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Project Acronym: [PedCRIN]
Project title: [Paediatric Clinical Research Infrastructure Network]

Periodic Technical
Report Part B

Period covered by the report: from [01/01/2017] to [30/06/2018]
Periodic report: [1st]
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<th>Description</th>
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</thead>
<tbody>
<tr>
<td>PedCRIN</td>
<td>Paediatric Clinical Research Infrastructure Network</td>
</tr>
<tr>
<td>AB</td>
<td>Advisory Board</td>
</tr>
<tr>
<td>ADRs</td>
<td>Adverse Drug Reactions</td>
</tr>
<tr>
<td>AEs</td>
<td>Adverse Events</td>
</tr>
<tr>
<td>BBMRI</td>
<td>Biobanking and Biomolecular Resources Research Infrastructure</td>
</tr>
<tr>
<td>C4C</td>
<td>Conect4Children</td>
</tr>
<tr>
<td>CA</td>
<td>Competent Authorities</td>
</tr>
<tr>
<td>CORBEL</td>
<td>Coordinated Research Infrastructures Building Enduring Life-science Services</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Criteria for Adverse Events</td>
</tr>
<tr>
<td>CTUs</td>
<td>Clinical Trial Units</td>
</tr>
<tr>
<td>DoA</td>
<td>Description of the Action</td>
</tr>
<tr>
<td>EATRIS</td>
<td>The European Advanced Translational Research Infrastructure in Medicine</td>
</tr>
<tr>
<td>EC</td>
<td>Ethic Committees</td>
</tr>
<tr>
<td>ECRIN</td>
<td>European Clinical Research Infrastructure Network</td>
</tr>
<tr>
<td>EJP-RD</td>
<td>European Joint Programme for Rare Diseases</td>
</tr>
<tr>
<td>EPTRI</td>
<td>European Paediatric Translational Research</td>
</tr>
<tr>
<td>ESFRI</td>
<td>Forum on Research Infrastructures</td>
</tr>
<tr>
<td>FGB</td>
<td>Gianni Benzi Pharmacological Research Foundation</td>
</tr>
<tr>
<td>FSJD</td>
<td>Fundació Sant Joan de Déu</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practices</td>
</tr>
<tr>
<td>GDPR</td>
<td>The General Data Protection Regulation</td>
</tr>
<tr>
<td>HUS FI</td>
<td>Hospital District of Helsinki and Uusimaa</td>
</tr>
<tr>
<td>IC</td>
<td>Informed Consent</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational medicinal product</td>
</tr>
<tr>
<td>INSERM</td>
<td>The Institut national de la santé et de la recherche médicale</td>
</tr>
<tr>
<td>OPBG</td>
<td>Ospedale Pediatrico Bambino Gesù</td>
</tr>
<tr>
<td>RUMC</td>
<td>Radboud University</td>
</tr>
<tr>
<td>ULIV</td>
<td>The University of Liverpool</td>
</tr>
<tr>
<td>VSOP</td>
<td>Vereniging Samenwerkende Ouder – en Patientenorganisaties</td>
</tr>
<tr>
<td>YPAGs</td>
<td>Young Person Advisory Groups</td>
</tr>
</tbody>
</table>
1. Explanation of the work carried out by the beneficiaries and Overview of the progress

The PedCRIN project was started on 1st January 2017 and will continue until end of December 2020 (except WP4). The project activities are being carried out as project tasks, milestones and deliverables under six work packages (WPs) i.e. project coordination and implementation of management decisions (WP1), sustainability, strategy, governance, business plan (WP2), tools for paediatric and neonatal trials (WP3), pilot trials (WP4) & communication, dissemination, empowerment (WP5) and ethics requirements (WP6). As a first step towards the smooth start of this project, project manager was hired one month prior to the start of this project. The PedCRIN kick-off meeting was held from 9 to 10 January 2017 in Paris. The Kick-off meeting was organised to discuss activities proposed in the project and to detail possible ways for successful implementation of the project. The meeting included presentations of PedCRIN project partners and two other ESFRI-landmarks, BBMRI-ERIC and EATRIS-ERIC which are also contributing to the project.

1.1 Objectives

The main objective of the PedCRIN project is to enhance ECRIN capacity for the management of multinational neonatal and paediatric clinical trials. For the first reporting period the objective were:

**Objective 1:** Access to transnational clinical trial management services for the PedCRIN funded pilot neonatal or paediatric multinational trials, already funded in the coordinating country, and requiring extension to other countries that are members of the PedCRIN consortium (WP4). Outcomes are detailed in section 1.2.4

**Objective 2:** Enrich the current ECRIN tools and actions with paediatric components (WP3)

**Objective 3:** To communicate and disseminate about PedCRIN with children, parents and families, industry, regulatory authorities, policymakers, healthcare providers and all the relevant stakeholders (WP5)

**Objective 4:** Establish a sustainability board including government representatives and plan the strategy for sustainability (WP2) based on the users’ community needs

**Objective 5:** Establish the organizational structure required for the effective coordination of the project. Specifically, the objective is to ensure the coordination and monitoring of the activity of the WPs (WP1 and WP6).

1.2 Explanation of the work carried per WP

1.2.1. Work Package 1: Project management and coordination of work package activities (M1-48)

*Task Leader: ECRIN*

**Objectives**

The objectives and aims of WP1 of the PedCRIN project during the reporting period and beyond are:

1. Pacing and coordinating the work package activities
2. Ensuring timely release of deliverables
3. Supervising the financial management
4. Organizing the project level meetings and issuing the minutes (management board, steering committee & advisory board)
5. Structuring a consortium communication flow, including deliverables, reviews, etc.
6. Coordinating the writing of the Interim report (M18)

During the first month of the project the main tools for the project management were set up (conference call system, deliverable and milestone calendars, contact lists,). Starting with the Kick off meeting (Milestone 1) hosted by the Project Coordinator in Paris a dedicated project manager was appointed to
develop and implement management processes (deliverable, review process and internal financial monitoring process), and to enhance the supervision of the implementation of the project both from scientific and administrative part. The main objectives for the first half of the project have been successfully achieved and the results of the management of the project are satisfactory: all commitments with the European Commission (deliverables and milestones) have been fulfilled on time; good communication among partners has been established; the prepayment has been paid to each partner soon after ECRIN received the payment from the EC; technical objectives of the project have been effectively carried out along the reporting period; and at every technical meeting project results have been presented and updated. During the reporting period ECRIN coordinated the following plenary meetings:

1. January 2017-Kick off meeting in Paris (Pitié Salpêtrière hospital)
2. February 2017-PedCRIN WP2 face to face meeting Paris (ECRIN)
3. June 2017-PedCRIN WP3 face to face meeting held in Paris (ECRIN)
4. July 2017-Scientific Board Meeting for the selection of the PedCRIN funded trials in Paris (ECRIN)
5. February 2018-PedCRIN Advisory Board Meeting 2018 in Paris (ECRIN)
6. April 2018-Management Board Meeting in Bergen, Norway

1.2.2.1. PedCRIN Management Board (M1 & M8)
The governance of the project is achieved by the Management Board. It is composed of at least one representative of the project beneficiaries and its role is to provide strategic direction. During the first year of execution of the PedCRIN project, two face to face meetings were organised; a kick-off meeting (January 2017) and an annual meeting (April 2018).

1.2.2.2. PedCRIN Steering Committee
The Steering Committee is composed of the work package leaders. Its role is to drive and coordinate the work package activities. During the first year of execution of the PedCRIN project, the coordination organized eight teleconferences with all the workpackage leaders and co-leaders to maintain good communication, update about the WP activities, discuss and approve actions to be taken.

1.2.2.3. Task 1.2: PedCRIN Advisory Board M8
The PedCRIN Advisory Board (AB) is an independent body, composed of representatives of major stakeholders in paediatrics and clinical research. Its mission is to provide strategic advice and recommendations for the development of the project in order to ensure its high quality and excellence. An initial list of experts coming from major stakeholders in global neonatal and paediatric clinical research was established. The experts were selected by PedCRIN on the basis of proven expertise in neonatal and paediatric clinical research including methodological expertise, good knowledge of the EU research and innovation policy and H2020 programme, and availability to fulfil their responsibilities for the duration of the project. The eventual AB is composed of the following members:

1. Pr Thierry Lacaze
2. Prof. dr. C.B. (Kit C.B.) Roes
3. Pr Régis Hankard

The first Advisory Board meeting was held in ECRIN Paris on 27th February 2018. The objective of the meeting was to update the Advisory Board members about the PedCRIN project and the challenges the consortium faces through presentations and discussions. The leaders and co-leaders of each work package (WP1-5) provided an update to the advisory board members about their activities (PedCRIN funded pilot trials, the sustainability, strategy, governance & business plan, development of tool for the multinational neonatal and paediatric clinical trials and communication and dissemination of the project).
Recommendations from the Advisory Board
The extensive discussions during the meeting were well appreciated by the members of the board as well as by the members of the PedCRIN consortium. The main recommendations of the Advisory Board are the following:

- Tools for paediatric trial design: ensure harmonisation across areas (medicinal products, medical devices, other intervention trials) and avoid duplication of tools or initiatives
- Pilot trials: clearly define the expected learnings and the data to be collected to benefit the further paediatrics trials and infrastructure
- Patients and parents involvement: ensure that previous experience especially in adults trials are taken into account and explain the additional challenges raised by paediatrics and by the diversity in approaches and culture. To optimize learnings parents and patients from different countries should be involved.
- Sustainability and strategic input: develop a business model for sustainability explaining the added value of the infrastructures, avoid duplication and overlap within projects currently running or in development (PedCRIN, EPTRI, C4C) and ensure clear communication towards the users.

1.2.2 Work package 2: Sustainability, strategy, governance, business plan (M1-36)

Task Leader: ULIV (Mark Turner)

Objectives
The objectives and aims of WP2 of the PedCRIN project during the reporting period were:
1. Drafting the Strategy Plan for PedCRIN by M4
2. Establishment of the Sustainability Board by M1, first meeting of the board by M6 and report from the Sustainability Board by M15

1.2.2.1. Task 2.1: Drafting the Strategy Plan for PedCRIN (M4)

Task Leader: ULIV (Mark Turner)

Establishment of Strategy Task Force: In M1, PedCRIN WP leads were invited to form a core group that would advise and develop the strategy of PedCRIN. This group met to decide on defining a series of options for the strategy of PedCRIN. On the advice of the Strategy Task Force, the draft strategy document information to date has been informed by:

- A public and partners engagement approach also referring to communication and engagement work in WP5
- Teleconferences with investigators to identify requirements - six qualitative interviews were undertaken, to complement information gathered through WP3
- A series of teleconferences with Clinical Trial Units (CTUs) were undertaken to identify current state

Investigator Interviews
In order to inform the discussions of the Strategy Task Force and the Sustainability Forum, the Investigator experience of conducting paediatric multicentre multinational clinical trials has explored through a series of interviews. Strategy Task Force members were requested to nominate researchers with experience of conducting multi-national research. Six interviews undertaken with range of experience from low to very experienced in multiple clinical trials, both commercial and publicly sponsored. The questions explored barriers and enablers for researchers (Table 1). The aim was to understand how many of the problems relate to process and management (activities that ECRIN and PedCRIN can help with) and how many relate to the context (national legal positions and /or inconsistencies) or to the investigation.
<table>
<thead>
<tr>
<th>Barriers</th>
<th>Lack of time and resource</th>
<th>Regulations and processes</th>
<th>Trans-national Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Time pressures to set-up sites</td>
<td>– EU regulation burdensome</td>
<td>– Support from national or inter-national organisations acknowledged as a huge benefit, e.g. PENTA, FinPedMed, SwedPedMed</td>
<td></td>
</tr>
<tr>
<td>– Lack of trained staff with dedicated time</td>
<td>– Regulatory part of trial very difficult</td>
<td>– However, in each instance the national remit of support or the lack of connectivity of such organisations across nations, were mentioned as restrictive to the facilitation of multi-national trials. In two instances, hospital R&amp;D departments were mentioned as facilitators within that particular site</td>
<td></td>
</tr>
<tr>
<td>– Money and support at national, regional level for paediatric research</td>
<td>– Submissions to ethics and regulatory committees</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Different rules to follow for different trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Lack of availability of rules across nations on above</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Enablers in the scope for PedCRIN

The following enablers were narrowed down as solutions to some of the issues highlighted by the investigator interviews and as being within the scope of PedCRIN:

- Harmonization across Europe required
- Support for multi-national collaboration to set up studies, specifically contracts
- Pre-written model contract agreements between different sites
- Administrative support for individual researchers for applications, legal etc.
- Touch points across different countries that can connect researchers to different expertise.
- Assistance with preparation of age appropriate information- blood samples, ICF drafts, metabolic tests

### Issues to be addressed for someone new to clinical research

- Collaboration across nations and sub-groups required.
- If hospitals were to be part of blanket organisations/ networks, this would improve patient access.

### Clinical Trial Unit (CTU) Interviews

**Task Leader: ECRIN**

In order to inform the discussions of the Strategy Task Force and the Sustainability Board, the clinical trial unit’s experience of conducting paediatric multinational clinical trials has explored through a series of interviews. The selected CTUs were proposed by the PedCRIN partners and 6 CTUs from France (1), Czech Republic (2), Spain (2) and Switzerland (1) completed the questionnaire and underwent structured interviews. The aim was to understand how the activities performed by the CTUs can answer the barriers identified by the investigators and in which area specific paediatric/neonatal expertise is needed in comparison to CTUs working with adult clinical research.

This survey and the interviews are not intended to provide an exhaustive feedback, nor to map the existing capacity but just to provide some thoughts to drive the writing of the strategic document.

Clinical trials units are defined within the scope of the PedCRIN project and within ECRIN as unit/ department/staff within an organisation, able to provide support to the Sponsor of a clinical trial/study in order to fulfill its responsibilities (according to ICH-GCP-E6 (R2)) in the development, the set-up, the management and the reporting of the study.

CTUs surveyed had the expertise to provide statistical, epidemiological, logistical and methodological advice, and the coordination to successfully undertake paediatric multicentre clinical trials, nationally and internationally. Moreover, CTUs are able to support the management of the study (sponsor responsibilities), submissions to ethic committees (EC) and competent authorities (CA), monitoring,
pharmacovigilance and designing case report forms thereby covering the barriers identified by the investigators (mentioned above). Most CTUs work in a collaborative approach and are able to coordinate clinical trials of investigational medical products (IMPs) in compliance with national and EU Regulations. CTUs from France and Spain are also linked with young patient advisory groups or patient representatives for their involvement and training in paediatric clinical research. This can be a model for development of national infrastructure to support the management of clinical trials and answer the barriers identified for investigator initiated clinical trials.

**Draft Strategy Document**

The first draft of PedCRIN draft strategy document was completed in April 2017. Since then ULIV has been progressing the options highlighted by the Strategy Task Force.

**1.2.2.2. Task 2.2: Establishment of the Sustainability Board by M15**

**Task Leader: ULIV (Mark Turner)**

The timeline of this work package has been affected by a number of recent initiatives. Since the project was planned, several new projects (each of them targeting a different aspect of paediatric research) were funded. These projects are:

1. European Paediatric Translational Research Infrastructure (EPTRI). EPTRI is currently defining a Conceptual Design Report in an INFRADEV1 project. EPTRI focuses on preparatory work that underpins the design of clinical trials for publically funded researchers (-omic technology, biomarker development, basic pharmacology, preclinical work, formulation science etc.) and will provide a clearing house for academic expertise within its scope. EPTRI opened in January 2018 and is also working on sustainability; this work includes PedCRIN members ULIV and CVBF.

2. The proposed European Joint Programme for Rare Diseases (EJP-RD) which application was submitted in April 2018. EJP-RD will focus on rare diseases to integrate public and academic work, with an industry interface. The proposed EJP-RD includes work on sustainability through PedCRIN members ULIV and CVBF.

3. Conect4Children (c4c) is a private public partnership funded by IMI2 that integrates clinical communities for the design and implementation of clinical trials. C4C project has a sustainability Work Package and includes several members of PedCRIN.

Each of these initiatives addresses a different segment of the needs of the paediatric community. It is imperative to avoid fragmentation and duplication of research infrastructures. Accordingly, the sustainability strategies of PedCRIN and the other initiatives need to present a united front to funders and users. The first task of the PedCRIN Sustainability Board will be the review of the Strategy Document in light of all the infrastructures that PedCRIN would be working alongside. Hence the scope of the PedCRIN Sustainability Board needs to take account of the whole landscape which has evolved significantly since 2017. Additionally, the members of the PedCRIN Sustainability Board may also be interested in members of similar groups relating to the other initiatives. In the light of these developments and uncertainties there has been a delay in inviting members to the Sustainability Board. These tasks and the deliverables are planned to be performed in coming months and the delay in achieving these tasks will in no way have any impact on the achievements of the project.

Scottish Grampian linked third party to ULIV patient engagement expert, has been involved in participating and contributing to teleconferences, attending a fact to face meeting (PedCRIN annual meeting) in Bergen (23-24 April, 2008) and reviewing and commenting on papers. The justification for the need of this party was to be inclusive of Scotland so that the entire United Kingdom could be represented. The sustainability aspect had been discussed with the expert from the Scottish Grampian and case studies are currently being collated into a brochure which will demonstrate what PedCRIN can offer. Likewise, the Scottish expert has also worked within WP5 supporting FSJD and VSOP in the development of a consultation plan for the existing YPAGs in Europe and the patients in the PedCRIN funded WE study. Six person months has been allocated by ULIV to cover this resource.
1.2.3 Work Package 3: Tools for paediatric trials (M1-36)

**Task Leader:** CVBF (Donato Bonifazi), INSERM (Evelyne Jacqz-Aigrain)

**Objectives**

The objectives and aims of WP3 of the PedCRIN project during the reporting period were:

1. Survey on infrastructure and service needs for paediatric and neonatal trials
2. Gap analysis based on survey data
3. Upgrade, maintenance and sustainability of tools for paediatric trials
4. Upgrade, maintenance and sustainability of tools for neonatal trials
5. Procedure for access to individual patient clinical trial data

### 1.2.3.1. Task 3.1: Survey on users’ needs among the paediatric community M1

**Task Leader:** Gianni Benzi Pharmacological Research Foundation - FGB, linked third party of CVBF (Adriana Ceci); **Tasks contributors:** CVBF, INSERM, VSOP & ECRIN

To identify the needs of paediatricians in terms of infrastructures and tools for clinical trials and to ensure that PedCRIN tools will respond to these needs. A survey targeting the paediatric and neonatal users and patients communities was launched. The preparation of the survey started in January 2017 and was concluded in March 2017. The final questionnaire consisted of three sections, i.e.:

1. General identification (asking information about the responder)
2. Previous experience in paediatric & neonatal clinical research
3. Needs for infrastructure services and tools for paediatric & neonatal clinical trials

Furthermore, in order to increase the survey’s acceptability and response rate, as many closed-ended questions (yes-no questions, multiple choice questions and ordinal-scale questions) as possible were included in the survey. All task contributors (CVBF, INSERM, VSOP and ECRIN) participated in drafting and finalization of the questionnaire. The web-based survey was distributed to 663 recipients, including representatives of the European paediatric clinical research community, between April and May 2017; 147 complete questionnaires were returned, achieving a response rate of 22.2%. A detailed description of the survey was provided in deliverable D3.1-Survey on infrastructure and service needs for paediatric and neonatal trials, submitted to the European Commission in March 2017.

On the basis of the survey results a manuscript entitled “Paediatric clinical research in Europe: an insight on experts’ needs and perspectives” was drafted and obtained the validation of the PedCRIN Steering Committee for publication. All task contributors participated in the review of the manuscript. The manuscript will be submitted for publication during the next reporting period.

### 1.2.3.2. Task 3.2: Gap analysis (M6)

**Task Leader:** CVBF (Mariangela Lupo); **Tasks contributors:** FGB (linked third party of CVBF)

Based on this survey and the evaluation of the existing tools developed by ECRIN and by other paediatric projects a gap analysis was performed to detect missing tools and services to support the management of paediatric and neonatal trials. To perform the PedCRIN gap analysis a 3-steps methodology was adopted (i) Analysis of the current situation (ii) Identification of the needs & (iii) Identification of the future actions and steps.

In line with ECRIN mission and services offered, six areas of interest were identified and explored according to survey (Task 3.1):

1. Scientific and methodological expertise (protocol design and statistics, target population and innovative designs)
2. Collaboration and support for clinical trials start-up (legal and financing, patient’s engagement and networking for site selections)
3. Regulatory expertise (interactions with agencies, preparing and submitting regulatory and ethical documents)
4. Paediatric pharmacovigilance (age adapted methods for assessment and reporting of ADRs)
5. Paediatric clinical trials conduct according to GCP and paediatric guidelines/recommendations (trial management, data management, monitoring, IMPs management)
6. Training (GCP, pharmacovigilance, trial management)

A detailed description of the gap analysis was provided in deliverable D3.2-Gap analysis, submitted to the European Commission in August 2017. On the basis of the survey results a manuscript entitled “Needs and gaps in the paediatric research community: where are we now?” was drafted and obtained the validation of the PedCRIN Steering Committee for publication. All task contributors participated in the review of the manuscript. The manuscript will be submitted for publication during the next reporting period.

1.2.3.3. Task 3.3: Upgrade, maintenance and sustainability of tools for paediatric trials (M12)

**Task Leader:** CVBF (Donato Bonifazi)

Activities of this task have been divided into 8 sub-tasks:

1. Ethical and regulatory database
2. Pharmacovigilance
3. Monitoring and appropriate knowledge of standard values by age group
4. Biosample management
5. Methodology guidelines for trials design for small sample size
6. Database of standard and patient-centered outcome measures
7. Certification of paediatric CTUs
8. Coordination with other research infrastructures (EATRIS, BBMRI)

The work carried out during the reporting period was mainly focused on the upgrade of the ethical and regulatory database, on the development of pharmacovigilance and biosample management tools, and on the preparation of the list of criteria for the certification of neonatal and paediatric CTUs.

**Ethical and regulatory database**

**Sub-task Leader:** CVBF (Cristina Manfredi); Tasks contributors: INSERM (Evelyne Jacqz-Aigrain), ECRIN (Christine Kubiak & Mihaela Matei)

An action plan was drafted for the upgrade of the CAMPUS database (an online database http://campus.ecrin.org/ developed by ECRIN, providing country-specific information on regulatory and ethical requirements in clinical research across Europe). The plan is comprised a 3-steps process:

1. Analysis of the contents currently available on CAMPUS concerning paediatric
2. Definition of the information to be added regarding the paediatric population
3. Inclusion of the new contents within the CAMPUS database

The first 2 steps were concluded in June 2017 with the identification of the information relevant for neonatal and paediatric trials to be added in the database:

- Official language(s) for the information sheet and the informed consent (IC)
- Legal age of consent
- Mandatory signatories on IC form
- Specifications regarding assent from the minor: age in which assent from the minor becomes mandatory or suggested
- Information on material used to describe the clinical trial to the minor: type of material, age classification, administration modalities
- Any other relevant supplementary information (e.g., existence of a national ethics committee dedicated to paediatric population, how to take into account the minor's will in case of conflicting informed consent and assent and details on experimental procedures if available, etc.).
Activities were centered on collecting the above mentioned information for 22 Countries already included in the CAMPUS database (Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Spain, Sweden, Switzerland, Turkey and United Kingdom). Data collection was not only limited to the countries included in the CAMPUS database but was also expanded to other EU and non-EU countries (Bulgaria, Croatia, Estonia, Latvia, Lithuania, Malta, Slovakia, Slovenia). The data collection process follows a two-step validation procedure which has currently been completed for a couple of countries and will be completed in the next reporting period with the support of all partners of the PedCRIN project.

**Pharmacovigilance**

*Sub-task Leader: CVBF (Mariagrazia Felisi); Tasks contributors: INSERM, ULIV & ECRIN*

Activities within this sub-task are aimed at the development of pharmacovigilance instruments, such as age-adjusted tools for the collection and assessment of adverse drug reactions (ADRs), to be applied during the conduct of a paediatric clinical trials. To achieve its objectives, the following 6-steps methodology was developed:

1. Literature search to identify the already available tools for collection and assessment of adverse events
2. Integration with results from gap analysis
3. Identification of those tools suitable for/adaptable to the paediatric population
4. Design of age-adjusted tools for AEs/ADRs collection and assessment in paediatric clinical trials.
5. Implementation of the tools in pilot trials
6. Evaluation of results

During the reporting period, the first 3 steps of the methodology were achieved and the fourth is ongoing. The systematic search on the scales used for the assessment of causality and of severity of adverse events was completed in September 2017. The results were shared with PedCRIN partners and a poster entitled “Identification of available tools for the assessment of causality and severity in paediatric population” was presented at the 18th World Congress of Basic and Clinical Pharmacology (WCP2018) which was held from 1 to 6 July 2018, in Kyoto (Japan). In addition, a manuscript on the results of this research is being finalised; a request for validation will be submitted to the Steering Committee in September 2018. The results of the gap analysis were integrated with the initial plan of action, confirming in particular the need for age-adapted scales for severity and causality assessment in paediatric patients and for targeted serious adverse events notification forms. An age-adapted scale for causality assessment (the Liverpool ADR causality assessment tool) was identified. As for the severity assessment, a version of the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) scale adapted for the neonatal population was found as a suitable candidate for validation. A proposal to test these two instruments within the PedCRIN funded pilot trials is currently under review.

In addition, activities related to the certification of centers being able to perform pharmacovigilance activities are ongoing; a working group is currently being set up and it will also include the paediatric specificities. ECRIN is also leading the activities related to the certification of pharmacovigilance centers.

**Biosample management**

*Sub-task Leader: FGB, linked third party of CVBF (Lucia Ruggieri); Tasks contributors: BBMRI-ERIC*

The aim of this sub-task is to include specific information on biosample-related aspects in the procedures for the management of neonatal and paediatric trials. This information will be included in a checklist of key items to be considered for the management of biological resources in paediatric/neonatal clinical trials, on the basis of the European applicable rules and legislation. During the reporting period, the following activities have been performed:
Identification of topics and research questions
In agreement with BBMRI-ERIC, five key topics were identified: (i) sample volume (ii) minimizing harm and maximizing welfare (iii) skills, training and facilities required for sampling (iv) consent and data protection and (v) long-term storage of biological sample. For each topic, specific research questions were developed to guide the research and consultation of official EU sources.

Search and analysis of relevant documents for checklist development
An extensive search and analysis of official European sources was carried out, as main reference documents. If official European documents have not been found literature database (PubMed) and other validate sources (e.g. International consolidated guidelines) has been consulted.

A report of the activities and the results of the research and analysis is currently being drafted. This document will be the basis for the preparation of the check-list of key items to consider for the management of biological resources in paediatric/neonatal clinical trials.

Certification of paediatric clinical trial units [CTUs] (M12)
Sub-task Leader: CVBF (Donato Bonifazi); Tasks contributors: Ospedale Pediatrico Bambino Gesù (OPBG), linked third party of CVBF, INSERM & ECRIN
A first draft of deliverable “D3.4-Criteria for certification of neonatal and paediatric CTUs” was prepared and shared with sub-task contributors. The main objective of this task is to outline an appropriate definition of the CTU that should assist to ensure a quality support for the management of academic or industry-sponsored neonatal & paediatric multinational clinical trials, which in turn will be raising the quality of trial management in the participating countries. In order to further discuss with all consortium partners and explore the best way to deliver the requirements, the deliverable was postponed and will be released in December 2018.

1.2.3.4. Task 3.4: Upgrade, maintenance and sustainability of tools for neonatal trials (M12)
Task Leader: INSERM (Evelyne Jacqz-Aigrain)
While neonates are part of the paediatric population, there are specific technical, ethical, and safety requirements that may be different from the paediatric population to be considered when designing and conducting a neonatal clinical trial. Nevertheless, some others are quite similar to paediatric clinical trials (e.g., methodology for trials design, regulatory and ethical requirements, etc.) therefore, activities of tasks 3.3 and 3.4 are closely related. Task 3.4 activities have been divided into the same 8 sub-tasks (similarly to task 3.3), adding particularities for neonates when necessary.

Pharmacovigilance
Sub-task Leader: INSERM (Evelyne Jacqz-Aigrain)
Though the general principles of pharmacovigilance such as assessment of causality, severity, seriousness for individual case safety reports and patient populations apply across all age groups including neonates, it is recognised that pharmacovigilance in neonates requires further specific expertise. Compared to older children and adults, there are notable differences that impact neonatal pharmacovigilance for example in pharmacokinetics and pharmacodynamics, reference values, disease aetiology, comorbidities, co-medications and prognosis. Furthermore, in-utero exposure and prematurity need to be taken into consideration during signal detection and at the time of causality assessment and evaluation of the benefit-risk balance. As actual commonly used approaches appear to be less reliable when applied to the neonatal population (Naranjo scale for example), pharmacovigilance tools need to be adapted to take into consideration the characteristics that are specific to neonates.

A literature review on neonatal pharmacovigilance was completed during the reporting period. Activities are now focusing on a population tailored-approach developing pharmacovigilance tools for neonatal adverse drug reaction (ADR) causality and severity assessment, but also prevention.

Monitoring & appropriate knowledge of standard values by age group
Sub-task Leader: INSERM (Evelyne Jacqz-Aigrain)
A well designed clinical trial must protect the patients enrolled and provide high quality data to achieve its objective. Monitoring of patient data is crucial in clinical trials for detecting and reporting any deviation or failure to the study protocol and ensuring an efficient and safe study conduct. To this objective, the conventional monitoring approach is moving to a risk-based monitoring approach (RBM) driven by regulations and is supported by initiatives like Transcelerate to prevent and mitigate sources of trial conduct errors, tailoring the monitoring to trials specificities and improve its effectiveness through centralized processes.

The difficulties of recruiting patients in neonatal clinical trials are well known, the population being scarce, and with the multiple comorbidities that patients of neonatal trials may suffer from. RBM is of major importance in neonatal clinical trials not only to ensure patients’ safety but also improving data quality while reducing costs of multiple on-site visits, and therefore facilitating and promoting paediatric trials development. Defining the most appropriate monitoring plan for neonatal trials also depends on the monitoring of patients’ biological values collected to identify their relevance according to the aim of the trial and detect abnormalities that could be associated with investigational drug administration. Therefore, a literature review was completed and data was compiled with references values routinely used in Robert Debré paediatric clinical investigation unit. However, these data must be carefully interpreted considering that technical aspects (analytical methods used) may have an influence on the laboratory values resulting in a possible variability among laboratories (e.g. serum creatinine).

Methodology guidelines for trials design for small sample size

Sub-task Leader: INSERM (Evelyne Jacqz-Aigrain)

Designing paediatric clinical trials is challenging and even more when it comes to the neonatal population. Due to the lack of data in this particular population, ethics plays a major role in neonatal trials orienting their design adding complexity to technical and practical issues already challenging paediatric/neonatal trials. Therefore, a first step has been achieved aiming to review and identify guidelines and recommendations papers on investigation of medicinal products in the neonatal population. As defining the right design for the appropriate question to be answered is the key step for a safe and efficient trial conduct, a methodological repertoire is being prepared along with a decision tree that would help answering questions that investigators and methodologists may have i.e. the existing type of studies and evidence they can provide, the data needed to demonstrate the study feasibility and the scientific relevance etc. Likewise, information on innovative approaches (statistical modelling) will be detailed.

1.2.3.5. Task 3.5: Disseminate tools to members of PedCRIN

Task Leaders: CVBF (Cristina Manfredi), INSERM (Evelyne Jacqz-Aigrain)

Dissemination activities among members of PedCRIN have not been started yet. At the PedCRIN Annual Meeting held in Bergen last 23rd and 24th April 2018, the Liverpool ADR causality assessment tool was presented and the Principal Investigators of the 3 pilot studies selected within WP4 have been proposed to use the Liverpool ADR causality assessment tool when assessing the causality of serious adverse events occurring in their studies.

1.2.3.6. Task 3.6: Procedure for access to individual patient clinical trial data (M6)

Task Leader: ECRIN (Jacques Demotes); Tasks contributors: CVBF

Providing the scientific community with access, upon request, to access to individual patient-level clinical trial data is part of the ECRIN eligibility criteria, assessed during the evaluation of projects asking for support to trial management. This eligibility criterion has been also used for the selection of projects for PedCRIN funding. In addition to the tool development task of WP3 another objective is to develop a framework in which, ultimately, all of the patient level data from these pilot paediatric clinical trials becomes available to those who can demonstrate they can make appropriate use of it. However, there is currently no established procedure (who should request data, what should be the content of the protocol for re-analysis / meta-analysis, who should be the data custodian providing access etc.).

To overcome this barrier PedCRIN members ECRIN & WP3 members are establishing a procedure for patient level data in paediatric and neonatal trials based on the principles and practical recommendations.
set by the H2020 funded project CORBEL (Coordinated Research Infrastructures Building Enduring Life-science Services). As the CORBEL principles and practical recommendations for providing access to individual participant data from clinical trials have focused particularly on non-commercial European trials. Therefore, the recommendations set by CORBEL project would not only assist PedCRIN members towards establishing a procedure for patient level data in paediatric and neonatal pilot trials (PedCRIN funded trials) but will also be a window of opportunity for implementing and testing in practice. The methods and procedures for data sharing that could be adopted for PedCRIN have been already detailed in the report submitted regarding this task by ECRIN therefore here only a summary is presented.

1.2.4 Work Package 4: Pilot trials (M1-48)

Task Leader & co-leader: ECRIN (Christine Kubiak), RUMC (Saskia De Wildt), HUS-FI (Pirkko Lepola)

Objectives
The objectives and aims of WP4 of the PedCRIN project during the reporting period were:
1. Launch a single stage call to provide management services for the extension of the selected studies in the countries other than the principal investigator’s one through translational access.
2. To establish criteria for eligibility and the selection of the trials and to set-up an independent Scientific Board for the selection
3. To select the projects
4. To provide transnational access to services for the selected clinical paediatric trials to facilitate extension to other countries that are members of the PedCRIN consortium
5. To evaluate the costs of transnational access for the selected pilot trials
6. To write a procedure for patient level data sharing

1.2.4.1. Task 4.1: Specification of the call (M1)

Task Leader & co-leader: ECRIN (Christine Kubiak), RUMC (Saskia De Wildt), HUS-FI (Pirkko Lepola)

Contents of the call was discussed and specified via multiple teleconferences and emails. Following the validation of the content by the members of WP4 a single stage call for application was launched at M1 (January 2017) to inform the scientific community, with a deadline at M4 (2nd May 2017, 17.00 CET), through members of WP5 (Communication, dissemination and advocacy), ECRIN website and ECRIN partners, the consortium partners, other international networks (eg.INCiPiT, ERA-net, Teddy Network & social media (Twitter).

Call specification included the full protocol, together with evidence of funding in the coordinating country, validated evidence of feasible recruitment plan, information about the regulatory or ethical issues, trial duration to primary outcome shorter than two years, the services requested, the evaluation of costs for services, the countries involved (at least 3 European countries within the PedCRIN consortium) and the extent of involvement of patients and parents in the design and implementation of the study. Applicants were asked to provide this information using a special template (PedCRIN call template). In the call application the list of management services to be covered was clearly mentioned (Call application page 2 (Figure 1). The management services offered were:
- Interaction with ethics committees and competent authorities (submission and follow up);
- Support for insurance contracting;
- Translation, back-translation of relevant documents and adaptation of informed consent;
- Local site monitoring;
- Local support to adverse event reporting;
- Investigational medicinal product (IMP) management;

Moreover, it was also clearly mentioned that this funding scheme does not cover:
- The cost of study management in the coordinating country
- The cost related to patient investigation (call application page 2
1.2.4.1.1. PedCRIN call outcome

In response to this call 13 applications were received (Figure 2) from (6) different EU countries. Of these studies neonatal were (3), paediatric (7) and both neonatal and paediatric (3).

<table>
<thead>
<tr>
<th>PedCRIN WP4 Call Application Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total No. Applications Received</strong></td>
</tr>
<tr>
<td>---------------------------------------</td>
</tr>
<tr>
<td>13</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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</tr>
</tbody>
</table>

Figure 2: PedCRIN Call application response
1.2.4.2. Task 4.2: Selection of the Projects (M1)

**Task Leader & co-leader:** Christine Kubiak (ECRIN), Saskia De Wildt (RUMC), Pirkko Lepola (HUS-FI)

The criteria used for the selection/evaluation of the projects (below) were also mentioned in the call specification and as well as in the proposal template (download here) which was provided for the submission of the applications.

**Eligibility**
- Multi-center paediatric or neonatal therapeutic interventional clinical studies on medicinal products
- Having secured funding in the coordinating country
- Investigator-initiated studies
- Studies conducted in at least three European countries, among the 18 members of the PedCRIN consortium

**Evaluation Criteria**

A scoring system from 0 to 5 will be used to evaluate the applications with respect to the different evaluation criteria. Each item (1 to 4) will be rated by using rating system of 0-5 scores per category. Proposals with a combined (total) score below 15/20 will be excluded, as well as a proposals whose one or more criteria are scored below 3/5 per item.

**Evaluation items**
1. Scientific excellence
2. Quality of the methodology
3. Medical relevance, impact on public health and ethical dimension
4. Feasibility of the study within the timelines and in line with the budget (including evidence of secured funding in the coordinating country)
   - Without obstacle to authorization by ethics committees and competent authorities
   - Evidence for rapid patient recruitment
   - Short follow-up period Budget for services in the range of €300k to €500k
   - Appropriate risk assessment and risk mitigation strategy to overcome potential roadblocks

**Scoring system:**
Based on the evaluation criteria the following scoring system was used (Table 2):

<table>
<thead>
<tr>
<th>Score</th>
<th>Rating</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Failure</td>
<td>The proposal fails to address the criterion in question, or cannot be assessed because of missing or incomplete information</td>
</tr>
<tr>
<td>1</td>
<td>Poor</td>
<td>The proposal shows serious weaknesses with regards to the criterion in question</td>
</tr>
<tr>
<td>2</td>
<td>Fair</td>
<td>The proposal generally addresses the criterion, but there are significant weaknesses that need corrections</td>
</tr>
<tr>
<td>3</td>
<td>Good</td>
<td>The proposal addresses the criterion in question well but certain improvements are necessary</td>
</tr>
<tr>
<td>4</td>
<td>Very good</td>
<td>The proposal addresses the criterion very well, but small improvements are possible</td>
</tr>
<tr>
<td>5</td>
<td>Excellent</td>
<td>The proposal successfully addresses all aspects of the criterion in question</td>
</tr>
</tbody>
</table>

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1 Austria, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, the Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland, United Kingdom
1.2.4.2.1. Task 4.3: Composition of Scientific Board (M1)

To select the projects for PedCRIN funding, a Scientific Advisory Board comprising of ECRIN, PedCRIN consortium members and external experts was formed (Table 3). This Scientific Advisory Board (SB) had a main task to evaluate grant submissions based on the criteria described above.

Table 3: Composition of Scientific Board

<table>
<thead>
<tr>
<th>ECRIN Scientific Board Secretariat &amp; Scientific reviewers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECRIN Scientific Board members</strong></td>
</tr>
<tr>
<td>Silvio Garattini (Italy) (Chair)</td>
</tr>
<tr>
<td>Pharmacology</td>
</tr>
<tr>
<td>Clinical trials</td>
</tr>
<tr>
<td>Xavier Carné (Spain)</td>
</tr>
<tr>
<td>Pharmacology</td>
</tr>
<tr>
<td>Clinical trials</td>
</tr>
<tr>
<td><strong>PedCRIN consortium</strong></td>
</tr>
<tr>
<td>Kalle Hoppu (Finland)</td>
</tr>
<tr>
<td>Paediatric</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
</tr>
<tr>
<td>Saskia de Wildt (The Netherlands)</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
</tr>
<tr>
<td>Evelyne Jacqz-Aigrain (France)</td>
</tr>
<tr>
<td>Neonatology</td>
</tr>
<tr>
<td>Paediatric pharmacologie</td>
</tr>
<tr>
<td>Pharmacogenetics</td>
</tr>
<tr>
<td>Kim Karsenberg (patient) (The Netherlands)</td>
</tr>
<tr>
<td><strong>External to PedCRIN consortium</strong></td>
</tr>
<tr>
<td>Prof. Anton van Kaam (The Netherlands)</td>
</tr>
<tr>
<td>Neonatology</td>
</tr>
<tr>
<td>Neonatal pulmonology, lung physiology, lung injury, neonatal ventilation</td>
</tr>
<tr>
<td>Dr Lissy de Ridder (The Netherlands)</td>
</tr>
<tr>
<td>Paediatric Gastroenterologist</td>
</tr>
<tr>
<td>Prof Imti Choonara (United Kingdom)</td>
</tr>
<tr>
<td>Toxicology, Clinical Pharmacology, Paediatrics</td>
</tr>
<tr>
<td>Prof Paolo Rossi (Italy)</td>
</tr>
<tr>
<td>Immunology, Paediatrics</td>
</tr>
<tr>
<td><strong>Observers (input on logistical review, recruitment, timelines, budget)</strong></td>
</tr>
<tr>
<td>Pirkko Lepola (Finland)</td>
</tr>
<tr>
<td>Clinical Trials Management, Pediatric Clinical Trials</td>
</tr>
<tr>
<td>Christine Kubiak (France)</td>
</tr>
<tr>
<td>Pharmaceutical Sciences</td>
</tr>
<tr>
<td>Joaquin Sáez Peñataro (Spain)</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
</tr>
<tr>
<td><strong>Methodologist</strong></td>
</tr>
<tr>
<td>Rebecca Lundin (Italy)</td>
</tr>
<tr>
<td>Social epidemiologist with expertise in policy analysis, data management and analysis, and planning and implementation of pharmacoepidemiology studies</td>
</tr>
<tr>
<td><strong>ECRIN Methodologist Panel</strong></td>
</tr>
<tr>
<td>Luis Azevedo</td>
</tr>
<tr>
<td>Janus Jakobsen</td>
</tr>
<tr>
<td>Marina Maggini</td>
</tr>
<tr>
<td>Philippe Ravoud</td>
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<tr>
<td>Ferran Torres</td>
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<tr>
<td>Valter Torri</td>
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</tbody>
</table>

1.2.4.2.2. Selection process

During the first selection procedure of 13 applications, one study was excluded; since this study related to the medicinal device did not include a medicinal product or intervention. The remaining studies were circulated for evaluation by the (co-) rapporteurs. Each SB member received all applications through secured web-based database for the assessment and evaluation. The evaluation was conducted in a written form within the database.
The applications were allocated to one Rapporteur, one co-Rapporteur, and one methodologist (not necessarily Scientific Board members). Observers provided input in operational review, recruitment, timelines and budget. The allocation of the projects was performed on May 8th, 2017 and the rapporteurs had a timeline to write the assessment for the advisory report by June 5th, 2017. The evaluation report was then circulated to the PedCRIN SB, PedCRIN consortium and external PedCRIN consortium to be scored and to identify the best projects to be invited to present their project during the face-to-face meeting in Paris at 3-4 July (Figure 3).

**Figure 3: Timelines for project selection**

1.2.4.2.3. **Method for project selection**

A scoring system from 0 to 5 (already explained in section 1.2.4.2 (Table 2) was used to evaluate the initial applications. After the preliminary evaluation by the scientific board four projects were shortlisted and their principal investigators were invited for the face-to-face with the SB members meeting in Paris. Finally three project were selected for PedCRIN funding (POPART, WE & OTBB3).
1.2.4.3. Task 4.4: Cost evaluation for the selected trials (M7)

**Task Leader & co-leader:** ECRIN (Christine Kubiak), RUMC (Saskia De Wildt), HUS-FI (Pirkko Lepola)

Following the selection of trials, each of the partner involved in the provision of services provided a cost estimate based on the real activities as discussed with the sponsors and coordinating investigators. A summary of the procedure is presented below Figure 4.

![PedCRIN Cost Estimation Procedure](image)

**Figure 4: PedCRIN Cost Estimation Procedure**

1.2.4.4. Services to multinational clinical trials & progress

The aim of the WP4 is to provide transnational access in order to facilitate the conduct of PedCRIN funded multinational neonatal & paediatric pilot clinical trials. To this aim, PedCRIN is covering the cost of operational & management services (Figure 5) for multinational implementation of clinical studies as selected through the competitive PedCRIN call for funding described in task “call specification”. Three projects are currently supported (POPART, WE & OTBB3). An additional objective of this activity will be to analyse the results of the support provided and to identify the gaps. For all the clinical trials, a first step was the agreement with the sponsor about the delegated tasks (detailed task delegation), the procedures, the communication flows and the contracts. The duration of this phase is highly depending on the readiness of the sponsor, the sites and the PedCRIN partners providing the services (see Figure 5).
Figure 5: Operational & management services to PedCRIN funded multinational paediatric and neonatal trials

The progress of the ongoing supported trials (countries involved, services provided, recruitment status, etc.) are reported below.

1.2.4.4.1. POPART trial

The POPART Trial: Prophylactic Oropharyngeal Surfactant for Preterm Infants: A Randomised Trial

**Sponsor:** University College Dublin/Ireland  
**Coordinating Country:** Ireland  
**Countries (No. of sites):** Ireland (2) Czech Republic (4), Norway (2), Belgium (1), Portugal (1), Italy (2), Sweden (1), and Denmark (1)  
**Study Design:** Randomised, parallel group, controlled trial (Phase III)  
**Investigational Medical Product (IMP):** Curosurf (Chiesi Farmaceutici, Parma, Italy) 120mg or 240mg given by injection into the oropharynx  
**Number of patients:** 250 patients are planned for study inclusion as per protocol  
**Objective:** To determine whether, among infants born before 29 weeks of gestation, does oropharyngeal surfactant at birth compared to no intervention reduce the rate of endotracheal intubation for respiratory failure within 120 hours of birth

Today, progress of the POPART trial is shown in Figure 6.
1.2.4.4.2. WE Study

WE study: Walking Easier with cerebral palsy

Sponsor: St. Olavs University Hospital/Trondheim, Norway  
Coordinating Country: Norway  
Countries (No. of sites): Norway (5) France (1), Poland (1)  
Study Design: A double blinded placebo controlled randomized parallel-group design. Multicenter study (Phase IV)  
Investigational Medical Product (IMP): Botox® (onabotulinumtoxin A), sterile vacuum-dried powder for reconstruction with sterile, non-preserved 0,9% Sodium Chloride injection USP & Sterile 0,9% Sodium Chloride injection (active comparator and placebo)  
Number of patients: A total of 96 participants are planned for study inclusion as per protocol  
Objective: Primary: to evaluate whether injections of BoNT-A in the calf muscles (mm.gastrocnemius and soleus) make walking easier in children/adolescents with cerebral palsy within a time span of 6 months.  
Secondary: to evaluate whether an improvement in energy cost during walking is associated with increased daily activity, less pain and perceived improved performance and satisfaction.  

Todate progress of the WE study is shown in Figure 7.
1.2.4.4.3. OTBB3 trial

**OTBB3 Trial:** Oxytocin Treatment in neonates and infants (BaBies) with Prader-Willi syndrome: effects of intranasal administrations of oxytocin in infants aged from 0 to 3 months vs. placebo on sucking and swallowing (phase III clinical trial)

**Sponsor:** University Hospital Toulouse/France  
**Coordinating Country:** France  
**Countries (No. of sites):** France (5) Belgium (1), Germany (1), Italy (1) and Netherlands (1)  
**Study Design:** Multicentre, prospective, randomized, placebo-controlled, double-blind clinical trial (Phase III)  
**Investigational Medical Product (IMP):** Not available yet  
**Number of patients:** 52 patients are planned for study inclusion as per protocol  
**Objective:** The primary objective is to assess the effect of OXYTOCIN (OXT) administration versus Placebo on sucking/swallowing after 1 month of 4IU intranasal OXT treatment administered every other day. The secondary objectives are to document: (i) the effect of OXT administration for 1 month on (sucking/swallowing, food intake, development (weight, growth and head circumference changes), behavior, circulating hormones involved in appetite behavior, growth and metabolism), (ii) the tolerance to repeated OXT administration for 1 month, (iii) the best duration for daily administration of OXT between 1 and 2 months of treatment for (sucking/swallowing troubles, social engagement, mother-infant interactions & development as measured at month 3).

The activities for the trial OTBB3 did not start yet, due to the need to produce the Investigational Medicinal Product. The initial timelines were then shifted in order to comply with the PedCRIN project.
timelines. The WP leaders maintain close follow-up and discussions with the coordinating investigator. The updated plan of OTBB3 trial is shown in Figure 8.

1.2.4.5. Task 4.7: Procedure for patient level data sharing (M6)
The procedure for patient level data sharing which will be used in PedCRIN is already mentioned in section 1.2.3.6 (Task 3.6: Procedure for access to individual patient clinical trial data M6).

1.2.5 Work Package 5: Communication, dissemination, empowerment (M1-48)
Task Leader: FSJD (Joana Claverol Torres), VSOP (Cor Oosterwijk)

Objectives
The objectives and aims of WP5 of the PedCRIN project during the reporting period were:

1. To communicate about PedCRIN with children, parents and families, industry, regulatory authorities, policymakers, healthcare providers and all the relevant stakeholders.
2. To ensure children, young people, parents and families are included in all PedCRIN activities.
3. To educate and empower young patients and their families during all the process of a clinical trial (recruitment, development, etc.)
4. Evaluate the impact of the education and empowerment activities to different target groups.

1.2.5.1. Task 5.1: Communication and Dissemination Plan (M3)
Task Leader: FSJD (Joana Claverol Torres)
A Communication and Dissemination Plan is developed and executed. The plan includes a definition of different target groups and audiences at local, regional and European levels, as well as methods and tools for internal and external communication, key messages, frequency of communication/dissemination and tasks and responsibilities of the members. The medium used to reach
different target group and audience includes social media, website, printed materials, webcasts, lecture materials etc. as appropriate.

1.2.5.2. Task 5.2: Project Website (M3)

Task Leader: FSJD (Joana Claverol Torres)
The public website is live at www.pedcrin.org as the main dissemination and communication tool, providing general information and access to the project relevant resources. The structure of the website enables visitors to easily navigate to the publicly accessible pages, namely: home page (overview of the project), activities, news, and call for projects, international collaborations and publication (Figure 9).

Figure 9: PedCRIN Home page

1.2.5.3. Task 5.3: Logo and Brochure (M3)

Task Leader: FSJD (Joana Claverol Torres), VSOP (Cor Oosterwijk)
Brochure was created to summarize the project background, objectives, planned work and project outputs. And was sent to partners, it is also available on the public website in Pdf format. A project logo was designed in agreement with the partners.

1.2.5.4. Task (5.4, 5.4, & 5.6): Project newsletters (M6, 12, 18)

Task Leader: VSOP (Cor Oosterwijk)
The PedCRIN project newsletter (Figure 10) is released twice a year, providing summary of the project progress and related events, as well as, information about the other paediatric European Commission-funded projects (H2020-EPTRI, IMI-C4C etc.). A Pdf copy of the newsletter is uploaded on the project website and a link to the newsletter was provided on the project’s social media accounts. Additionally
the newsletter distributed by email to the consortium partner organisations and other members who have subscribed to it by registering online. The consortium members also had the responsibility of circulating the newsletter among their contacts. During the 18 months of the project three newsletters are released.

1.2.5.5. Task 5.12: Press release and factsheet (M1)

**Task Leader:** FSJD (Joana Claverol Torres), VSOP (Cor Oosterwijk)

To communicate and explain the PedCRIN project to a lay audience (general public, young people, parents and families), a factsheet was developed in English and translated in 6 additional EU languages i.e. French, Finnish, German, Spanish, Italian and Dutch (Figure 11). The factsheet is accessible via the project website [http://www.ecrin.org/projects/pedcrin/newsroom/publications](http://www.ecrin.org/projects/pedcrin/newsroom/publications).

A Press Release was performed at the start of the project. Partners were asked to distribute and post it on their websites as well as on social media accounts. Efforts are being made to contact press and media to increase awareness of the project, both at local and European level. These measures are promoting awareness on the importance of clinical trials in the paediatric population while educate the general society.
1.2.5.6. Task 5.13: Report on patient engagement and perspective integration (M6)

**Task Leader:** VSOP (Cor Oosterwijk)

The role of children, young people, parents and carers during the management of multinational paediatric trials is identified through consultation with advocacy groups and young person advisory groups (YPAGs). The education and empowerment activities will be performed in the PedCRIN funded multinational multicentre pilots in WP4 (WE, POPART & OTBB3). The principal investigator of each trial provided the study-protocol and informed consent material. Patients, parents, patients’ associations and YPAGs, are enabled to give feedback on the presented protocol. In the case of diseases that affect very young children, the activity will be carried out by caregiver’s advocacy experts or experts from the patients’ association. As the funded pilot trials were already initiated in the coordinating country and had previously obtained ethical approval. Therefore, it is not feasible to make adjustments in the protocols, informed consent procedure and materials based on the feedback given by the parents, children and YPAGs. The feedback will however be provided to the principal investigators so they can use it for future research and protocol development. At present one consultation activity has been performed with the YPAG from Barcelona and will be replicated with three additional teams. These teams will contribute to review and will provide feedback to the principal investigator of the POPART-trial so they can use it in case improvements to the assent, consent and patient information sheet can be made. Similar activities are in process for the consultations of the patients/parents and patient representatives. VSOP will compile (disease) specific advocacy groups consisting of either parents, patients and/or patient representatives for the PedCRIN pilot trials. The first consultation with parents (WE-study) will take place in July 2018.

1.2.5.7. Social media

**Task leader:** FSJD (Joana Claverol Torres)

The PedCRIN project has taken benefit of the possibilities of social media as an economical set of channels for sharing updates from the project with children, parents and families, industry, regulatory authorities, policymakers, healthcare providers and all the relevant stakeholders (both existing and new contacts). Social media channels have been useful for the project in numerous ways. This includes instant updates (e.g. project news, multimedia content, announcements on upcoming project events etc.). The project has used two primary social media (Facebook & Twitter) channels shown in (Figure 12) additionally the LinkedIn profile will also be created shortly to increase the visibility of the project among professionals (researchers, scientific community, industry, institutions, outside PedCRIN consortium).
1.2.6 Work Package 6:

Task Leader: ECRIN

The objective of this workpackage is to ensure the compliance with ethics requirements in particular related to the information (including the data protection) provided to the participants, the consent process, the recruitment procedures and rights of participants in the clinical trials funded by the PedCRIN project.

In addition, the procedure for data collection, processing, storage has to comply with the EU regulation (The General Data Protection Regulation (EU) 2016/679 (“GDPR”) and with national regulations. This activity is on-going and all protocols and information and consent forms for the participants are submitted to the Ethics Committees for approval and as a pre requisite for the inclusion of the participants in the clinical trials.

This activity will be continued in the next reporting period and evidence of the compliance provided in the deliverable (6.1 & 6.2)

1.3 Impact

The main goal of this project is to enhance the capacity of ECRIN for the management of multinational multicentre neonatal and paediatric clinical trials, to enrich tools for neonatal and paediatric trials and to communicate with paediatric stakeholders including advocates for children, parents and families, industry, regulatory authorities, policymakers, healthcare providers and all the relevant stakeholders.

Therefore the accomplishment of these objective is efficiently going on by PedCRIN through providing the access to management services for the extension of the PedCRIN funded pilot trials (WP4), the development of the tools in WP3 and communication activities of WP5. Therefore project is on target and the information on section 2.1 of the description of the action (DoA) is thus still relevant, as it will contribute to the expected impacts. Hence, no updates are required.
2. Update of the plan for exploitation and dissemination of result (if applicable)
There is no need to update the original plan for exploitation and dissemination of results.

3. Update of the data management plan (if applicable)
PedCRIN does not manage research data by itself therefore, ECRIN recommends clinical trial data sharing, following the recommendations published in 2017 by Ohmann C et al «Sharing and reuse of individual participant data from clinical trials: principles and recommendations » and those mentioned in deliverable 3.3 & 4.7 on pediatric clinical trial data sharing.

4. Follow-up of recommendations and comments from previous review(s) (if applicable)
This is the first review and there are no recommendations or comments to follow up on.

5. Deviations from Annex 1 and Annex 2 (if applicable)
There are no major deviations from Annex 1 and 2 however some deliverables (Table 4) were not produced on the planned dates and an extension was requested in the submission date in discussion and agreement with the project scientific officer.

Table 4: List deliverable not produced on actual planned dates

<table>
<thead>
<tr>
<th>WP</th>
<th>Deliverable No. &amp; Title</th>
<th>Dates</th>
<th>Reason for delay</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Actual</td>
<td>Extended</td>
</tr>
<tr>
<td>1</td>
<td>D1.1: Advisory Board report 1(M8)</td>
<td>31.08.2017</td>
<td>31.08.2018</td>
</tr>
<tr>
<td>1</td>
<td>D1.2: Advisory Board report 2(M20)</td>
<td>31.08.2018</td>
<td>31.08.2019</td>
</tr>
</tbody>
</table>
| 1  | D1.3: Advisory Board report 3(M32) | 31.08.2019 | 31.08/2020 | It was important to postpone the discussions on strategy and sustainability, due to the initiation of the three other new projects in the pediatric clinical research ecosystem.  
- ID-EPTRI design study on translational research in pediatrics (started on Jan 1st 2018)  
- IMI c4c on the creation of a pediatric investigation network (started in May 2018)  
- And the SC1 EJP on rare diseases, with multiples possible overlaps (expected to start in Jan 2019)  
Note: The date of the deliverable was postponed in discussion and agreement of the scientific office (Ref: Ares(2018)723765) |
| 2  | D2.1:Strategy plan draft (M4) | 30.04.2017 | 30.04.2019 | It was important to postpone the discussions on strategy and sustainability, due to the initiation of the three other new projects in the pediatric clinical research ecosystem.  
- ID-EPTRI design study on translational research in pediatrics (started on Jan 1st 2018)  
- IMI c4c on the creation of a pediatric investigation network (started in May 2018)  
- And the SC1 EJP on rare diseases, with multiples possible overlaps (expected to start in Jan 2019)  
Note: The date of the deliverable was postponed in discussion and agreement of the scientific office (Ref: Ares(2018)723765) |
| 2  | D2.2: Report from the Sustainability Board (M15) | 31.03.2017 | 31.03.2020 |                  |
3 D3.4: Criteria for the certification of neonatal & paediatric clinical trial units [CTUs] (M12) 31.12.2017 31.12.2018 As the set of quality criteria for the neonatal and paediatric CTUs are still under discussion in ECRIN, this deliverable is pending and extension in submission date is requested in the current amendment. A first draft of the deliverable was prepared by the WP3 members and was shared with concerned project partners however, it is not finalized due to the above mentioned reason. 
Note: The date of the deliverable is postponed in subject to the current amendment

5.1 Tasks
The tasks which were not fully achieved and are not being on schedule are already detailed in Table 4. The delay in achievement of these tasks will not have any effect to the project and the resources available.

5.2 Use of resources (not applicable for MSCA)
There are no any deviations of the use of resources between actual and planned use of resources in Annex 1, in relation to person-months per work package.

5.2.1 Unforeseen subcontracting (if applicable) (not applicable for MSCA)
Subcontractors providing services for the PedCRIN funded trial (WP4) not already foreseen however subject to the current amendment.

5.2.2 Unforeseen use of in kind contribution from third party against payment or free of charges (if applicable)
To date there are no unforeseen in kind contribution from any third party against payment or free of charges