# Report from the 2022 Enpr-EMA/c4c workshop on quality criteria/standards of paediatric clinical trial sites.

## Co-organised by the European network of paediatric research at the EMA (Enpr-EMA) and conect4children (c4c)[1]

## Date: Monday 3 October 2022

A workshop co-organised by the European network of paediatric research at the EMA (Enpr-EMA) and conect4children (c4c) was held virtually on the 3rd October 2022. Participants included members of Enpr-EMA and of c4c, members of the European Medicines Agency's (EMA) Paediatric Committee (PDCO) as well as members of EMA's Paediatric Medicines Office, along with invitees representing pharmaceutical industry and clinical research organisations (CRO), patients and academia.

The workshop covered the topic of site suitability for participation in paediatric clinical trials and the need to identify a standardised set of quality criteria to enhance the development of high-quality trial sites and to support site selection in the context of paediatric clinical trials.

This workshop also contributes to the objectives of the "Accelerating Clinical Trials in the EU (ACT EU)" initiative for better clinical trials that address patients' needs.

Chairpersons: Pirkko Lepola, Mark Turner

### *Objectives of the workshop*

Heterogeneity in site capabilities and individualised requirements by sponsors have been identified as causes of delays and performance inefficiencies of paediatric clinical trials, which already face many specific challenges due to the vulnerability and scarcity of paediatric study populations.

In this context, the possibility of improving clinical sites' capabilities via quality requirements has arisen as a way of ameliorating the performance and quality of the clinical trials.

The objective of the workshop was to initiate and catalyse a discussion around the topic of site suitability and the need to identify a set of quality criteria that could be accepted by the different stakeholders involved in paediatric medicine development, that could demonstrate sites' capability to participate in paediatric clinical trials. The workshop aimed to reach a common understanding on the

[1] Conect4Children (c4c)- is a collaborative pan-European network that aims to facilitate the development of new medicines and other therapies for the paediatric population. The c4c project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777389. The Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

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need for such criteria, their potential use, and the process to have these criteria developed and recognised.

The workshop was based on the work on the topic of site quality requirements that had been performed by Enpr-EMA's working group on international collaboration and by c4c. The two groups have addressed this topic from different perspectives, however, applying similar methodologies. c4c has been dealing with the clinical sites' perspective, by developing a questionnaire on the standard criteria for the sites working in connection with c4c. The Enpr-EMA working group has focused its attention on the industry's views by conducting an online survey and follow up interviews targeting industry and CROs to identify the characteristics considered important by sponsors when selecting clinical trial sites to participate in paediatric clinical trials. Both questionnaires covered some overlapping topics or "domains", such as site personnel requirements regarding training and resources, requirements regarding site facilities and requirements regarding contracting and regulatory processes.

The preliminary results of the work from both groups on the overlapping domains were presented at the beginning of the workshop and discussed. This was followed by discussions during two break-out sessions to define the expectations, next steps and actions needed that could lead to the building of a quality framework for sites to increase capabilities and to ultimately improve the available medicines for children.

## *Results from industry/contract research organisation (CRO) survey (Enpr-EMA)*

Breanne Stewart presented the results of the work of the Enpr-EMA working group on international collaboration that is comprised of regulators and networks representing 6 jurisdictions (Australia, Canada, EU, Japan, UK, USA). This survey was conducted between April 2022 and August 2022.

The aim of the work done by the group was to collect the requirements from sponsors (industry and CROs) for the clinical sites to participate in paediatric clinical trials. The requirements were divided into four sections: investigator and supporting staff qualifications, site infrastructure requirements, administrative cycle times, and decentralised processes.

The survey was followed up with optional interviews. The results were summarised using descriptive statistics, obtaining overall 33 responses from 21 countries as well as 7 virtual interviews.

The results showed that sponsors had the same expectations in terms of required experience for the principal investigator as well as for sub-investigators, namely that they required a site investigator to be a medical doctor having at least 1 to 2 years of experience and having performed at least 3 to 5 paediatric clinical trials. For the coordinating staff less years of experience and no previous involvement in paediatric clinical trials were needed. The documentation required to prove experience included a curriculum vitae (CV), a certificate of attendance of Good Clinical Practice (GCP) training, license, list of clinical trials performed, certificate of biospecimen training and a financial disclosure form. Regarding infrastructure requirements, laboratory and pharmacy services as well as reliable IT infrastructure were considered essential, while imaging services, a dedicated paediatric unit and paediatric appropriate hospital level clinical environment were only considered optional. Moreover, in terms of timelines, on average 90 days was considered an acceptable timeframe for the contract revision with a budget finalisation within 60 days, and an average timeline of 60 days was found appropriate for the institutional review board (IRB)/research ethics board (REB) revision. In addition, some remote capabilities were considered required for sites to conduct decentralised clinical trials. In general, the requirements for infrastructure, staffing and decentralised processes were considered trial and population dependent.

During follow-up interviews the main challenges for conducting paediatric clinical trials at a site were elucidated, such as recruitment issues, lack of resources, time pressure and lack of knowledge of clinical trials and regulations. The interviews also brought to light that paediatric research networks could have a role in increasing site attractiveness for global study participation e.g. via standardisation of site capabilities including training, providing recruitment tools and templates, building on existing efforts to reduce study start up timelines.

## *Results from the internal site survey (c4c)*

Sabrina Pierre presented the results of the work of the c4c consortium, a collaborative network for European clinical trials for children, composed of academic partners, pharmaceutical companies, national hubs and clinical sites, specialty networks and other partners. This survey was conducted between August 2022 and September 2022.

The aim of the work done by the group was firstly to define c4c site standards as a core set of pre-agreed norms or criteria against which the sites involved in clinical trials could be evaluated, and secondly to define the purpose and use of the defined site standards, considering the advantages that they will bring to the sponsors and sites (e.g. ensuring certain site capabilities are reached, enabling accurate feasibility assessments, improving adherence to paediatric studies, decreasing site variability, and increasing trial performance). Moreover, site standards could also serve as a minimum criterion to be recognised as a c4c site, depending on the fulfilment of the minimum criteria, and provide pathways to further site development.

A sites standards questionnaire was developed using a structured approach, with input and review by a working group of c4c national hubs and exemplary research sites. The questionnaire, which was distributed among all c4c sites, covered 8 domains, 4 of them overlapping with the work of the Enpr-EMA working group (training, resources and staff, facilities and technical equipment, contracting and regulatory processes). Preliminary results were shown based on 116 responses from 250 sites in 19 countries.

In the majority of the trial sites, there was a process in place to identify potential trial subjects, either by use of electronic files, databases or based on the clinical team's knowledge. There were also quality tools in place to support the quality management process, mostly standardised operational procedures but also quality manual, corrective and preventive actions, quality control and audits. Regarding facilities and technical capabilities, the answers were heterogeneous almost all of the sites have locked refrigerators/freezers with temperature control and controlled access to the investigational medicinal products as well as to case report forms. Results on timelines to support regulatory submissions were shown.

## *Report from the break-out groups, Session I*

To foster discussions, the audience was divided into four break-out groups. Each group discussed the same five pre-created questions.

During the first break-out session the following questions were discussed:

1) Is there a need to identify/develop quality criteria for clinical sites to participate in paediatric clinical trials?

2) To what purpose would quality criteria be used by the different stakeholders (sites/networks/industry/academic sponsors)?

There was a general agreement on the need to define quality criteria for clinical sites to participate in paediatric clinical trials. Participants indicated that a common set of standardised, agreed and publicly available criteria would help sites to fulfil the requirements. However, the terms "guidance" or "recommendations" were found to be more appropriate to be used in this context to cover global developments as the term "standards" might be understood as referring to some country specific characteristics. Moreover, it was considered that only minimum criteria should be defined, identifying the needs and the achievable objectives, which should also be measurable and controlled.

It was highlighted that the availability of such pre-defined criteria could help to accelerate the set-up of paediatric trials, to facilitate the feasibility assessment process, and to ensure the maintenance of high-quality trial conduct.

Furthermore, it was noted that to be able to develop trial sites in order to reach these criteria in a real-life setting, resources, time and training would be needed. Networks and industry could play an important role in this development process. As a caveat it was mentioned that differences between trials in terms of design complexity, study population and applicable jurisdiction would need to be taken into consideration. Finally, it was commented that the ICH Guideline for Good Clinical Practice (E6) also sets out some quality criteria for clinical trial sites and would thus need to be taken into consideration.

## *Report from the break-out groups, Session II*

During the second break-out session the following questions were discussed:

3) How could industry/academic sponsors/networks and sites discuss and agree on quality criteria?

4) How could sites be supported to achieve quality criteria?

5) Is it necessary to have sites accredited, and if so how could/should this be done?

It was agreed that coordinated efforts, allowing flexibility and open communication were needed in order to discuss the definition of the quality criteria, and that the discussions should involve all stakeholders, including representation of different types of sites, patients, industry and CROs, and possibly representatives of associations like the European Forum for Good Clinical Practice (EFGCP) who could collaborate on the drafting of specific guidance/recommendations. The role of paediatric research networks was highlighted as potential mediators in this process.

It was indicated that the definition of these quality criteria should allow for adaptations to specific areas, as differences could apply depending on diseases, trial types and patient ages.

Furthermore, participants agreed that there would be a need for education and training for the sites to support them in achieving these criteria. A step-by-step plan performing an initial diagnosis, defining the required measures and then identifying how to advance the development would be needed, along with the establishment of a collaboration between sites on specialised groups. Mentorship programmes that could support knowledge transfer between sites were found to be essential measures for the sites to achieve certain quality criteria. Moreover, on national levels, the creation of funds and exchange programmes for site staff was advocated, along with the support from the networks and sponsors.

Regarding the possibility of having sites accredited by some official body different views were shared. Some participants said they would find accreditation in terms of the fulfilment of general criteria useful for sponsors in order to facilitate feasibility studies and to increase the sites' motivation. Others highlighted the difficulties of such a process considering the uncertainties regarding the identification of a body that could perform such an accreditation process, the procedure to make these accreditations

globally recognised, and the negative implications for a site that does not achieve such accreditation, as well as the resources, time and budget that sites would need to invest in the process to maintain the accreditation status.

## *Conclusions and action points*

There was general agreement on the need to define quality and some kind of standardised criteria, with the aim to accelerate trial set-up, support site selection, ensure high-quality data and to enhance the development of sites in a collaborative process with open discussions and involving all stakeholders including sites, patients, industry and CROs, and possibly regulators.

The efforts should be focused to obtain a flexible, harmonised and global understanding that could be accepted by all the parties, avoiding potential burden to the sites.

With the aim to set up a list of criteria, three action points were identified:

1) Definition of quality: Identify different understandings of quality, scope and sources

2) Identification of standards

3) Application of standards

To further advance these action points, one or more working groups will be created to work on the definition of quality criteria, the mapping of the existing standards and ultimately on the implementation of the new recommended quality criteria/standards. Participants that expressed interest to be part of such working group(s) will be invited in a follow-up meeting in early 2023 where further actions will be decided upon.

The meeting was concluded by the chairs thanking all participants for their contributions.

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**Speakers:**

- Attar, Sabah. Conect4children Network Infrastructure Office, University of Liverpool, UK
- Egger, Gunter. European Medicines Agency
- Fernandes, Ricardo. Conect4children National Hub lead, Network Infrastructure Office and STAND4kids (Portuguese paediatric research network)
- Geest, Tessa van der. Pedmed-NL - Medicines for Children Research Network Netherlands
- Lacaze, Thierry. MICYRN (Maternal Infant Child and Youth Research Network, Canada)
- Lepola, Pirkko. Enpr-EMA and FINPEDMED (Finnish paediatric research network)
- Pierre, Sabrina. Conect4children and PEDSTART (French paediatric research network)
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- Stewart, Breanne. MICYRN (Maternal Infant Child and Youth Research Network, Canada)
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