Quality criteria for paediatric clinical trial sites – an Enpr-EMA initiative

Working group on criteria for paediatric clinical trial site standards

2024 annual meeting of Enpr-EMA

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October 1st, 2024

Agenda for today

c4c & Enpr-EMA workshop on site standards

Challenges and gaps in paediatric trials

Objectives & scope

Working Group methodology

Results

Conclusions

Discussion

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European network of paediatric research at the European Medicines Agency

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c4c & Enpr-EMA workshop on sites standards

On Oct. 3, 2022: Workshop on paediatric site quality requirements co-organised by Enpr-EMA and conect4children (c4c) ➔ Identified Action Points

- Definition of quality of paediatric trial sites: how can conduct be optimised, what matters to different stakeholders, including children, young people and their families
- Identification or mapping of existing quality standards
- Implementation of the recommendations for quality criteria and or standards: Roadmap – how to? Publication of a recommendation document

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COLLABORATIVE NETWORK FOR EUROPEAN CLINICAL TRIALS FOR CHILDREN

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

Challenges and gaps in paediatric trials

- Known barriers to the conduct of paediatric clinical trials, leading to delays in site identification, setup & recruitment
- Research infrastructure that is limited and not always fit for purpose
- Sites delivering paediatric clinical research need to meet unique requirements to ensure quality and performance
- Individualized and fragmented requirements by sponsors are compounded by the multinational and multijurisdictional nature of many paediatric trials
- Heterogeneous landscape of site capabilities and development stages, across different settings, capacity, experience, and legal and regulatory context

Objective

Deliver combined findings and recommendations

Two diverse* working groups of stakeholders were set up to:

WG 1: Develop a common understanding of what quality of paediatric sites means with regards to paediatric clinical trial sites and what matters to the different stakeholders involved in the conduct of a clinical trial, including children and their parents/caregivers

WG 2: Identify/map existing quality criteria/standards for paediatric sites

Scope for this work:

Paediatric site standards across jurisdictions, paediatric age ranges, and types of sponsor

The work intends to drive opportunities for rollout of site standards and improvement of sites, with adequate resources

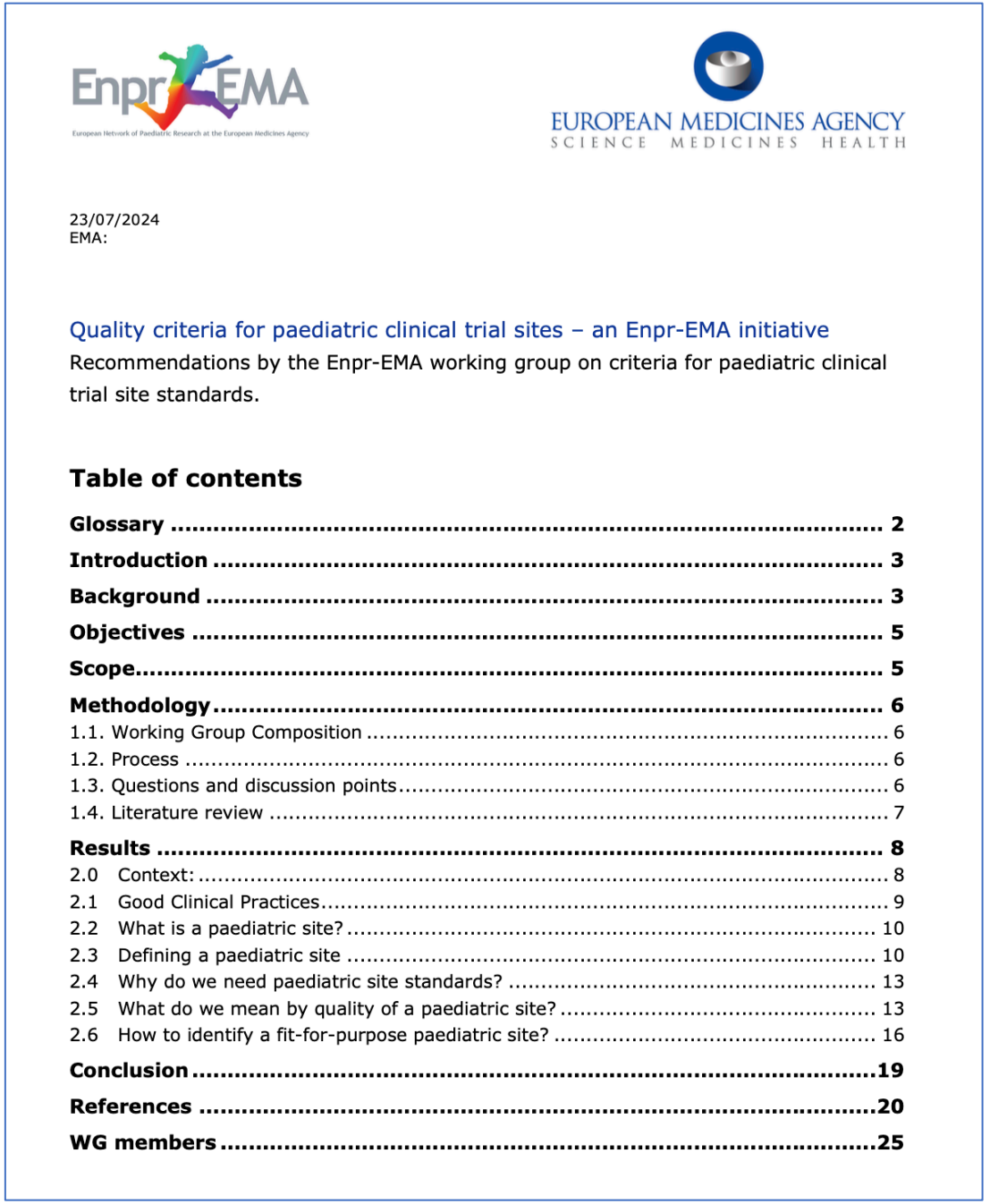
** 27 representatives from patient groups, site networks, academic institutions, industry sponsors, contract research organizations, regulatory bodies, non-profit organizations and c4c from Europe, Canada and the USA*

Working Group Methodology

Process	Questions and Discussion Points	Literature Review	Findings & Recommendations
Adhered to working methods and instructions outlined by the EMA for multistakeholder Working Groups	*Relevant input to work (site quality and rare diseases, paediatric specialties, research networks, innovative treatments…);*	*Extensive literature search and thematic mapping*	*Alignment across WGs for synergy*
Regular separate remote meetings	*Focused on specific questions*	*Selected sources of information: survey conducted by Enpr-EMA international working group to understand how drug developers and CROs select investigational sites*	*Input GCP IWG, Enpr-EMA Chairs*
Interim updates and draft reports provided throughout the year	*Identified relevant evidence and scope*	*Work by the c4c consortium to identify standard criteria for the clinical sites delivering trials in a large clinical trial network, including preliminary results from a c4c questionnaire on site standards*	*Compilation into one joint document*

Results

- A document focusing on 4 questions:
  - What is a paediatric site?
  - Why do we need paediatric site standards?
  - What do we mean by quality of a paediatric site?
  - How to identify a fit-for-purpose paediatric site?



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23/07/2024
EMA:

Quality criteria for paediatric clinical trial sites – an Enpr-EMA initiative

Recommendations by the Enpr-EMA working group on criteria for paediatric clinical trial site standards.

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Context & GCP

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31 August 2020
EMA/56009/2019

Preparedness of medicines' clinical trials in paediatrics

Recommendations by the Enpr-EMA working group on trial preparedness

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COLLABORATIVE NETWORK FOR EUROPEAN CLINICAL TRIALS FOR CHILDREN

EUCT

ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GOOD CLINICAL PRACTICE (GCP)

E6(R3)

Draft version
Endorsed on 19 May 2023

Final version
Adopted on 18 August 2017

HMA Heads of Medicines Agencies
European Commission
EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

RECOMMENDATION PAPER ON DECENTRALISED ELEMENTS IN CLINICAL TRIALS

Version 01, 13 December 2022

Draft agreed by DCT project team (experts from Clinical Trial Coordination Group, Clinical Trial Expert Group, EMA scientific committees, EMA working parties, and EMA staff)	December 2022
Draft agreed Clinical Trial Coordination Group	December 2022
Draft agreed by Clinical Trials Expert Group	December 2022
Draft agreed by GCP Inspector Working Group	December 2022
Adopted by ACT EU Steering Group	December 2022

For questions related to this document, please write to secretariat of CTCG: ctcg@hma.eu

23 May 2022
EMA/298712/2022

Complex clinical trials – Questions and answers

Version 2022-05-23

Draft agreed by Drafting Group experts (from EMA scientific committees, EMA working parties, EMA staff and Clinical Trials Coordination Group)	May 2022
Draft agreed by Clinical Trials Coordination Group	May 2022
Draft agreed by Clinical Trials Expert Group	May 2022
Adopted by ACT EU Steering Group	23 May 2022

Keywords	Clinical trial; complex clinical trial; clinical trial authorisation application; marketing authorisation application; trial design; trial analysis; Clinical Trials Regulation; master protocol; platform trial; biomarker; adaptive design; modifications; Bayes; control data; transparency

For questions related to this document, please write to ACTEU@ema.europa.eu.

Key findings 1: What is a paediatric site?

Defining a paediatric site:

- *A core definition of a paediatric site is a specific location where drugs, medical devices, and other therapeutic interventions are evaluated in paediatric participants, that may include a specific or a broader age spectrum from neonates up to less than 18 years of age*
- *Paediatric sites are composed of a team led by a principal investigator, usually a paediatrician, with appropriate location(s)/facility(ies) to execute the trial according to the protocol*
- *The evolving nature of a site across the trial lifecycle should be kept in mind (e.g., considering trials across levels of care, innovations such as decentralized elements in clinical trials).*
- *These distinctions however do not change site and investigators responsibilities under GCP guidelines, laws, and regulations*

Key findings 2: Why do we need paediatric site standards?

Because:

We need to identify sites that are most likely to conduct a trial on time, on budget and according to the specifications outlined by the sponsor, regulators, and GCP

Therefore:

- *Paediatric standards should reflect the level of the quality of a paediatric site*
- *Recommendations should facilitate site selection and initiation of paediatric trials, as well as support the development of paediatric research infrastructure, without placing unwarranted burden of requirements to existing regulations for trial sites*

Key findings 3: What do we mean by quality of a paediatric site?

- Quality of a site relates to different concepts and approaches: trial protocol/goals, GCP, capacity, preparedness, performance, quality domains and measures
- Factors that may influence and are interconnected with quality requirements
- Results from the Enpr-EMA survey and c4c questionnaire
- Results from the literature review

Category Headings	Descriptions & Queries
Staff Experience	Does the staff have the appropriate experience in studies & years? Are they adept at conducting trials or willing to learn?
Requirements (Training)	Is there adequate training? Access and review of relevant guidance documents
Documentation (Quality Management)	Presence of an internal Quality Assurance procedure Are evaluation processes established?
Infrastructure	Is the environment child-friendly? Required equipment and services for study Staff adept at working with children and families
Cycle Times (IRB, Contracts, Budget)	Use of standard templates (agreements, indemnities, etc.) Personnel for budget negotiations with sponsors
Patient Engagement	Conduct of patient orientation Provision of general information to participants Relevant participant material availability

Key findings 4: How to identify a fit-for-purpose paediatric site?

- *All sites that set out to enrol children and young people, whether they are paediatric-only or also (or mainly) recruit adults, should meet the same specific site requirements; there should be no opportunity to downgrade those requirements in case of "adult"- mainly sites*

- *There are examples of sponsor or network-driven assessments of known and recognised paediatric sites of excellence (with existing frameworks to identify these sites)*

- *Recommendations with illustrative examples*
  - Qualifications and experience rolling into preparedness & performance
  - Facilities
  - Site performance
  - Quality management
  - Patient engagement

Conclusions

- *GCP and regulatory requirements dictate minimum standards that can be expected of all clinical sites involved in a clinical trial, there are additional considerations beyond these standards that should be implemented for paediatric sites*
- *Valuable to implement a methodical approach in the work of identifying and mapping quality criteria in paediatric clinical trials*
- *Tools that build on, but go beyond, ICH-E6(R3) GCP guideline may provide a roadmap towards more exemplary practices in paediatric clinical trials*
- *The establishment and adoption of a core set of site preparedness practices and quality assessment criteria that are applicable across sites, irrespective of size and geography or clinical specialty, should help streamline the process of site assessment for organizations, research teams, sponsors, and participants. Well established paediatric research networks could play a key role in this regard*

Italian Journal of Pediatrics

LETTER TO THE EDITOR Open Access

The Investigational Clinical Center: a clinical-supportive and patient-centered trial unit model. Ten years of experience through normal and pandemic times of a large pediatric trial center in Italy

Giuseppe Pontrelli[1*], Marco Ciabattini[2], Franco De Crescenzo[1,3], Isabella Biondi[1], Rossana Cocchiola[1], Giorgia Copponi[1], Claudia Frillici[1], Francesca Molinari[1], Francesca Rocchi[4], Alessandra Simonetti[1,5], Paolo Rossi[1,5] and Susanna Livadiotti[1]

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https://doi.org/10.1007/s43441-022-00382-4

DIA

REVIEW

Developing a More Tailored Approach to Patient and Public Involvement with Children and Families in Pediatric Clinical Research: Lessons Learned

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Received: 4 October 2021 / Accepted: 24 January 2022 / Published online: 19 February 2022

Abstract
Listening to, and acting on, the voices of children and families during clinical research and innovation is fundamental to ensuring enhanced pediatric health care, medicines development, and technological advances. While this is often discussed as an important step in ensuring patient-centered care, involving children and families across the life cycle of clinical research is not currently routine. The pediatric research community needs to address how to meaningfully involve children and families if they are to succeed in designing clinical research that suits the needs of pediatric patients and their families. This paper describes how an international community working under the umbrella International Children's Advisory Network (iCAN) and European Young Person's Advisory Group Network (eYPAGnet) has involved children and families in the design and delivery of pediatric clinical research. It offers practical solutions through various case studies assessed against seven patient engagement quality criteria within the Patient Engagement Quality Guidance (PEQG) tool, highlighting some of the lessons learnt from involving and engaging with children and families across different stages of clinical research, including pediatric trials for drug development programs.

Keywords Pediatric clinical research · Children · Families · Involvement · Patient-centricity

Therapeutic Innovation & Regulatory Science (2024) 58:953–964
https://doi.org/10.1007/s43441-024-00663-0

DIA

ORIGINAL RESEARCH

Harmonizing Quality Improvement Metrics Across Global Trial Networks to Advance Paediatric Clinical Trials Delivery

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Received: 20 December 2023 / Accepted: 1 May 2024 / Published online: 20 June 2024

Abstract
Background Despite global efforts to improve paediatric clinical trials, significant delays continue in paediatric drug approvals. Collaboration between research networks is needed to address these delays. This paper is a first step to promote interoperability between paediatric networks from different jurisdictions by comparing drivers for, and content of, metrics about clinical trial conduct.
Methods Three paediatric networks, Institute for Advanced Clinical Trials for Children, the Maternal Infant Child and Youth Research Network and conect4children, have each developed metrics to address delays and create efficiencies. We identified the methodology by which each network identified metrics, described the metrics of each network, and mapped consistency to come to consensus about core metrics that networks could share.
Results Metric selection was driven by site quality improvement in one network (11 metrics), by network performance in one network (13 metrics), and by both in one network (five metrics). The domains of metrics were research capacity/capability, site identification/feasibility, trial start-up, and recruitment/enrolment. The network driven by site quality improvement did not have indicators for capacity/capability or identification/feasibility. Fifteen metrics for trial start up and conduct were identified. Metrics related to site approvals were found in all three networks. The themes for metrics can inform the development of 'shared' metrics.
Conclusion We found disparity in drivers, methodology and metrics. Tackling this disparity will result in a unified approach to addressing delays in paediatric drug approvals. Collaborative work to define inter-operable metrics globally is outlined.

Next steps and future directions

- *Circulate draft report to other Enpr-EMA networks for comments after annual meeting*
- *Compile feedback into final draft report*
- *Draft posted on Enpr-EMA website for a one-month public consultation*
- *Paper for publication (journal profile: well reputed, broach reach, peer-reviewed and open access)*
- *Dissemination and awareness, aligned with existing initiatives and other stakeholders*

Discussion

- *Dissemination and training – how do we reach the audience and who is the audience?*
- *Better medicines for babies, children and young people – is this work a step on the road?*
- *What is the selling point?*
- *Yes, it is possible to map existing quality criteria/standards for paediatric sites – how to proceed*?

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Thank you to all members in WG 1 & 2

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