3 September 2019
EMA/56009/2019 Corr.1[1]

Preparedness of medicines' clinical trials in paediatrics

Recommendations by the Enpr-EMA working group on trial preparedness

Enpr-EMA invites relevant stakeholders, including clinical trial sites, investigators, networks, sponsors, patients and anyone involved in the preparation and conduct of paediatric clinical trials to send comments on this draft framework on trial preparedness to enpremasurveys@ema.europa.eu **by 15 November 2019**.

The aim of this consultation is to identify potential gaps and present a more comprehensive view.

Enpr-EMA will publish an updated version of the framework after the public consultation.

[1] Information on public consultation was added on 12 September 2019

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

Glossary

Term	**Definition** (used in this document)
Clinical diagnosis	A term that is used pragmatically by clinicians or clinical researchers to label a disease in order to guide practice or to capture exposures or outcomes in research: may not be consistently defined or applied
Drug development plans	A generic term to mean Paediatric Investigation Plans (PIP), Pediatric Study Plans (PSP) and similar documents.
Preparedness concept	A detailed description of trial preparedness that is based on explicit data sources and/or explicit reasoning, and can be modified iteratively in the light of experience. A preparedness concept could allow data-driven discussions between sponsors and regulators.
Sponsor readiness	A collection of measures taken by a sponsor to allow them to open and conduct a study while respecting governance norms and promoting efficiency
Study design	The selection of methods to answer a research question reliably (or set of research questions) in a manner that minimises the burden on study participants
Trial preparedness	A structured assessment of the key factors that could increase the likelihood of a smooth and timely course of a paediatric clinical trial, integrating information from multiple stakeholders on what is possible within individual studies and/or a development plan.

1. Aims and Scope of this document

This document was developed by a Working Group of the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) [2] and sets out recommendations for discussions about trial preparedness in paediatrics.

We define trial preparedness as a structured assessment of the key factors that could increase the likelihood of a smooth and timely course of a paediatric clinical trial, integrating information from multiple stakeholders on what is possible within a development plan[3] and/or individual studies. This includes several activities that are labelled as study "feasibility". However, here a global assessment of all aspects of trial preparation is addressed which goes beyond "feasibility" aspects and therefore this term is not used.

The design of drug development plans and individual studies in paediatrics overlaps with preparedness to some extent. By design, we mean the selection of methods to answer a research question (or set of questions such as biostatistics, Model Informed Drug Discovery and Development (MID3), extrapolation). Design needs to take account of the specificities of infants, children and young people while maximising the use of extant data (including preclinical data such as toxicity) and minimising the burden of research in these populations. There are many sources describing details specific to the design of paediatric development programmes and studies. Section 5 on methodology provides an overview of the activity undertaken by the Enpr-EMA working group on trial preparedness in collecting stakeholders' points to consider during preparation of a study as basis for this document.

Trial preparation should be initiated before and conducted in parallel to the designing of the development plan and the individual studies, and in parallel to sponsor readiness.

The recommendations in this document target both sponsors as well as principal investigators and trialists. However, it should be noted that this document does not describe all aspects of 'sponsor readiness', such as operational aspects within sponsors and intermediary organizations, e.g. Contract Research Organizations (CRO), or strategic factors, such as patient need and economic opportunities.

Furthermore activities to support marketing of products using data about market size are out of scope of this document.

Standards for site readiness and practical arrangements for sites and participants in public and patient involvement relating to the preparation of programmes and studies are under development by other initiatives.

2. Need for good preparedness of clinical trials in children

Paediatric drug development plans and studies can be difficult to carry out for many reasons which have been analysed in the literature. The survey specifically mentioned the often limited number of eligible paediatric patients rendering a timely study completion unlikely and requiring further considerations with respect to study design. Patients may be reluctant to enrol into a trial because of the burden which goes along with type and number of assessments, that may not be acceptable to participants and/or their families. The extent of these difficulties varies between studies. According to the results of our survey (see 'Methodology') sites often over-estimate what is possible and it was

[2] Membership of the Working Group can be found in the following link https://www.ema.europa.eu/documents/other/mandate-european-network-paediatric-research-european-medicines-agency-working-groups_en.pdf

[3] We use the term "development plan" as a generic term to mean Paediatric Investigation Plans (PIP), Pediatric Study Plans (PSP) and similar documents.

reported that sponsors, regulators and ethics committees can disagree about what should be done or is possible during drug development.

Study conduct is often improved iteratively, by learning during the execution of a study.

The perspective of participants, and their advocates, can make significant contributions to the design of the development plan and study preparation. Considering patient needs and experience can help to optimise the whole trial design and reduce amendments, delays and further expenses. However, at present, this perspective is not always included in the preparation of programmes or studies.

Insufficient consideration of these complexities at the planning stage of a trial leads to delays in the delivery of study results or sometimes even failure of the trial.

For studies conducted with the aim to be used for regulatory purposes, i.e. a paediatric label or for authorising a paediatric indication, it is necessary to identify and enrol a patient population that is likely to benefit from the product in order to be able to demonstrate an effect while determining an acceptable safety profile. The available paediatric study population is often small especially in rare diseases. The number of available patients is further decreased by exclusion criteria (e.g. relating to safety or the risk of drug-drug interactions). If these constraints are not properly factored into the calculation, sites may overestimate their capacity to recruit patients. Paediatric data on natural history and epidemiology are often very limited and further research in this field is urgently needed with adequate allocation of resources. Systematic literature reviews might help to identify variability in endpoints or difficulties in their measurements upfront but are not universally conducted. Existing patient registries might be consulted or built upon by integrating further prospective data in order to increase the knowledge base of the natural history but this is not often done.

There is often no resource allocated to support trial preparation.

3. Trial Preparedness

These problems can be addressed by using all available data to estimate what is possible using a structured approach. Preparation cannot remove all of the difficulties or estimate achieved patient numbers with complete accuracy. However, a well-prepared, well-designed trial is likely to require fewer changes during its course, be run in a shorter timeframe and achieve expected objectives.

3.1. Principles of good preparation

3.1.1. Collect relevant information

1. Develop an understanding of the context for planning of the study [how many sites (with facilities required by the trial), how many participants at each site, costs of the study] and implementation of the study that is a combination of qualitative and quantitative information derived from multi-method assessments (questionnaires, site visits, broader discussion).
2. Contributions to preparedness can be data, estimates, judgments or opinion. These contributions need to include an explicit statement about the source of information, the basis for estimates and an indication of the extent of confidence of those estimates. Justifications of judgments or opinions need to be explicit. All contributions to preparedness should be verifiable.
3. Look for sources of data and state methods used to find information (identify sources according to established levels of evidence)

    a) Consistent multisite data

i. Literature data on disease prevalence (including reviews, case reports, disease registries as applicable)

ii. Population based registry

iii. Patient registry

iv. Drug registry

v. Real life data repositories, electronic health records

b) Inconsistent multisite data

i. Site data, spliced together

c) Opinion from experts based on experience

d) Opinion provided by a small number of opinion leaders

4. Use information from other studies (RCTs , case-control studies as applicable) to inform preparedness when possible
5. Take into account the available data on the natural history (including prognosis) of the condition and relevant subsets of the condition under investigation when assessing the number, location and readiness of potential participants
6. Develop awareness of other studies that may lead to competition for resources or recruits, or opportunities for co-enrolment
7. Variation in clinical practices across countries and between therapeutic areas should be considered during preparation as it may have an impact on the study conduct later on.
8. Take account of clinical reality
    i. Standards of care, existing treatments, and differences between centres
    ii. Relationship between standards of care and research
        1. Differences between medicines and procedures used in the trial
        2. Will standard care and research procedures be conducted in the same location?
    iii. Is there a need for post-study treatment access and how will that need be met?
9. Identify the 'critical to quality factors' for the study and the risks that threaten their integrity, determine the impact of those risks and decide whether they can be accepted or how they should be mitigated.
10. Identify ethical and legal issues of the research and responses to potential questions / objections.
11. Take account of the regulatory environment and requirements for drug development.
12. The social-economic status of the research locations should be taken into account as paediatric clinical trials often need to be performed at an international level. In such cross-cultural interactions, ethical, social and legal issues may have different resolutions depending on the resources available and locally prevalent cultural assumptions.
13. Burdens on participants and their families
    i. Attendance at study visits (time, cost, inconvenience)
    ii. Impact on school and leisure activities

iii. Parent burdens of a child's participation in a trial including effects on work including the possibility to reimburse costs

14. Time course of the trial

    i. Assess local timelines for approvals

        1. Clinical trial authorisation

        2. Ethics review

        3. Site approval

    ii. Do not assume a linear rate of recruitment, particularly at site opening

15. Consider need to gather data that supports health technology assessment and reimbursement decision, integrated with, or in parallel to, clinical development

3.1.2. Involve relevant contributors

16. Involve sites and networks (including clinical and methodological expert groups), patients and Patients Advocacy groups to promote the quality of protocol and process design, thereby increasing the fitness for purpose of the clinical study. To this end, these groups should be approached as early as possible in the process of study planning and certainly before key elements of protocols are defined to elicit:

    a) Number of potential participants

    b) Burden of study compared to standard clinical practice and to other research projects

    c) Facilities

    d) Relationships between sites that recruit participants and other health care facilities (continuing care sites, specialist centres that refer participants for research projects, family doctors)

17. Seek regulatory input early (for example on study design or regulatory requirements)

18. Integrate input from potential participants[4], families and advocate groups as early as possible bearing in mind Conflict of Interest aspects

    a) Likelihood of recruitment (acceptability of protocol, relevance of endpoints)

    b) Burden of study compared to standard clinical practice with the aim of study protocols which are as close to the routine care as possible

    c) Facilities

    d) Impact on daily life (school, work, travel, other family members)

19. Ensure transparency about any real or potential conflicts of interest.

20. Networks, sites and investigators should be explicit about the source of resources they receive.

21. Ideally, there is global alignment of the contributions to preparedness, but equally the contributions should reflect the diversity in elements of trial preparedness needed to develop an appropriate development plan.

[4] Participant views include views of parents and other carers expressed directly or through advocates or representative organizations. The views of potential participants and families are best gathered through groups such as Young Persons' Advisory Groups who provide training, facilitation and support for members in a conflict-of-interest free zone, rather than ad hoc from individuals or through sponsor-convened sessions.

3.1.3. Follow a structured process

22. Demonstrate that due care has been taken to avoid a futile trial.
23. Identify key influences on preparedness, e.g.
    a) Likelihood of recruitment
    b) Likelihood of retention until key study assessments are done
    c) Data and documentation completeness (ensure adequate data protection)
24. Construct flow diagram from epidemiology to eligibility (see Figure 1 Components of a flow diagram about participant availability during preparation of a medicines development plan) and from eligibility to contents of locked database.
25. Conduct clinical trial simulations: in silico and in clinical simulation facilities
    a) Impact of changes to protocol (change in dosing regimen, sampling scheme)
    b) Impact of approval timelines for amendments to protocol
    c) Sensitivity analysis for recruitment
    d) Model dropouts to simulate study withdrawal and do a sensitivity analysis for dropout
26. Prepare and test all study procedures, including recruitment, consent and assent, participants' retention and stopping rules, for example through clinical trial simulation of a range of scenarios.
27. Justify why the sample size required by the study design is compatible with the number of participants that can realistically be expected to be recruited to the trial. Ideally, the study design should be selected to meet the opportunities provided by the pool of available participants. In any case other innovative methods should be explored (always consider extrapolation or modelling and simulation if applicable).
28. The information gathered to support preparedness should be linked clearly to the development plan / study, allowing stakeholders to assess how changes in assumptions, estimates and judgments affecting the development plan / study.
29. Consolidate this information into a structured justification that the trial has been prepared adequately (see Table 1).
30. Use information to inform risk management
    a) Hazards, assessment
    b) Safety Reporting and burden it entails (Documented PV Plan)
    c) Mitigation
31. Conduct ongoing review of preparedness: regular review during a programme or trial to check the assumptions and data used to develop preparedness, and trial performance so that any necessary alterations can be made in trial delivery (e.g. number of sites) or design.

3.1.4. Use appropriate resources

32. Expend adequate effort on preparation that is proportionate to its benefits. Assurance of trial preparedness needs to be efficient without undue increase in documentation needs.

33. Good communication between all parties involved including investigators, patient organisations and experts in the disease as well as regulators early during the planning of the development programme. Clear lines of communication between Sponsor, experts and clinical sites during the design phase are essential. Complete information about the context for a programme/study should be provided (within appropriate confidentiality arrangements) so that contributors can effectively feedback on preparedness aspects, in terms of both benefits and risks arising from their contribution. Feedback to the contributors about the value of their input is useful.
34. Ensure clear definition of roles and responsibilities during preparation in a similar way to the clear definition of roles and responsibilities during the execution of the clinical trials including data ownership and future dissemination of results. Clear lines of communication are necessary between sponsor and/or intermediary organization and sites (preferably through shared infrastructure such as a network).
35. During the preparation of development plan/studies, groups of experts or investigators with clear governance, composition and accountability are to be preferred to individuals.
36. Sites and networks need to accept responsibilities and work towards quality and reflect regulatory and commercial reality. Motivation of investigators is important even for studies that could be considered less "cutting-edge".

It is noted that from a clinician's perspective, remuneration for well-conducted preparedness activities facilitates, from an operational perspective, the high-quality conduct of studies in terms of recruitment figures and produce complete data, thereby avoiding expenditure for poorly prepared plans and studies.

3.2. Approaches to prepare plans and studies

3.2.1. Structured justification of adequate preparation

See Table 1 for an outline of a document that provides an explicit description of trial preparedness.

The description of preparedness – one might call it a preparedness concept – needs to be based on explicit data sources and explicit reasoning, and can be modified iteratively. A preparedness concept could allow data-driven discussions between Sponsors and regulators. This will contribute to the development of realistic expectations and reduce the risk of infeasible trials. An explicit preparedness concept could promote the development of common ground during discussions between Sponsors, researchers and regulators. Proposals to handle points of difference between Sponsors and regulators could be evaluated according to explicit criteria during the preparation or conduct of development plans/studies. These evaluations could prompt iterative, well-justified changes to the preparedness concept and design of development plans/studies

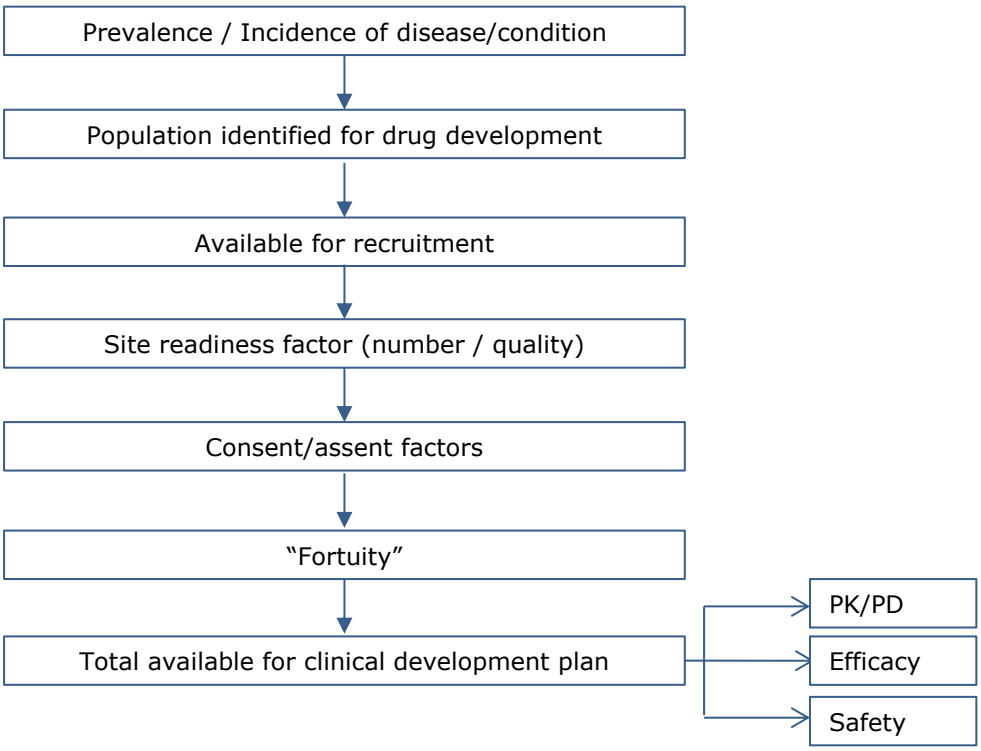

Figure 1 Components of a flow diagram about participant availability during preparation of a medicines development plan

It is important to be aware of potentially different uses of the same terms for conditions and diseases in different contexts where different classification systems are used. Terms used by clinicians for example do not necessarily have identical definitions, e.g. for "asthma", so it is important to be specific about the term that is used. Other classification systems have been for example developed for the area of reimbursement of health care costs. For regulatory purposes e.g. for safety reporting MedDRA[5] is used which is one of the classification systems which could also be used as a guide to determine conditions to be waived in the context of the EU Paediatric Regulation. The goal is that the final approved wording in the product information (summary of product characteristics (SmPC) and package leaflet (PL)) reflects a clinically meaningful indication.

The number "available for recruitment" is the number of, in this case children, who have the disease/condition, which depends on its nature and prevalence, and the proportion of patients who are not excluded (for example they are not treatment naïve or not in terminal illness) depending on the product and condition, or those who have multiple conditions or morbidities that limit the studies they can contribute to (e.g. renal failure).

"Fortuity" captures the concept that things often do not go as planned due to a multitude of reasons. Even with skilled management there are always events that are beyond the control; these unexpected events combine to have effects that are difficult to specify in advance and therefore this situation has to be made part of the plan.

[5] Medical Dictionary for Regulatory Activities (MedDRA), https://www.meddra.org/ (accessed 8/5/2019)

Table 1 Exemplar of a structured outline of a preparedness concept

1) **Statement of starting point:** therapeutic need; clinical indication; aim of plan/study including regulatory purpose; scope of information needs (as laid out in the PIP/PSP)

Subsequent steps are needed for all studies; for plans each study should be considered and a synthesis presented.

2) **Availability of participants**
   a) Patient flow diagram annotated with sources of information and estimates of variation, particularly at key decision points
   b) Sensitivity analysis of patient availability
3) **Sites**
   a) Availability of suitable sites with relevant expertise both in the area of interest and also in clinical research.
   b) Extent of modifications needed to sites
   c) Estimates of participants at each site that can be validate
   d) Account for other competing trials
4) **Completeness of data**
   a) Retention of participants, based on acceptability of key study assessments
   b) Sensitivity analysis of data completeness
5) **Implications**
   a) Trade-off between need for information and availability of participants
   b) Areas of concern, anticipated weak links in the preparation
   c) Actions required to optimize setup and conduct
   d) Actions required to maximize recruitment and retention

An explicit, justified trade-off should be made between participant availability and the need for information that is scientifically robust and which meets regulatory requirements, see Table 2.

Table 2 Trade-offs between demand for information and supply of participants.

		Need for information		
		High	**Low**	**Unclear**
Availability of potential participants	**High**	Consider traditional development design as necessary, with appropriate numbers of recruits leading to high confidence about efficacy/safety	Match design to information needs; limit numbers to meet information needs and generate high confidence about efficacy/safety	Plan as if participants available
	Low	Maximise recruitment and recognize limits to confidence about efficacy/safety, explore innovative study designs and possibility to extrapolate	Match design to information needs; limit numbers to information needs; Define required confidence about efficacy/safety	Include pilot studies and revise plans quickly when data is available
	Unclear	Include natural history / registry studies, before the programme is started, and revise plans quickly when data is available		

High information needs: new product, new class; new indication; no, limited or sub-optimal treatment options, uncertainties about natural history, or subsets of condition, serious or even life-threatening condition

Low information needs include: limited but still detectable benefits from new treatment options

Unclear information needs occur when there is a clear therapeutic need for a product with an obligation to agree a PIP / PSP but neither the academic community nor sponsor has done the work to support the preparation of a development plan. It is essential to gather sufficient information about the availability of participants, and to clarify the information needs that the plan/study will address, very early during the preparation of plans/studies.

As new information becomes available, the trial basis / concept should be updated and the implications on the development plan re-assessed.

3.2.2. Site contributions to preparedness

Sites, and networks of sites, should be involved as early as possible in those aspects of study preparation that they can contribute to. This work is separate from clinical work and the sponsor should derive high value from the work of the sites, taking into consideration potential conflicts of interest. This document states this principle but does not address how this will be done.

Site activities include:

- Share meta-data about data sources, such as scope of each data source
- Use electronic health records and other informatics approaches (data standards, data linkage etc.) using standardised methods when possible
- Share anonymised information in response to requests to prepare plans/studies (with appropriate protections for confidentiality)
- Identify and annotate data appropriately to reflect clinical context and need of the plan/study under preparation
- Provide sufficient data to the sponsor to support estimation of trial costings
- Use best judgment to provide estimates of recruitment
- Provide adequate research personnel at the site and facilitate their early preparedness input – to recruit, consent, assent, conduct study, complete case report forms (CRF)
- Avoid conflicts of interest and declare any issues.
- Identify resources and facilities that are required and whether the site has access to these resources and facilities – taking account of requirements such as temperature logs and maintenance contracts for freezers – this can be done generically, not waiting for specific studies.

These contributions are best-managed by integrated activity within each site so that each site has a standing infrastructure that is ready to provide information, estimates and judgments in a timely manner upon request. Networks of sites (national and specialty) support consolidation by standardising the contributions of sites: the optimal benefits of standardization that will come with these networks are available to all Sponsors and CROs.

Sites should also support study preparation by meeting agreed standards for such site preparation, with appropriate monitoring and service contracts etc. These standards are not included in this document.

3.2.3. Participant contributions to preparedness

The perspectives of potential participants are central to the preparation of plans and studies. Early consultation with patients' advocacy groups, ideally consultation with patient / parent panels, should be considered since they may improve the communication with the target population and allow to identify potential practical barriers for the conduct of the study. Their input should be heeded as far as possible. It is beneficial to present planned studies at meetings of patients associations as and to plan for a newsletter dedicated to patients during and after the trial. Support from patients' associations before, during and after the trial can also be helpful for trial participants and increase participant retention.

This is particularly important in paediatrics because children and young people have views that are less accessible to adults unless asked, and because families have complex dynamics during acute and

chronic illness. It is highly important to learn from patients and caregivers which elements of the trial proposal are acceptable to them and which are not and which might therefore hamper the conduct of a study. Protocols should then be made flexible enough to reflect this input if possible. In such a case, it is beneficial to obtain also regulatory input on the acceptability of these changes. In case of a study which is part of an agreed PIP this is mandatory.

Advocacy groups can contribute to the preparation of plans and studies with:

- Training of people who supply their contributions
- Considering relevant endpoints, time points of assessment, quality of life effects
- Communication with patient community and awareness on new drug development
- Review and contribution to creation of some study related documents (eg consent / assent, information / awareness documents)

Feedback to children, young people and families who contribute to study preparation is essential and sponsors need to plan how and when to provide this.

3.2.4. Implications for sponsor readiness

Think ahead: include work on preparedness in processes for approval of protocols within Sponsor organizations.

Anticipate, allocate, deploy and expend relevant resources to meet the needs of good preparedness.

Cultivate relevant contacts in advance – become aware of the capabilities of paediatric clinical research networks in advance so that questions can be posed rapidly.

Standing arrangements with sites (confidential disclosure agreements etc.) will facilitate timely work on preparedness.

Clinical research networks can support preparedness by providing consistent relationships with a range of sites and rapid dissemination of requests for information and the collation of responses.

Feedback to sites is valuable for them and to build relationships with them.

Risks and hurdles identified by sites should not be under-estimated at risk otherwise of re-appear at a later stage of study conduct, likely to be then a major constraint in the conduct of the study.

4. Improving the context for trial preparedness

Other actions are needed beyond the preparation of individual trials.

In order to improve the landscape for medicines research over the next 5 – 10 years, the paediatric community needs to:

1. Develop strategies to improve site selection and management such as:
    a) Training about preparation for sites, Sponsors and CROs
    b) Site qualification and accreditation
    c) Site registries, e.g. through clinical research networks
    d) Identification and training of new research centres

2. Continue to undertake collaborative and constructive dialogue between patients' representatives, academics, industry and regulators to facilitate and accelerate treatment development for paediatric diseases, including rare diseases. More emphasis could be given to research opportunities that target a disease with the aim to create data that can be used across different drugs (or groups of drugs), for example supporting extrapolation.
3. Tackle critical trial practicalities such as location of sites and traveling costs for participants as a way of minimizing the burden of research.
4. Collect data that can be used to support and improve future trial preparation including systematic collection of feedback from all involved (patients' representatives, researchers and academics, industry and regulators) to facilitate a culture of lessons-learned.
5. Lobby for greater recognition of the importance of research and readiness to participate in research amongst healthcare professionals and across society. Public and professional awareness around clinical trials needs to be improved, especially for paediatric trials.
    a) Communication programmes devoted to patients and parents should be implemented. Contemporary approaches to social and other media are needed. Establishing a widespread, positive image of clinical trials (CTs) is key and the experiences of clinical trial participants ("expert children") could enhance these communication programmes. Unfortunately, the level of awareness on paediatric research is still poor, and the general population needs to learn that children are protected "through" science rather than needing protection "from" science. There is a need to create a different culture in the population with informative campaigns directed to the broader audience to be agreed, designed, and conducted with the patients. In addition, time should be spent to educate young generations about whatever concerns their health because this can increase in the future the level of knowledge of research.
    b) Educational programmes that support the involvement of Health Care Professionals (HCP) in research that contribute to paediatric drug development is needed. These programmes need to justify the way in which drug development is done and provide the skills needed for high quality contributions to drug development. Educational programmes need to be accessible and relevant; a range of programmes is needed to meet the needs of different groups of HCP.
6. Disseminate good practice across paediatric clinical research networks
7. Consider efficient, patient focused study designs and identify how regulatory requirements have implications for preparation
    a) Pool data across studies, consider innovative study design such as basket trials if applicable
    b) Conduct multi-arm, multi-sponsor studies
    c) Include adolescents into adult trials when regulatory-scientifically warranted
8. Promote transparency about results and preparation

There is still a need to improve understanding of paediatric study requirements across the regulatory network and ethics committees.

These issues that are not specific to individual products, need a generic, pre-competitive approach with contributions from multiple stakeholders.

5. Methodology

To identify the main barriers in paediatric clinical trials leading to delays, or impairment of study feasibility as well as the good practice and lessons learned, and to build further on experience, the group has collated together all existing resources, such as current regulatory guidance, outputs from previous initiatives and Enpr-EMA Working groups, and published literature (see next section).

More importantly the team sought to collect the experience and suggestions from different stakeholders, by developing a survey and performing direct interviews.

Stakeholders from fourteen different categories were included to provide the broadest spectrum of knowledge and experience. They have answered an extensive questionnaire covering questions about four different areas of the planning and conduction of a paediatric clinical trial: Planning phase, Preparation of the study, Study Conduct, and the Post-Study aspects. A total of about seventy questions, tailored for each stakeholder category, was answered by more than fifty participants, covering different categories of organizations involved in paediatric clinical trials, including paediatricians, European regulatory bodies and ethics committees, pharmaceutical industry and Clinical Research Organisations (CRO), sites representatives, patients and families associations, European Reference Networks (ERN) and Enpr-EMA Networks. In addition, whenever possible, personal interviews have been conducted either in presence or over the phone, totalizing discussions with thirteen stakeholders representing seven different categories (general paediatricians, clinical trial networks, European Reference Networks (ERN), patient associations, site study coordinators, Regulatory Authorities representatives and Networks). Finally, an adapted version of the survey has been prepared for the Young People's Advisory Groups (YPAGs) that have been interviewed during the KIDS face to face meetings.

The key messages identified during these surveys and interviews have been included in the main body of the document and supported the conclusions of the proposed document. A detailed paper of the research findings as well as the literature findings and inputs from other initiatives and Enpr-EMA WGs will be made available in due course.

Literature

1. **Enhancing the Pediatric Drug Development Framework to deliver better pediatric therapies tomorrow**

Christina Bucci-Rechtweg

Clinical Therapeutics 2017-10-01, Volume 39, Issue 10, Pages 1920-1932

2. **Clinical Trials: Kids are not just little people**

Fludiona Naka, Bruce Strober and Mona Shahriari

Clinics in Dermatology, Copyright © 2017

3. **drug development**

Saintpierre, Ségolène et al

Regulatory Rapporteur 14.7-8 (2017): 23-27.

4. **More on Altruism, Moral Behavior, and Assent by Children for Research**

Richard Shader MD

Clinical Therapeutics, 2017-10-01, Volume 39, Issue 10, Pages 1907-1910,

5. **Forgotten No More: How Policy Guideline Changes Are Bringing Newborns, Infants, and Children to the Forefront of Drug Discovery and Testing**

Jill L. Maron MD, MPH

Clinical Therapeutics, 2017-10-01, Volume 39, Issue 10, Pages 1918-1919

6. **Enrollment of Neonates in More Than One Clinical Trial**

Jonathan M. Davis MD et al

Clinical Therapeutics, 2017-10-01, Volume 39, Issue 10, Pages 1959-1969,

7. **Facilitating orphan drug development: Proceedings of the TREAT-NMD International Conference, December 2015, Washington, DC, USA**

Hoffman, E.P

Neuromuscular Disorders July 1, 2017. Volume 27, Issue 7. 693-701.

8. **Patient-Reported Outcome and Observer-Reported Outcome Assessment in Rare Disease Clinical Trials: An ISPOR COA Emerging Good Practices Task Force Report**

Benjamin, Katy, et al

Value in Health. July 1, 2017. Volume 20, Issue 7. Pages 838-855. © 2017.

9. *__CTTI RECOMMENDATIONS: IMPROVING PEDIATRIC TRIALS IN ANTIBACTERIAL DRUG DEVELOPMENT Feb, 2017__

10. ***European network of paediatric research: 2016 annual workshop***

Mendum, Jo Regulatory Rapporteur 14.1 (Jan 2017): 30-32

11. ***Stratification, Hypothesis Testing, and Clinical Trial Simulation in Pediatric Drug***

Development

McMahon, Ann W et al, Food and Drug Administration,

Therapeutic Innovation and Regulatory Science 50.6 (Nov 1, 2016): 817-822

12. ***Improvement of Pediatric Drug Development: Regulatory and Practical Frameworks***

Tsukamoto, Katusra et al

Clinical Therapeutics 38.3 (Mar 1, 2016): 574-581

13. ***Stakeholder cooperation to overcome challenges in orphan medicine development: the example of Duchenne muscular dystrophy***

Volker Straub MD et al

Lancet Neurology, 2016-07-01, Volume 15, Issue 8, Pages 882-890

14. ***Ethical issues in neonatal research involving human subjects***

Alan R. Fleischman MD

Seminars in Perinatology, 2016-06-01, Volume 40, Issue 4, Pages 247-253

15. ***Optimizing operational efficiencies in early phase trials: the Pediatric Trials Network experience.***

Amanda England et al

Contemporary Clinical Trials, 2016-03-01, Volume 47, Pages 376-382

16. ***Publications describing the StaR Child Health Project:***

- ***Evidence-based guidelines for pediatric clinical trials: focus on StaR Child Health***

Mario R Sampson, Daniel K Benjamin, and Michael Cohen-Wolkowiez

Expert Rev Clin Pharmacol. 2012 September; 5(5): 525–531. doi:10.1586/ecp.12.52.

- ***StaR Child Health: developing evidence-based guidance for the design, conduct and reporting***

of paediatric trials

William van't Hoff,1 Martin Offringa,2 for the Star Child Health group

(http://www.starchildhealth.org)

Arch Dis Child. Published Online First: 26 September 2014 doi:10.1136/archdischild-2012-303094

- ***Standards for Research in Child Health: The StaR Child Health Project (Supplement to PEDIATRICS, June 2012, Volume 129 / Supplement 3)***
  http://pediatrics.aappublications.org/content/129/Supplement_3

17. ***Recommendation for Practice*** **in the 6 supplemented articles published in Pediatrics Jun 2012, Volume 129 (Supplement 3).**

18. **Ethical Issues in Pediatric Global Health**

Lisa Adams MD, Gautham K. Suresh MD, DM, MS and Tim Lahey MD, MMSc

Pediatric Clinics of North America, 2016-02-01, Volume 63, Issue 1, Pages 195-208

19. Successful private–public funding of paediatric medicines research: lessons from the EU programme to fund research into off-patent medicines

Ruggieri, L. et al

European Journal of Pediatrics 174.4 (2015): 481-491.

20. **Inclusion of patient-reported outcome measures in registered clinical trials: Evidence from ClinicalTrials.gov (2007–2013)**

E. Vodicka et al

Contemporary Clinical Trials, 2015-07-01, Volume 43, Pages 1-9,

21. Changing the Outcomes of Pediatric Drug Trials: APNs Making a Difference

Michelle Dickey and Peggy Clark

Journal of Pediatric Health Care, 2013-05-01, Volume 27, Issue 3, Pages 222-225,

22. The European Union Pediatric legislation: Impact on pharmaceutical research in pediatric populations

Auby, Philippe

Clinical Investigation 4.11 (Nov 1, 2014): 1013-1019.

23. Progress review of the European Paediatric Regulatory Framework after six years of implementation

Mentzer, Dirk

International Journal of Pharmaceutics 469.2 (Aug 5, 2014): 240-243.

24. Paediatric drug development: The impact of evolving regulations

Turner, M.A. et al

Advanced Drug Delivery Reviews 73 (Jun 30, 2014): 2-13.

25. Paediatric pharmaceutical legislation and its impact on adult and paediatric drug development: The EU regulatory view

Wang, Siri and Huemer, Karl-Heinz

Germany: Springer Verlag, 2014.

26. A healthy nation: strengthening child health research in the UK

Neena Modi et al

Lancet, The, 2013-01-05, Volume 381, Issue 9860, Pages 73-87,

27. The globalization of pediatric clinical trials.

Dunne J, Murphy MD, Rodriguez WJ

Pediatrics - December 1, 2012; 130 (6); e1583-91

28. Regulatory intervention in paediatric medicines

Jessop, Nathan

Pharmaceutical Technology Europe 24.9 (Sep 1, 2012).

29. **Impact of the new european paediatric regulatory framework on ethics committees: Overview and perspectives**

Altavilla, A. et al

Acta Paediatrica, International Journal of Paediatrics 101.1 (Jan 2012): e27-e32.

30. **Innovative clinical trial design for pediatric therapeutics**

Matthew M Laughon et al

Expert Rev Clin Pharmacol. 2011 Sep; 4(5): 643–652

31. **Drug development for pediatric populations: Regulatory aspects**

Zisowsky, Jochen et al

Pharmaceutics 2.4 (Dec 2010): 364-388.

32. **Regulatory aspects of drug development in children: Change and resistance to change**

Raymond, Agnés Saint

Expert Review of Clinical Pharmacology 3.5 (Sep 2010): 593-595.

33. **Pharmaceutical research in paediatric populations and the new EU Paediatric Legislation: An industry perspective**

Auby, Philippe

Child and Adolescent Psychiatry and Mental Health 2 (Dec 8, 2008).

34. **Pharmaceutical industry in pediatric drug development: partners and collaborators with academia and the FDA**

Mulberg, Andrew E. et al

Journal of Pediatric Gastroenterology and Nutrition 47.5 (Nov 2008): 711-713.

35. **ICH E11: CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION (dated July 2000)**

36. **Addendum to ICH E11: CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION; (dated July 2017)**

37. **ICH guideline E8 (R1) on general considerations for clinical studies (draft); (dated May 2019)**

EMA guidelines and reflection/concept papers on paediatric topics:

EMA provides a substantial number of guidance and reflection documents relevant for paediatrics and addressing quality, non-clinical and clinical topics.

Quality

- Pharmaceutical development of medicines for paediatric use:
  general considerations related to age, condition/indication and duration of therapy are discussed. Main topics discussed in detail are:
  1) Route of administration and different dosage forms
  2) Excipients in paediatric formulations
  3) Patient acceptability
  4) Administration devices and packaging of paeditric drugs
- Formulations of choice for the paediatric population:
  this reflection paper gives more details on the topics of:
  1) Age groups, developmental pharmacology
  2) Routes of adminsitration
  3) Excipients
  4) Taste, smell, texture, acceptability
  5) Dosing/delivery devices
- Excipients in the dossier for application for marketing authorisation of a medicinal product:
  General guideline that describes required information on excipients in the context of applications for marketing authorisations. Relevant but not specific for paediatrics.
- Ethanol content in herbal medicinal products and traditional herbal medicinal products used in children:
  reflection paper on the need for safety limits for ethanol exposure by oral herbal medicinal products intended for the paediatric population.

Non-clinical

- Need for non-clinical testing in juvenile animals on human pharmaceuticals for paediatric indications:
  Guideline on the use of juvenile animal studies to investigate findings that cannot be adequately, ethically, and safely assessed in paediatric clinical trials, including recommendations on the timing and utility of juvenile animal studies in relation to phases of clinical development.

Clinical

General

- EMA makes reference to the ICH E11 guideline (summarized above)
- Extrapolation of efficacy and safety in paediatric medicine development:
  this reflection paper describes in detail the framework for extrapolation as a methodology to generate evidence for regulatory assessment in a target population. Guidance is given on the main regulatory requirements that are expected to be met for the evaluation of extrapolation approaches in development of medicines for paediatric patients.

- Role of pharmacokinetics in the development of medicinal products in the paediatric population:
  Guideline on the use of PK studies in paediatric drug development and on methodological issues concerning PK studies in paediatric patients. Adds detailed PK considerations to the above mentioned reflection paper on extrapolation.
- Conduct of pharmacovigilance for medicines used by the paediatric population:
  Guideline on particular aspects of pharmacovigilance and risk minimisation relevant for the paediatric population in addition to general guidance for planning pharmacovigilance activities.
- Clinical trials in small populations:
  This Guideline discusses issues associated with clinical trials when there are limited numbers of patients available. This guideline addresses trials in small populations in general, not specifically focused on the paediatric setting. No special methods for designing, conducting or analysing clinical trials in small populations are available but approaches to increase the efficiency of clinical trial are discussed. This guideline complements the reflection paper on paediatric extrapolation.

Topics specific to neonatology/organ immaturity

- Investigation of medicinal products in the term and preterm neonate:
  This guideline addresses the considerations and requirements for the design and conduct of clinical trials in premature and term neonates. It includes background information on the maturation of organs and body functions, formulations and route of administration, and special trial design considerations (including stratification/subgrouping, endpoints, PK, blood sampling etc).
- Concept papers on organ immaturity: A series of documents reflects aspects of organ immaturity to be considered especially during studies of medicinal products intended for neonatal use. Each concept paper dicusses a specific organ / system and how immaturity impacts on clinical studies. Four organs / systems are addressed: brain, liver, lung/heart and kidney:
- Impact of brain immaturity when investigating medicinal products intended for neonatal use
- Impact of liver immaturity when investigating medicinal products intended for neonatal use
- Impact of lung and heart immaturity when investigating medicinal products intended for neonatal use
- Impact of renal immaturity when investigating medicinal products intended for paediatric use

Indication/Condition specific topics

- Clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy (DBMD):
  This guideline addresses general principles in the development of drugs to treat DBMD. General guidance is provided on identification of the target population/patient selection, study design, efficacy and safety endpoints.
- EMA issued guidance documents on the clinical investigation of drugs in specific indiations/conditions. These indication/condition specific guidelines are focused on clinical development in adult patients; additional specific guidance for the paediatric aspects of clinical

development in selected indications/conditions is given in separate documents (addenda) to supplement the general (adult) guidance documents. Paediatric addenda are published for the indications/conditions bacterial infections, heart failure, hypertension, lipid disorders, oncology, pulmonary arterial hypertension and weight control.

- Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements
- Paediatric addendum on the CHMP guideline on clinical investigation of medicinal products for the treatment of acute heart failure
- Paediatric addendum to the guideline on clinical investigation on medicinal products in the treatment of hypertension
- Paediatric addendum to the guideline on clinical investigation of medicinal products in the treatment of lipid disorders
- Evaluation of anticancer medicinal products in man - addendum on paediatric oncology
- Paediatric addendum to the guideline on clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension
- Clinical evaluation of medicinal products used in weight control - addendum on weight control in children