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Preparedness of medicines' clinical trials in paediatrics

Recommendations by the Enpr-EMA working group on trial preparedness

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Glossary

Term	**Definition (used in this document)**
Trial feasibility	The likelihood of completing a clinical trial in a timely manner as planned.
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 therefore also for the overall drug development plan. It is based on explicit data sources and/or explicit reasoning and can be modified based on emerging experience.
Sponsor readiness	A collection of measures taken by a sponsor to allow them to open and conduct a trial and promote efficiency while complying with applicable laws and regulations and ethical principles.
Paediatric drug development plans	A generic term to mean Paediatric Investigation Plans (PIP) in the European Union, Pediatric Study Plans (PSP) in the United States and similar regulatory documents, as well as other strategic considerations for paediatric drug development.

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) [1] and sets out recommendations for discussions about clinical trial preparedness in paediatrics. Section 5 'Methodology' provides an overview of the activity undertaken by the Enpr-EMA working group on trial preparedness as preparation of this document in collecting stakeholders' points to consider. Enpr-EMA held a two-month public consultation on the draft document from September 2019 until November 2019, with the aim of identifying potential gaps and presenting a more comprehensive view. The feedback received during the consultation period has informed the final version of this document.

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 individual studies and therefore also for the overall drug development plan within which a trial is embedded. This document focuses on preparedness for individual trials. However, as a development plan would normally constitute a number of trials, it is implicit that the same elements would also be relevant for preparation of a complete plan. Trial "feasibility" is the likelihood of completing a trial in a timely manner. This document moves beyond the definition of "feasibility" to present a global determination of all aspects of a trial that need to be prepared.

One significant factor of preparedness is the study design, but this is not the only influence on preparedness. 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). When working with the paediatric population, it is essential to establish explicitly the rationale of the benefit of the research question for children. In parallel, trial design needs to take account of the specificities of neonates, 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 trials such as ICH E8 (R1) (General considerations for clinical studies) as well as national legislations.

Trial preparation should be initiated before, and conducted in parallel to, the designing of the development plan and the individual trials, and in parallel to 'sponsor readiness'. The latter describes a collection of measures taken by a sponsor to allow them to open and conduct a clinical trial and promote efficiency while complying with applicable laws and regulations and ethical principles.

The recommendations in this document target both sponsors as well as investigators. However, it should be noted that, whereas trial preparedness has implications for 'sponsor readiness' (see 3.2.4), this document does not describe all aspects of 'sponsor readiness', such as operational aspects within sponsors and intermediary organisations, e.g. Contract Research Organisations (CRO), or strategic factors, such as patient needs and economic opportunities (see ICH E6(R2) Guideline for good clinical practice).

Furthermore, activities relevant to development of age-appropriate formulations to pharmaceutical quality standards (including Chemistry, Manufacturing, and Controls (CMC)), as well as activities to support marketing of products using data about market size are important factors influencing paediatric trials but are out of scope of this document.

[1] 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

Standards to be proposed for site readiness and practical arrangements for sites and participants relating to the preparation of drug development plans and clinical trials are in progress by other initiatives.

2. Need for good preparedness of clinical trials in children

Paediatric drug development plans and clinical trials can be difficult to carry out for many reasons which have been analysed in the literature. The survey conducted by the Enpr-EMA working group on trial preparedness (see Section 5 'Methodology') specifically mentioned that the number of eligible paediatric patients is often limited. This renders timely trial completion unlikely and requires particular attention to study design. Patients and their parents may be reluctant to enrol into a clinical trial because the burden, which goes along with type and number of assessments, may not be tolerated by the participants and acceptable to their families. The extent of these difficulties varies between clinical trials (for example depending on the condition/disease). According to the results of our survey (see Section 5) sites often over-estimate what is possible, and it was reported that sponsors, regulators and ethics committees can disagree about what should be done or is possible during drug development.

Trial conduct is often improved iteratively, by learning during the execution of a clinical trial.

The perspective of participants, parents/carers and of patients' advocacy groups, can make significant contributions to the design of the development plan and trial preparation. Considering patient needs and experience can help to optimise the whole trial design, increase patient retention, and reduce protocol amendments, delays and further expenses. However, at present, this perspective is not always included in the preparation of programmes or trials.

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

For trials 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 the targeted patient population that is likely to benefit from the product. This is needed in order to be able to demonstrate an effect while determining an acceptable safety profile. The available paediatric trial population is often small and even more so in rare diseases. In these instances, clinical trials in rare diseases need to draw on a global patient population to overcome small patient pools in any given country. The number of available patients is further decreased by inclusion/exclusion criteria (e.g. relating to safety or the risk of drug-drug interactions). If these constraints are not properly factored into the estimates of available patients, 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.

Resources often are not allocated or correctly estimated to support trial preparation by the trial centres or sponsors, although, from an operational perspective, investing in well-conducted preparedness activities would facilitate the high-quality conduct of trials (including recruitment figures and complete data sets), thereby avoiding expenditure for poorly conducted, inconclusive trials and development plans.

3. Trial Preparedness

For the majority of paediatric clinical trials problems can be addressed by using all available data to estimate what is possible using a structured approach. Adequate preparation however cannot remove all of the difficulties or estimate achievable patient numbers with complete accuracy. However, a well-prepared, well-designed clinical trial is likely to require fewer changes during its course, be run in a shorter timeframe and achieve expected objectives. The following aspects (not in order of prioritisation) should be considered if applicable and/or relevant.

Before planning any clinical trial, it is important to consider whether there is sufficient scientific rationale and a real clinical need to answer a specific research question. It remains critical to define clearly the trial objective and whether the trial addresses a relevant paediatric unmet need.

3.1. Principles of good preparation

3.1.1. Collect relevant information

1. Develop an understanding of the context for

- planning of the trial e.g. with respect to the number of sites adequately equipped for the trial and available (and needed) participants per site, trial costs, and
- implementation of the trial that is a combination of qualitative and quantitative information derived from multi-method assessments (questionnaires, site visits, broader discussion).
  This process is often time-sensitive and therefore might cause delays if not adequately planned in advance.

2. Contributions to preparedness can be data, estimates, judgments or opinions. 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 from experts need to be explicit (including e.g. conflict of interest). 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). Data from multiple sources

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

   ii. Preclinical evidence

   iii. Population based registry

   iv. Patient registry

   v. Drug registry

   vi. Real life data repositories, electronic health records

   vii. Site data, spliced together

   viii. Paediatric research networks or initiatives

b). Opinion from experts based on experience, including nurses and physicians from all sites not just large teaching hospitals.

c). Opinion provided by a small number of opinion leaders

4. Use information from other trials (RCTs, case-control trials as applicable) to inform preparedness when possible. Information that contributes to extrapolation may also be relevant to trial preparedness.

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 trials that may lead to competition for resources or recruits, or opportunities for co-enrolment

7. Take account of clinical reality across all trial sites. Variation in clinical practices across countries and between therapeutic areas should be considered during preparation as it may have a significant impact on the conduct of the trial.

a). Standards of care, existing treatments, and differences between centres. Note the emerging availability of newly authorised medicines for impact on study design/endpoints.

b). Relationship between standards of care and research

   i. Are there differences between medicines and procedures used in the trial versus standard of care?

   ii. Will standard of care and research procedures be conducted in the same location?

   iii. Is there a need for post-trial treatment access and how will that need be met?

   iv. Settings where various paediatric cohorts receive care (for example adolescents).

8. Identify the 'critical to quality factors' for the clinical trial 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.

9. Identify ethical and legal issues of the research and responses to potential questions / objections (for example direct benefit, risk minimisation, child assent, confidentiality).

10. Take account of the global regulatory environment and the different requirements for drug development across regions.

11. Ensure appropriate development and availability of age-appropriate formulations based on target populations.

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. Burden on participants and their families and possibilities for minimisation of burden

a). Attendance at trial visits for the child such as time, inconvenience, impact on school and leisure activities (when possible use of available technology by participants at home)

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

c). Clinical burden on patients on top of standard of care treatment (e.g. blood sampling).

14. Time course of the trial

a). Assess local timelines for approvals

i. Clinical trial authorisation

ii. Ethics review and Independent Ethics Committee (IEC) approval

iii. Site selection

b). 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, parents/carers and patients' advocacy groups to promote the quality of protocol and process design (including information leaflet and consent forms), thereby increasing the fitness for purpose of the clinical trial. To this end, these groups should be approached as early as possible in the process of trial planning and certainly before key elements of protocols are defined to elicit:

a). Number of potential participants (by paediatric age group)

b). Burden of trial 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 as early as possible (for example on study design, the need for age-appropriate formulations, on preclinical studies or other regulatory requirements). This would harness synergies between adult and paediatric developments (for example inclusion of adolescents in adult trials if appropriate, design of adult studies to optimally inform paediatric drug development).

18. Consider seeking early health technology assessment advice in parallel with scientific advice.

19. Integrate input from potential participants[2], families and advocate groups as early as possible bearing in mind conflict of interest aspects

a). Likelihood of recruitment (acceptability of protocol including the use of placebo, relevance of endpoints)

b). Burden of participating in the trial compared to standard clinical practice with the aim of trial protocols being designed as close to the standard clinical practice as possible

c). Facilities

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

20. Ensure transparency about any real or potential conflicts of interest and include specific confidentiality and data protection agreements.

[2] Participant views include views of parents and other carers expressed directly or through advocates or representative organisations. The views of potential participants and families are best gathered through groups such as Patient Associations and their Community Advisory Boards (CABs) and also from 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.

21. Networks, sites and investigators must be explicit about the source of resources they receive.

22. For global clinical trials consider clinical trial designs, endpoints, and the timing of trials to be coordinated between requirements of regulatory agencies globally.

3.1.3. **Follow a structured process**

23. Demonstrate that due care has been taken to avoid a futile trial by outlining robust methodological considerations during trial preparation, taking into account identified uncertainties, limitations and potential solutions.

24. Identify key influences on preparedness, e.g.

a). Likelihood of recruitment

b). Likelihood of patient retention until key trial assessments are completed and likelihood of missing data if treatment is stopped

c). Data and documentation completeness (ensure adequate data protection)

d). Length of regulatory interactions

25. Construct flow diagram from epidemiology to eligibility (Figure 1: Flow diagram about participants' availability) and from eligibility to contents of locked database ensuring all assumptions are explicit.

26. 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 trial withdrawal and do a sensitivity analysis for dropout

e). Include in the design, where appropriate, simulations that consider extrapolation data, or use modelling and simulation to support the data collected during the trial.

f). Update preparedness work in case of significant delay or interfering event that may have affected the relevance of the previous simulation.

27. Prepare and test all trial procedures, including recruitment, consent and assent, participants' retention and stopping rules, for example through clinical trial simulation of a range of scenarios.

28. 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 clinical trial. Ideally, the trial design should be selected to meet the opportunities provided by the pool of available participants. In any case other innovative methods should be explored to facilitate the generation of data in the most efficient way (always consider use of validated preclinical tools, extrapolation, modelling and simulation if applicable, assess the availability and use of historic data if appropriate).

29. The information gathered to support preparedness should be linked clearly to the development plan/trial, allowing stakeholders to assess how changes in assumptions, estimates and judgments affect the development plan/trial.

30. Consolidate this information into a structured justification that the trial has been prepared adequately (see Table 1).

31. Use information to determine risk management

g). Hazards, assessment

h). Safety Reporting and burden it entails (Documented Pharmacovigilance Plan)

i). Mitigation

32. 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.

33. Plan for a futility analysis to assess the likelihood of a lack of treatment effect and determine stopping rules to prevent children being exposed unnecessarily to an ineffective treatment.

3.1.4. **Use appropriate resources**

34. 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.

35. 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 sponsors (including clinical trials supply and manufacturing), experts and clinical sites during the design phase are essential. Complete information about the context for a programme/trial 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 needed.

36. 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, data sharing and future dissemination of results (consider the role and the timing of a data safety monitoring board (DSMB) and the ICH GCP delegation log). Clear lines of communication are necessary between sponsor and/or intermediary organisation and sites (preferably through shared infrastructure such as a network).

37. During the preparation of development plan/trials, groups of experts or investigators with clear governance, composition and accountability are to be preferred to individuals.

38. Sites and networks need to accept responsibilities and work towards quality and reflect regulatory and commercial reality. Motivation of investigators is important even for trials that could be considered less "cutting-edge".

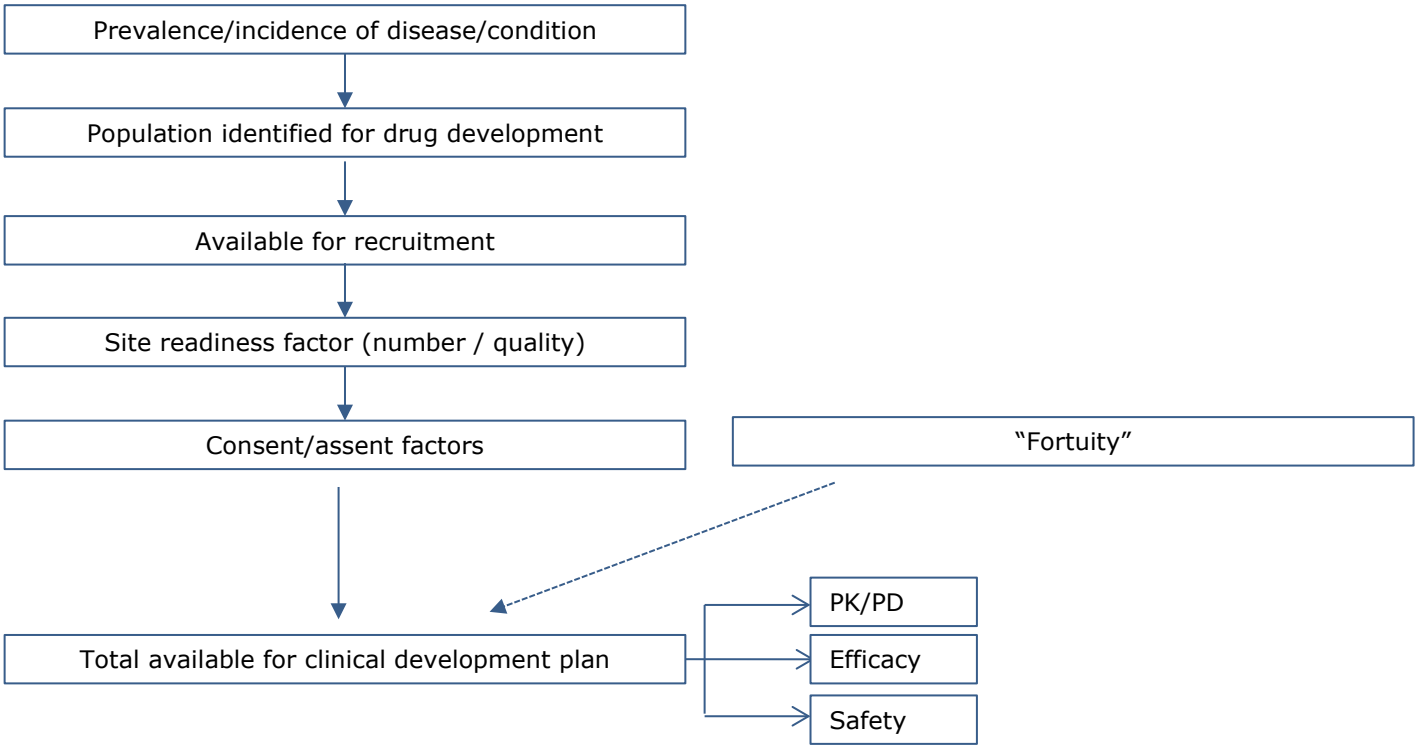

Figure 1. Flow diagram about participants' availability

3.2. Approaches to prepare plans and trials

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 needs to be based on explicit data sources and explicit reasoning and can be modified iteratively. This could allow evidence and data-driven discussions between sponsors and regulators and will contribute to the development of realistic expectations and reduce the risk of infeasible trials. It could also promote the development of common ground during discussions between sponsors, researchers and regulators and assist when points of difference arise during the preparation or conduct of trials and therefore development plans. These discussions amongst all stakeholders could prompt iterative, well-justified changes to the preparedness concept and design of development plans/trials.

It is important to be aware of potentially different uses of the same terms for conditions and diseases in different contexts e.g. where different classification systems are used. Terms used by clinicians for example do not necessarily have identical definitions, 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[3] 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 label/product information reflects a clinically meaningful indication.

The number "available for recruitment" (Fig. 1) 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

[3] Medical Dictionary for Regulatory Activities (MedDRA), https://www.meddra.org/ (use same version during whole trial conduct)

product and condition, or those who have multiple conditions or morbidities that limit the trials they can contribute to (e.g. renal failure). Any assumptions on the number of children available for recruitment should be made explicit and justified.

"Fortuity" (Fig. 1) 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.

Table 1. Exemplar of a structured outline of preparedness assessment

1. **Statement of starting point:** therapeutic need; clinical indication; development and availability of suitable age-appropriate dosage form(s); aim of plan/ trial including regulatory purpose; scope of information needs

Subsequent steps are needed for all trials; for plans each clinical trial should be considered and a synopsis 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 in clinical research.
    b) Extent of modifications needed to sites
    c) Estimates of participants at each site that can be validated
    d) Account for other competing trials
4. **Completeness of data**
    a) Retention of participants, based on acceptability of key trial assessments including what the expected retention is anticipated to be
    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) Uncertainties in assumptions being made
    d) Actions required to optimise setup and conduct
    e) Actions required to maximise recruitment and retention

An explicit, justified evaluation should be made between participant availability and the need for evidence that is scientifically robust and which meets regulatory requirements.

As new information becomes available, the trial basis/concept should be updated and the implications on the development plan re-assessed. This should be done in any case also if the clinical trial has been agreed some time ago, e.g. for a PIP, in order to check if the trial characteristics are still up to date.

Patients should be informed about the different treatment options and should freely give informed consent/assent.

3.2.2. **Site contributions to preparedness**

Sites, networks of sites, and other external vendors (such as central laboratories, biobanks, drug suppliers etc) should be involved as early as possible in those aspects of trial 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. Early consultation is critical as well as on-going dialogues to ensure any changes to the study are accommodated by all relevant vendors. Roles and responsibilities need to be clearly defined as well as the organisation of the sites having to meet industry and regulatory standards. This document states these principles but does not address how these aspects of preparedness or 'sponsor readiness' 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/trials (with appropriate protections for confidentiality)
- Identify and annotate data appropriately to reflect clinical context and need of the plan/ trial under preparation
- Provide sufficient data to the sponsor to support estimation of trial costings
- Use best judgment to provide estimates of recruitment and provide explicit assumptions
- Provide adequate research personnel at the site and facilitate their early preparedness input – to recruit, consent, assent, conduct trial, 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 trials

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 standardisation that will come with these networks are available to all sponsors and CROs.

Sites should also support trial 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 trials. Early consultation with patients' and children's advocacy groups, ideally consultation with patient/parent panels and Community Advisory Boards (CABs), should be considered since they will improve the communication with the target population and allow to identify potential practical barriers for the conduct of the trial. Their input should be heeded as far as possible and should include but not be

limited to relevant endpoints, time of assessments, quality of life effects, tolerance of tests and assessments. It is beneficial to present planned trials at meetings of patients' associations as and to plan e.g. 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 trial. Protocols should 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 trial which is part of an agreed PIP this is mandatory, also remember regulatory documents (such as agreed PSPs) which may be affected.

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

- Training of people who supply their contributions
- Considering relevant endpoints, including where possible biomarkers and validated scales, time points of assessment, quality of life effects
- Communication with patient community and awareness on new drug development (including age appropriate dosage form when applicable)
- Review and contribution to creation of some trial related documents (e.g. consent / assent, information / awareness documents)

Feedback to children, young people and families who contribute to trial 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 organisations.

Design adult programmes and trials in view of informing paediatric programmes and trials as appropriate.

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.

- Clinical and methodological 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.
- With respect to sites:
  - standing arrangements with sites (confidential disclosure agreements etc.) will facilitate timely work on preparedness.
  - feedback to and communication with sites is valuable for them and to build relationships with them.

- when risks and hurdles are identified by sites, they should not be under-estimated as they might re-appear at a later stage of trial conduct, likely to be then a major constraint in the conduct of the trial.

4. Improving the context for trial preparedness

Other actions are needed beyond the preparation of individual clinical trials.

In order to improve the landscape for medicines research over the next 5 – 10 years, the paediatric community (clinicians, patients and families, researchers, regulators, ethicists, sponsors, CROs) 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, external vendors qualification
    c) Site registries (compliant with data protection legislation and ensuring high data standards, e.g. FAIR principles), 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 medicines (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 minimising the burden of research. Explore the option of virtual or home clinical trial visits and remote data collection technologies and the use of continuous data collection and innovative digital technology if applicable.
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, but also designed under FAIR principles and Open Access Schemes.
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 with the contribution of regulatory authorities and patients' advocacy groups. Contemporary approaches to social and other media are needed. Establishing a widespread, positive image of clinical trials including bioethics 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) as well as Industry sponsors in research that contribute to paediatric drug development is needed with the contribution of regulatory authorities. 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.

6. Disseminate good practice across paediatric clinical research networks. Since the patients are often minors, there needs to be sensitivity to privacy, parental consent, data protection with such communication efforts.

7. Consider efficient, patient focused trial designs and identify how global regulatory requirements have implications for preparation

   a) Pool data across trials, consider innovative trial design such as basket trials if applicable

   b) Use, where appropriate, extrapolation and modelling and simulation, to support, complement, or replace patients required to be assessed in a clinical trial, and ensure the minimal number of paediatric patients are exposed to clinical trials especially placebo and/or control arm.

   c) Conduct multi-arm, multi-sponsor trials

   d) Actively include adolescents and/or children into adult trials (i.e. allow in the inclusion criteria) when scientifically acceptable.

   e) Training on novel trial designs and Bayesian statistical methods is needed for all stakeholders e.g. investigators, regulators and clinicians.

   f) Actively work towards global convergence regarding regulatory requirements.

   g) Promote data sharing, high quality data (e.g. FAIR principles) and return of the individual data to the study participants

8. Promote transparency about results and preparation

There is still a need for improved, mutual understanding of paediatric trial requirements and challenges across the regulatory network, companies, clinicians, researchers and ethics committees as well as the public. 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 clinical trial feasibility as well as the good practice and lessons learned, and to build further on experience, the group has collated 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 seventy questions, tailored for each stakeholder category, was answered by more than fifty participants, covering different categories of organisations 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 with thirteen stakeholders in total 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 document.

6. Literature

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6.2. Selection of related EMA guidelines and documents

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 paediatric drugs

- Formulations of choice for the paediatric population: this reflection paper gives more details on the topics of:
  - Age groups, developmental pharmacology
  - Routes of administration
  - Excipients
  - Taste, smell, texture, acceptability
  - 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 (summarised 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 discusses 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 indications/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
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  - Clinical evaluation of medicinal products used in weight control - addendum on weight control in children