viability results", that is results generated that relate to the functioning and/or viability of the c4c network itself (e.g., quantitative data about trial performance, quality and/or efficiency, narrative data as to what worked and did not work, trial timelines, ...), provided that such results can be used independently from the IMP evaluated and/or the IMP background.
- "IMP results", that is clinical results generated that directly relate to the IMP evaluated.

The applicant investigator further acknowledges that such output will be treated as outlined directly below.

### A. Clinical trials using IMP from c4c industry parties

In case the trial sponsor uses an IMP from an EFPIA party who is a member of the c4c consortium, ownership and access rights to any viability or IMP results will be as per the terms and conditions of the c4c Consortium Agreement.

### B. Clinical trials using IMP from industry third parties (external to c4c)



In case the trial sponsor uses an IMP from an industry third party who is not a c4c consortium member, any viability results shall always remain exclusively owned by the c4c consortium member who generated them, and the access rights to such results will be as per the terms and conditions of the c4c Consortium Agreement.

In this case, the ownership of any IMP results will be transferred to the sponsor of the trial, and the sponsor will grant to the industry third party that contributed the IMP, to the extent allowed by applicable laws and regulations, a payable, non-exclusive, any-purpose license to any IMP results. If applicable law does not allow for such license to be granted by the sponsor to the IMP contributor, the latter will receive a study report on any IMP results. The aforementioned transfer/license shall not apply to IMP results which are strictly improvements to and/or modifications of the Background IP (to the extent these are not already captured by the definition of viability results) owned or controlled by an academic third party (who is not a c4c consortium member) and which are not severable therefrom and which can be used independently of the IMP contributed, in which case the IMP results shall remain exclusively owned by the academic third party owning or controlling such Background IP.

## Notes

Applications that register their interest within a month of the publication of the call text and have a prima facie consistency with the call objectives, will be allocated up to €5000 to support the development of the application. This money can be used to support meetings, travel and other activities that will enhance the quality of the application and will be reimbursed upon provision of costs justification in the first c4c periodic report. The €5000 will be allocated to the c4c Beneficiary that proposes the application. Costs relating to the development of unsuccessful applications will be met.

Webinars will be held to explain the call; details will be announced later.

Questions about the call should be directed to [trial.applications@conect4children.org](mailto:trial.applications@conect4children.org). There will be no discussions about specific projects, these discussions will relate only to the scope and process of the call. Informal suggestions about potential collaborations can be provided.

**c4c** will not sponsor trials. Each Sponsor will retain full responsibility for the assurance of all aspects of the trial. For the avoidance of doubt, c4c will not be able to provide funding for costs that are incurred after November 30<sup>th</sup> 2023. After that time, the Sponsor will need to take responsibility for any remaining requirements for resources.

Trial selection will be done in two phases:

1. The utility of clinical trials to the network will be assessed by the **c4c** Trial Commissioning Committee (chaired by Dr. Turner of the University of Liverpool) made up of senior clinicians familiar with c4c, and a patient advocate, who do not have any conflicts of interest with any of the applications. This will generate a short-list of trials that are capable of contributing to the evaluation of the viability of the network.
2. The scientific value of the applications of most use to the network as “proof-of-network viability” studies will be assessed by an independent international advisory panel taking account of the utility of the trials to the network. The international advisory panel will rank the applications and reconcile the costs of the trials with the capacity of the network and with the views of patients and their families. This reconciliation will guide the selection of the trials by the international advisory panel.

Applicants are encouraged to make contact with **c4c** national hubs, through [trial.applications@conect4children.org](mailto:trial.applications@conect4children.org), during the preparation of their applications. All communication with applicants will be confidential.

This is the only funding opportunity for non-industry trials that **c4c** will provide.