European network of paediatric research at the European Medicines Agency

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 December 2018

Enpr-EMA Working group on public-private partnership: Network consultation recommendation

Members of Enpr-EMA offer opportunities for advice and information during all stages of paediatric medicines development. Enpr-EMA suggests that all companies consider using these opportunities in a spirit of shared learning about the best way to collaborate during PIP planning and. This offer is to assist companies in taking advantage of the scientific and logistical expertise in paediatric clinical research, available from the paediatric clinical research networks of the Enpr-EMA (European network of paediatric research at the European Medicines Agency).

To contact these paediatric research networks of the Enpr-EMA, send an e-mail to: enprema@ema.europa.eu. You may check the current paediatric research networks availability, and the services offered by these networks by visiting the Enpr-EMA database: http://enprema.ema.europa.eu/enprema/. This includes updated list of available networks, including information of the capabilities & services provided by each network, and the web-link to the network´s websites for further contacts.

This offer is suitable to all organizations and companies including those operating outside Europe if applicable according to local regulations and company rules.

Paediatric research network expertise is available for the entire drug development cycle, therefore this offer covers the whole drug development process – from scientific idea to clinical studies of the PIPs and safety follow-up after Marketing Authorization.

The offer includes four different time points with detailed consultation issues at each point.

These right time consultations can offer key benefits for companies by:

- **meeting the patients' needs, with a targeted and evidence-based feasibility**
- **enhancing the product development process by helping to create a relevant drug development plan**
- **optimising the PIP development focusing on key studies and developing a long term strategy**
- **making an efficient clinical trial conduction**
- **saving time and costs**

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Recommended timing for the network consultations:

1. Consultation: SCOPING / EXPLORING

– 1st contact to selected network

TIME POINT: Very early on drug development process and before preliminary

This is the recommended initial option especially for rare diseases and conditions. At this point, it is possible to discuss with the sponsor the following information:

- **Identification of condition or mechanism of action with potential for paediatric use/confirmation of unmet therapeutic need**
- **Identification of knowledge gaps & plans to fill those knowledge gaps including pre-clinical studies required**
- **Designing global clinical development plan**
  - **Target population and age categories**
  - **Primary & secondary endpoints / outcome selection**
  - **Use of modelling & simulation and other tools** including PK and PD modelling
- **Concepts for PIP / PSP (U.S.) studies and plans for other jurisdictions**
- **Feasibility of studies** The availability and the number of possible trial subjects according to the prevalence and health care status and practices (including off-label use) in each country to lead to more realistic recruitment targets and timelines. Also important to take into account the number of other products in development for the same condition.
- **Risk-benefit analysis**
- **Study design and methodology, as well as relevant ancillary studies**
- **Natural history of the disease in children/ current standard of care & response to standard of care therapy**
- **Need for long-term follow-up**
- **Early information on the similarity of drug disposition (ADME)**
- **Genetics & pathophysiology & similarity of disease between adults and children**
- **Exploratory advice; concept proof – YES / NO:** product/indication/trial/inclusion-exclusion criteria/study design applicability to paediatric population
- **Details of specific challenges;** in recruiting & set-up times e.g. consider screening programmes to find the targeted patient population
- **Discussion about deferrals and waivers;** including analysis of the relevant information from trials in the adult similar indication and timelines for trial implementation. Whether it is appropriate

to apply for a waiver for some age groups and how many subjects in each age group is feasible to aim for.

- **Review of preliminary PIP plans/study protocol:** as much information as possible that can be disclosed without concerns about confidentiality should be made available, although this may only be a brief outline.
- **Supporting information about the suitable population and availability in Europe and possibly outside Europe by country**: which countries, number of sites and an estimate of potential recruitment could be possible depending on the level of information shared
- **Details of any specific challenges in recruiting & set-up times and with targeted patient population**
- **Possibility of using extrapolation of efficacy & role of extrapolation from adult population;** The knowledge about the latest disease specific scientific information on efficacy, extrapolated from adult population (if available and applicable), including input regarding degree of similarity or not, between the disease in adults and children (all paediatric age groups), and the similarity or not of the expected treatment response between adults and children.
- **Evidence based analysis of currently used treatments and selection of comparator/control group;** discussion and validation of the reference treatment(s), use of placebo, active comparator(s) and add-on therapies.
- **Identification of relevant networks to approach for next consultations steps 2 and 3**

2. Consultation: DOABILITY / TARGETING

- 2nd contact to selected network

TIME POINT: Confirmation to scoping - before PIP submission

This is the most suitable initial option before PIP submission (in order to avoid several amendments rounds and a delayed PIP process) for all diseases and conditions. At this point, it is possible to discuss the following information:

- **Adult and paediatric indications:** Confirmation as to whether the paediatric indication is relevant/appropriate with regards to the unmet medical needs including the identification of the clear scientific question.
- **Target population including age categories**
- **Inclusion criteria relevancy**: The possible hurdles in inclusion criteria, which might prevent relevant PIP protocol development according to the disease, knowledge of the specialty and current practices in individual health care systems.
- **Formulation and dosing issues**: Whether these are appropriate for the target population
- **Protocol relevancy to practice**: Scientific knowledge about the condition or disease, and the relevant and best endpoints/surrogate endpoints to be used, together with methodological knowledge

reflecting the current practices and realistic timelines to supplement the Regulatory Authority Scientific Advice (EMA PDCO and National Regulatory Authorities).

- **Ethical issues including drug provision after the trial ends (important for chronic conditions)**
- **General ethical considerations**: A realistic national based evaluation as to whether the planned trial procedures would be acceptable to national level ECs with reference to national regulations and guidelines.
- **Practical trial procedures for the protocol**: Knowledge about current practice and available services regarding laboratory, radiology and pharmacy services, and other extra services (e.g., medicine logistics), can be very important for protocol development, and especially, protocol implementation in practice. This includes detailed knowledge about frequency of blood sampling, and allowed volumes, availability of appropriate sites, special equipment and trained personnel available at site.
- **Preliminary site identification and network involvement; qualification, experience, readiness, performance:** an indication of what type of possible sites might be suitable and/or interested, the availability of patients at the site that could be used to query the number of subjects.
- **Patient and family involvement:** advice and support on the involvement of patients, and families in protocol relevancy, formulation and dosing issues, ethical issues and practical trial procedures.
- **Needs for long-term follow up measures**: what information is raising concern for patients exposed to the drug in terms of long-term toxicity and what long-term follow up measures should be considered.
- **Timelines for protocol and case report forms finalisation and target date for first patient enrolment.**

3. Consultation: FEASIBILITY / IMPLEMENTING

- 3rd contact to selected network

TIME POINT: after agreed PIP / adoption of opinion or requested PIP modification

This contact should be made as soon as possible and in any case before the protocol and case report forms development after the agreed PIP by EMA PDCO in order to implement latest changes in the clinical practice and in the occurrence of competing trials and to discuss/confirm the following information:

- **Confirmation of target population**: The availability and the number of possible trial subjects in each country should be checked before the full feasibility is done, as it saves time and money.
- **Confirmation of the protocol relevance vs. practice**: Assistance with the feasibility process including drafting and review of any feasibility questionnaires to be used, in order to avoid possible conflicts with ethical guidance or local medical practice.
- **Compliance with timelines including patient recruitment**: Review of the planned and agreed timelines taking account of available resources for completion (at local and national level) in order to avoid simultaneous competing trials, or limited resources at the study start.
- **Trial sites identification and capability**: Feasibility problems can be minimized by having national level advance information about potential and available trial sites (number & quality),

interested investigators and available study personnel. The time saved can be very helpful when potential trial sites are aware of up-coming trials at a very early stage.

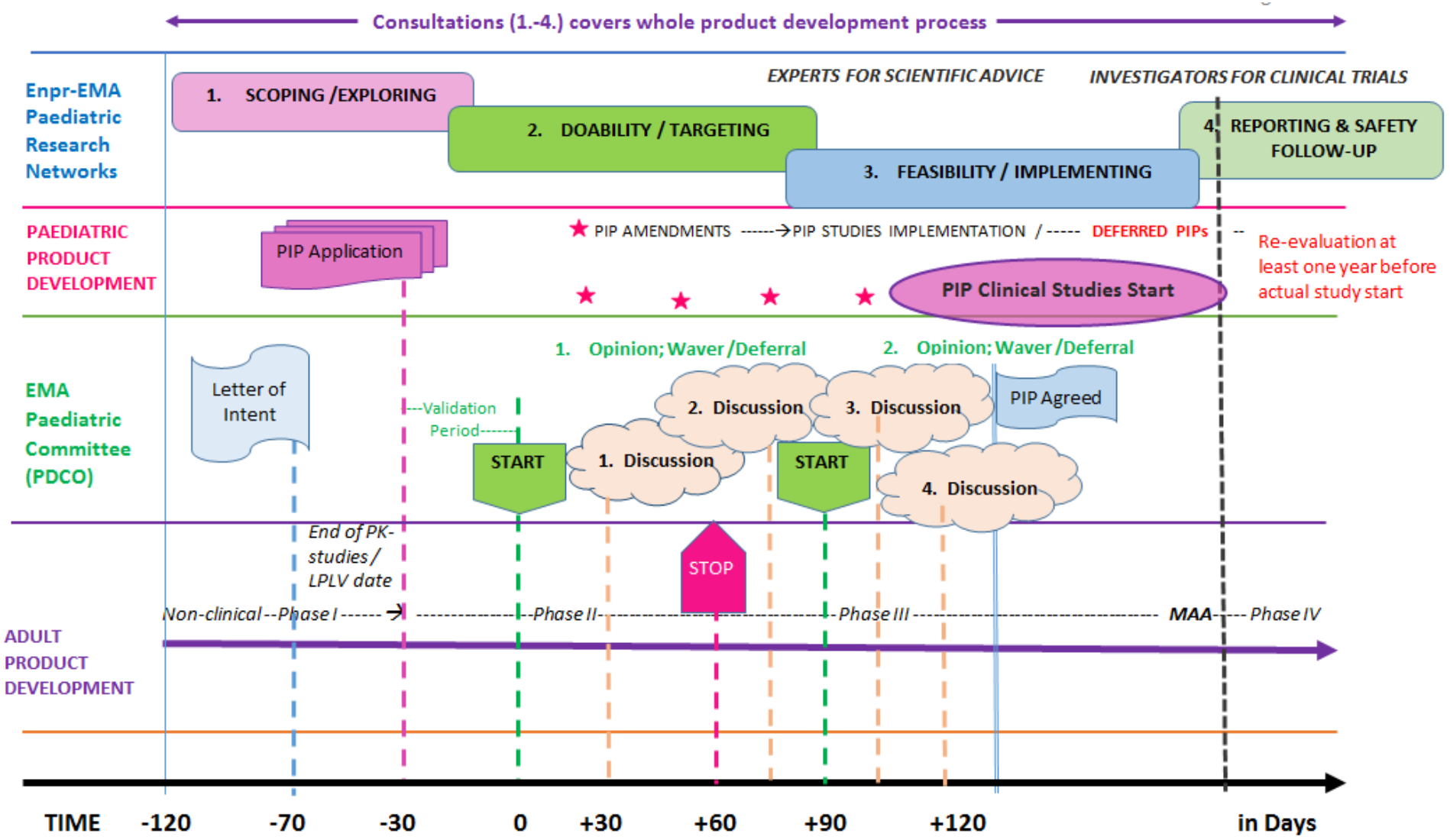
- **Confirmation on ethical issues including drug provision after trial closure**: The current Informed Consent (and Assent) requirement and practices can be confirmed and the content can be evaluated via existing international young people's and parent advisory groups before feasibility , and can save time due to avoiding amendments before the trial starts.
- **Confirmation on practical procedures**: Confirmation about current practice and services for laboratory, radiology and pharmacy systems will speed up the trial start process.
- **Patient and family involvement**: Obtaining the views of patients and families in the feasibility stages will ultimately result in a patient centred research study that is child and family appropriate. Additionally, advice about the protocol practicalities, understandable ICF/assent texts and information about the trial.
- **Protocol and Case Report Forms Finalization in line with PIP to ensure compliance with PIP**
- **PIP Revisions as needed** (eg. after revision of the results from phase III trials in the adult populations when applicable)
- **Independent outcome assessment as needed**
- **Protocol amendments**
- **Trial conduction at sites;** including investigator(s), study nurses, trial facilities & equipment, and other resources.
- **Long term objectives including pharmacovigilance for example through network registries**

4. Consultation: REPORTING & SAFETY FOLLOW-UP

– 4th contact after implementation of PIP studies and adult Marketing Authorization

At this point, some of the research networks are capable to provide assistance after trial phases for final reporting and long-term safety follow-up procedures. Sponsors have the opportunity to discuss following issues to finalize trial documentation and organize needed safety follow-up procedures:

- Revision of the reports to Regulatory Authorities
- Manuscript preparation including authorship selection (ICMJE criteria with choice left to the networks)
- Long-term objectives including pharmacovigilance / safety follow-up eg. through network registries or systems


Consultations (1.-4.) covers whole product development process
Enpr-EMA Paediatric Research Networks
EXPERTS FOR SCIENTIFIC ADVICE
INVESTIGATORS FOR CLINICAL TRIALS
1. SCOPING /EXPLORING
2. DOABILITY / TARGETING
3. FEASIBILITY / IMPLEMENTING
4. REPORTING & SAFETY FOLLOW-UP
PAEDIATRIC PRODUCT DEVELOPMENT
PIP Application
PIP AMENDMENTS ------→PIP STUDIES IMPLEMENTATION / ----- DEFERRED PIPs --
Re-evaluation at least one year before actual study start
PIP Clinical Studies Start
1. Opinion; Waver /Deferral
2. Opinion; Waver /Deferral
EMA Paediatric Committee (PDCO)
Letter of Intent
---Validation Period------
START
1. Discussion
2. Discussion
3. Discussion
START
4. Discussion
PIP Agreed
STOP
End of PK-studies / LPLV date
Non-clinical--Phase I------→----------Phase II----------Phase III----------MAA----Phase IV
ADULT PRODUCT DEVELOPMENT
TIME -120 -70 -30 0 +30 +60 +90 +120 in Days