



Procedures for the set up and management of paediatric trials in the PedCRIN project

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TEDDY General Assembly – Madrid, 29 March 2019



PAEDIATRIC CLINICAL RESEARCH INFRASTRUCTURE NETWORK



January 2017



GA number 731046

**Four year
project**



- Develop capacity for the management of multinational paediatric & neonatal clinical trials
- Conduct pilot multinational paediatric trials (investigator initiated)



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PedCRIN has received funding from the European Union's Horizon 2020 programme under grant agreement number 731046

PedCRIN CONSORTIUM

ECRIN & national partners & most relevant European Networks and organizations in the field of paediatric clinical trials



ECRIN & linked third parties

ECRIN
CH: SCTO
CZ : CZECRIN
DE : KKS
ES : SCReN
FR : F-CRIN
HU : HECRIN
IT : ISS
NO : NorCRIN
PT : PiCRIN
BBMRI
EATRIS

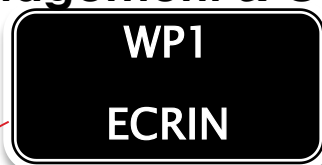
EPCT-RI partners

AT : OKIDS
CH : SCTO
EE : UTartu
ES : FSJD
FI : HUS
FR : INSERM
GR : AUTH
IRL : NCRC
IT : CVBF
NL : RUMC, VSOP
NO : HUS
SW : KI
UK : ULIV



PedCRIN PROJECT

Project Management & Coordination



Ethics



Governance-sustainability



PedCRIN

Tools for neonatal & paediatric clinical trials

Communication



Trial Support



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WP3 – TOOLS FOR NEONATAL & PAEDIATRIC TRIALS

- **Develop** tools specific for paediatric trials or **upgrade** tools already developed by ECRIN to take into consideration paediatric specifications
- Disseminate tools to members of PedCRIN and to ECRIN partners
- Train members and support the use of the tools

WP3 TASKS AND DELIVERABLES

TASKS

- 3.1: Survey on users' needs among the paediatric community
- 3.2: Gap analysis
- 3.3: Upgrade, maintenance and sustainability of tools for paediatric trials
- 3.4: Upgrade, maintenance and sustainability of tools for neonatal trials
- 3.5: Disseminate tools to members of PedCRIN and to ECRIN partners
- 3.6: Procedure for access to individual patient clinical trial data



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DELIVERABLES

- D3.1 Survey on infrastructure and service needs for paediatric and neonatal Trials
- D3.2 Gap analysis based on survey data
- D3.3 Procedure for access to individual patient clinical trial data
- D3.4 Criteria for certification of neonatal and paediatric CTUs
- D3.5 Procedures for setup of neonatal trials
- D3.6 Procedures for setup of paediatric trials
- D3.7 Procedures for management of neonatal trials
- D3.8 Procedures for management of paediatric trials



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SURVEY OF NEEDS

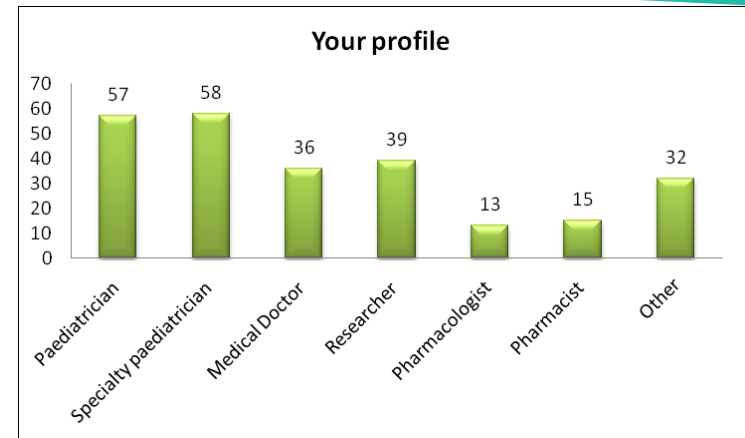
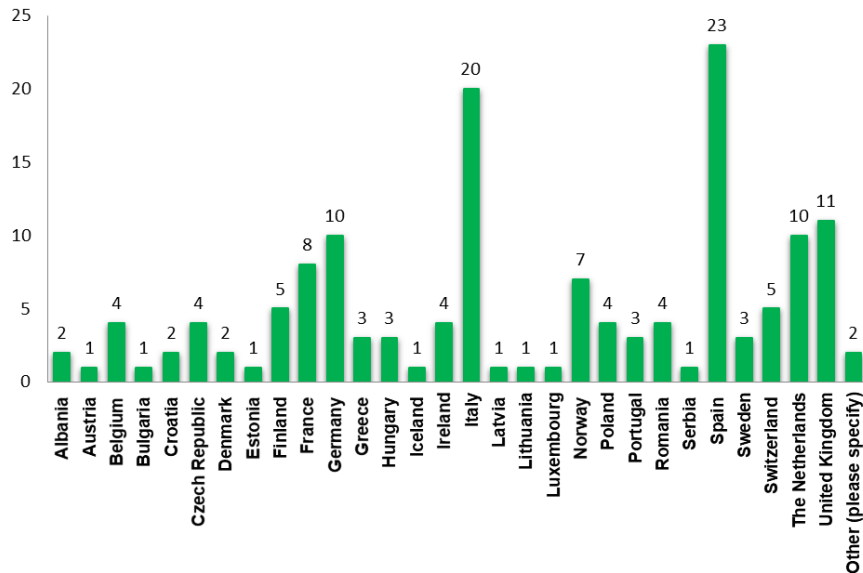
- ▶ To better understand the real needs of the scientific and users community
- ▶ 3 groups of questions:
 - a. General: personal information, country, education profile, therapeutic area*
 - b. Previous experience in paediatric clinical research: previous involvement and role in paediatric clinical trials (paediatric/neonatal)*
 - c. Needs for infrastructure services and tools for paediatric clinical trials: 29 activities referred to 6 items. Likert-scale ranging 0–4*
- ▶ Open from April 4th to May 15th, 2017

SURVEY OF NEEDS – RESPONDERS

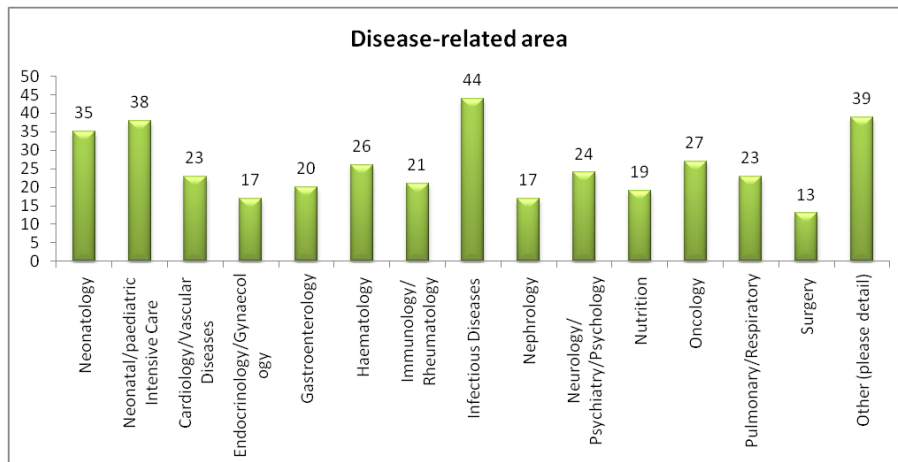
663 recipients

147 completed questionnaires from 30 countries

Response rate: 22.2%



- Paediatricians/specialty paediatricians are quite well represented, followed by researchers and Medical Doctors
- Also pharmacologists, pharmacists, regulatory experts, nurses, research managers/coordinators



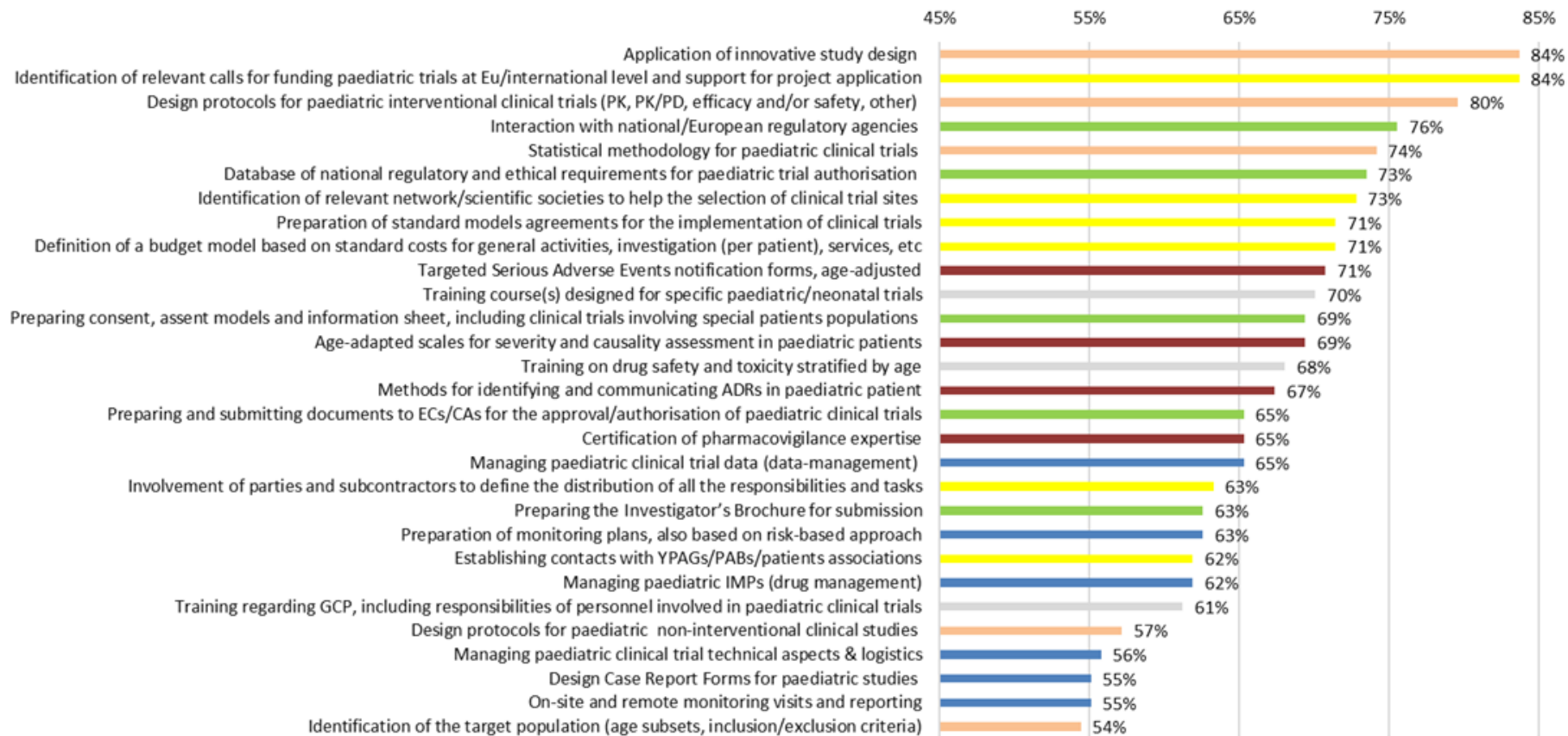
- 'Infectious diseases' is the most represented therapeutic area
- Neonatologist and paediatric/neonatal intensive care expertise are also well represented



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SURVEY OF NEEDS – RESULTS

Frequency of respondents expressing high need for each of the activities

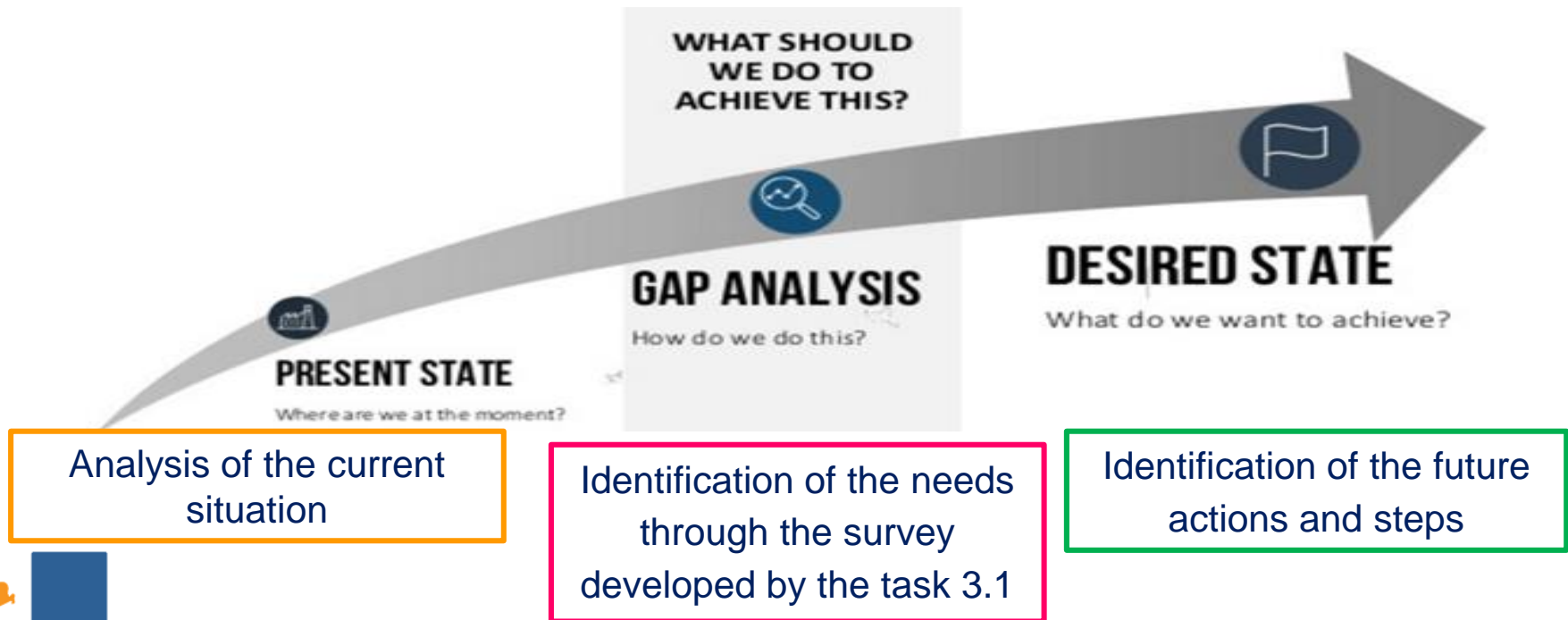


SURVEY OF NEEDS – CONCLUSIONS

- Support for the preparation of protocols for paediatric interventional clinical trials, including the application of **innovative approaches** in the design of studies → HIGHEST NEED
- Application of innovative study design → “**extreme**” for 40% of respondents
- Less request of support in case of respondents from centres belonging to a **National Network**, with respect to the others centres
- **No particular difference** emerged between neonatologists and non-neonatologists

GAP ANALYSIS


- Verify if and how the perceived gaps identified with the survey could be covered thanks to the existing and planned initiatives in the paediatric field and mainly in the framework of the PedCRIN project



GAP ANALYSIS – CONCLUSIONS

- Several paediatric initiatives and projects, funded by the EU, the TEDDY Network and the GRiP Project, Enpr-EMA and numerous specialty paediatric networks, have provided the paediatric clinical research community with several tools and expertise.
- Notwithstanding all these efforts, the survey highlighted that urgent needs are still perceived by the responders in all the aspects investigated.

Is PedCRIN able to cover the gaps identified?



The PedCRIN project is a further step to analyze the perceived and demonstrated gaps in the paediatric clinical research community and is a relevant support to other initiatives in the paediatric landscape (c4c, the IMI2 panEuropean network for paediatric clinical trials, and EPTRI, the European Paediatric Translational Research Infrastructure) that will substantially contribute to reduce the gap

TASKS 3.3 – 3.4: THEMATIC AREAS

1

- Ethical and regulatory

2

- Pharmacovigilance

3

- Monitoring and appropriate knowledge of standard values by age

4

- Biosample management

5

- Methodology guidelines for trial designs for small sample size

6

- Standard and patient-centred outcome measures

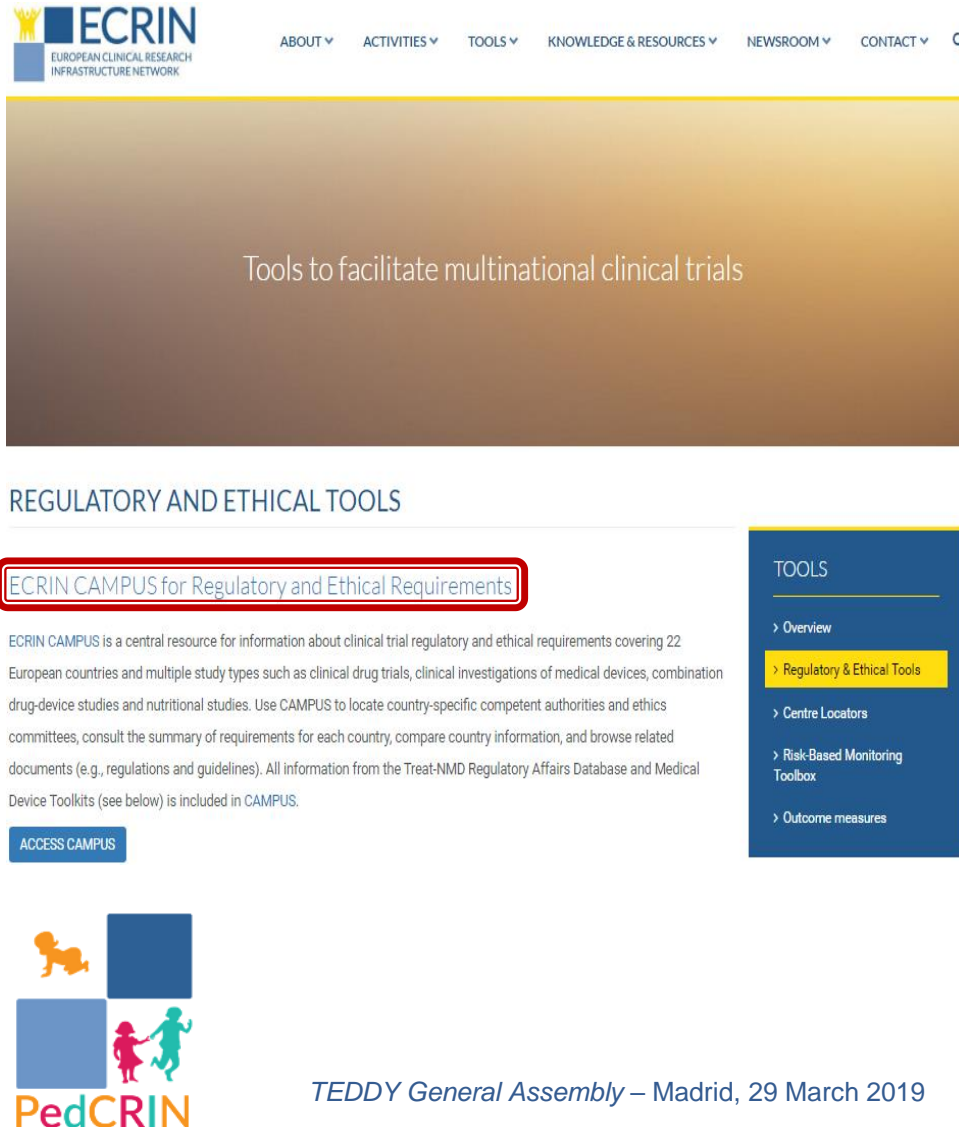
7

- Certification of paediatric CTUs

8

- Coordination with other research infrastructures (EATRIS, BBMRI)

ETHICAL/REGULATORY DB: CAMPUS



The screenshot shows the ECRIN CAMPUS website. At the top is the ECRIN logo (European Clinical Research Infrastructure Network) and a navigation menu with links: ABOUT, ACTIVITIES, TOOLS, KNOWLEDGE & RESOURCES, NEWSROOM, and CONTACT. Below the menu is a large banner with the text "Tools to facilitate multinational clinical trials". Underneath the banner is the section "REGULATORY AND ETHICAL TOOLS". A red box highlights the link "ECRIN CAMPUS for Regulatory and Ethical Requirements". Below this link is a paragraph describing ECRIN CAMPUS as a central resource for information about clinical trial regulatory and ethical requirements covering 22 European countries and multiple study types. It mentions that users can use CAMPUS to locate country-specific competent authorities and ethics committees, consult the summary of requirements for each country, compare country information, and browse related documents (e.g., regulations and guidelines). It also states that all information from the Treat-NMD Regulatory Affairs Database and Medical Device Toolkits (see below) is included in CAMPUS. Below the paragraph is a blue button labeled "ACCESS CAMPUS". To the right of the main content is a sidebar with the heading "TOOLS" and a list of links: Overview, Regulatory & Ethical Tools (highlighted in yellow), Centre Locators, Risk-Based Monitoring Toolbox, and Outcome measures. At the bottom left of the screenshot is the PedCRIN logo, which features stylized figures of a parent and a child.

ECRIN
EUROPEAN CLINICAL RESEARCH
INFRASTRUCTURE NETWORK

ABOUT ▼ ACTIVITIES ▼ TOOLS ▼ KNOWLEDGE & RESOURCES ▼ NEWSROOM ▼ CONTACT ▼ Q

Tools to facilitate multinational clinical trials

REGULATORY AND ETHICAL TOOLS


ECRIN CAMPUS for Regulatory and Ethical Requirements

ECRIN CAMPUS is a central resource for information about clinical trial regulatory and ethical requirements covering 22 European countries and multiple study types such as clinical drug trials, clinical investigations of medical devices, combination drug-device studies and nutritional studies. Use CAMPUS to locate country-specific competent authorities and ethics committees, consult the summary of requirements for each country, compare country information, and browse related documents (e.g., regulations and guidelines). All information from the Treat-NMD Regulatory Affairs Database and Medical Device Toolkits (see below) is included in CAMPUS.

[ACCESS CAMPUS](#)

TOOLS

- > Overview
- > **Regulatory & Ethical Tools**
- > Centre Locators
- > Risk-Based Monitoring Toolbox
- > Outcome measures

 PedCRIN

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- Online database including country-specific information on regulatory and ethical requirements in clinical research across Europe
- Aimed at **promoting and facilitating** multinational clinical research projects in Europe
- Currently includes information for over **22 European countries**



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ETHICAL/REGULATORY DB: CAMPUS

Medicinal Products for Human Use - AUSTRIA

[Competent Authority](#)[Competent Authority](#)[Ethics Committee](#)[Study Specific Requirements](#)[National Legislation](#)[Definitions](#)[PDF](#)[Back](#)[Contact Details](#)[Contact Details](#)

Medicinal Products for Human Use - AUSTRIA

[Trial Authorisation](#)[Ethical Review – G](#)[Competent Authority](#)[Ethics Committee](#)[Study Specific Requirements](#)[National Legislation](#)[Definitions](#)[PDF](#)[Back](#)[Submission of Ap](#)[Single-Centre Stud](#)[Study Pa](#)

Medicinal Products for Human Use - AUSTRIA

[Competent Authority](#)[Ethics Committee](#)[Study Specific Requirements](#)[National Legislation](#)[Definitions](#)[PDF](#)[Back](#)[Submission Form](#)[Multi-Centre Studie](#)[Study Pa](#)[General Information: Applicable Legislation & Conventions](#)[Language of Sub](#)[Submission of App](#)[Data Prot](#)[Clinical Trials on IMPs in Humans](#)[Submission Fees](#)[Submission Forma](#)[Insurance](#)

Medicinal Products for Human Use - AUSTRIA

[Competent Authority](#)[Ethics Committee](#)[Study Specific Requirements](#)[National Legislation](#)[Definitions](#)[PDF](#)[Back](#)[Timelines Authori](#)[Language of Subm](#)[Quality A](#)[IMP/IMP Study](#)[Amendments/ Su](#)[Submission Fees](#)[Archiving](#)[Safety Reporting](#)[Timelines Ethical R](#)[Data Protection](#)[End of Trial](#)[Amendments/ Substantial Ame](#)[CA operations/ Fees](#)[Additional Inform](#)[Safety Reporting](#)[Additional Information & Specifics](#)[End of Trial](#)

ETHICAL/REGULATORY: UPDATE DB

Informed Consent for Paediatric Clinical Trials

COUNTRY	REFERENCE LEGISLATION	AD HOC PROVISIONS FOR PAEDIATRIC CLINICAL RESEARCH	OFFICIAL LANGUAGE(S) FOR THE PATIENT INFORMATION SHEET AND THE INFORMED CONSENT FORM (ICF)	LEGAL AGE OF CONSENT	MANDATORY SIGNATORIES ON ICF	SPECIFICATIONS REGARDING ASSENT FROM THE MINOR	INFORMATION ON MATERIAL USED TO DESCRIBE THE CLINICAL TRIAL TO THE MINOR	ANY ADDITIONAL INFORMATION
Italy	http://www.aifa.gov.it/content/normativa-differimento-usi-speciali-e-sperimentazione-clinica	<ul style="list-style-type: none"> Legislative Decree no. 211 of 24th June 2003, art. 4 "Sperimentazione clinica sui minori" Regulation (EC) N. 1901/2006 of 12/12/2006 of the European Parliament and of the Council CPMP/ICH/2711/99 Ministerial Decree 14 July 2009 	Italian (for CTs to be conducted in Alto Adige, PIS and ICF must also be in German)	18	Both parents	<p>Assent not mandatory, but Decree 211/2003 states that the minor will must be taken into consideration. Most ECs require also assent for age > 6 years, written in simple words and adequate to age.</p> <p>Minors who come of age while participating in a clinical trial must sign an ICF tailored to adult patients.</p>	Generally assent is suggested for ages 6-12 and 12-18, but different age groups may be considered.	Specific requirements concerning insurance for clinical trials on paediatric subjects apply (Ministerial Decree 14 July 2009)

PHARMACOVIGILANCE

Literature search to identify the already available tools for AEs/ADRs assessment

Systematic review

- ▶ Period: 1966– 2017
- ▶ Focus: paediatric clinical studies using tools for causality and/or severity assessment
- ▶ Results: **151** studies

CAUSALITY ASSESSMENT TOOLS

- 25.16% Naranjo
- 5.96% WHO-UMG
- 25.16% Others
(Karch&Lasagna, Liverpool ADR CAT, Barkley's, etc.)
- **43.70% Not Reported**

SEVERITY ASSESSMENT TOOLS

- Further research using only 2 keywords: ADR and severity
- Results: **14/149** publications mention tool
 - Hartwig&Seigel – the most used
 - Karch&Lasanga
 - National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) – Cancer specific
 - Barkley's Side-Effect Rating Scale (SERS) – Attention Deficit Hyperactivity Disorder (ADHD)

PHARMACOVIGILANCE

Identification of tools suitable for/adaptable to paediatric/neonatal population

- ▶ Liverpool ADR causality assessment tool
 - Further validation by PedCRIN participants
 - Assess the usability and likeability of this new tool
- ▶ National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE)
 - Validation of the adapted CTCAE scale – possibility under review
- ▶ Certification of centres being able to perform PhV activities
 - Working group set up by ECRIN
 - Paediatric specificity requirements to be included

PHARMACOVIGILANCE

► 9 tools for neonatal pharmacovigilance:

- Data Safety Monitoring Boards: *Points to consider*
- Guidelines for pharmacovigilance: *Points to consider for the neonatal population*
- Methods for causality assessment in neonates
- Neonatal diseases and complications: *Incidence and clinical implications during trial conduct*
- Serious adverse events in neonatal care and implications in clinical trials
- Biological parameters: *Normal values for neonates*
- Evaluation of pain related to trial procedures
- Severity assessment in neonatal trials
- Targeted follow-up forms for serious adverse events: *Points to consider*

MONITORING & STANDARD VALUES

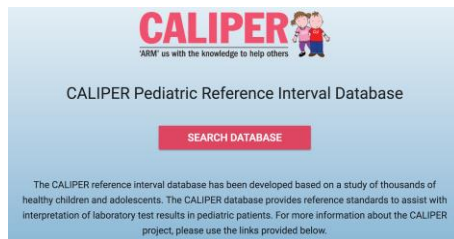
► Paediatric/Neonatal reference values:

- Set of biological values expected in a healthy children and related “*normal*” ranges (laboratory medicine)
- Precise “*healthy*” reference intervals in clinical trials: *detect patient harm or any underlying condition*
- **Difficulty:** Variability of values across analytical techniques

► Review and summary of existing references:

- Classification by age groups
- Classification by analytical method

SickKids



Canadian Laboratory Initiative on
Paediatric Reference Intervals Database

Age and sex-stratified reference interval database established for over 170 biochemical markers, endocrine and fertility markers, as well as many special chemistry assays.

BIOSAMPLE MANAGEMENT

- ▶ To help the investigators, sponsors and other research actors involved in paediatric clinical trials in the management of biosamples
- ▶ Topics:
 - Small sampling volumes
 - Minimizing harm and maximizing welfare
 - Skills, training and facilities required for sampling
 - Assent, consent and data protection, particularly with respect to long-term storage of samples
 - Long-term storage of biological sample

BIOSAMPLE MANAGEMENT

Checklist

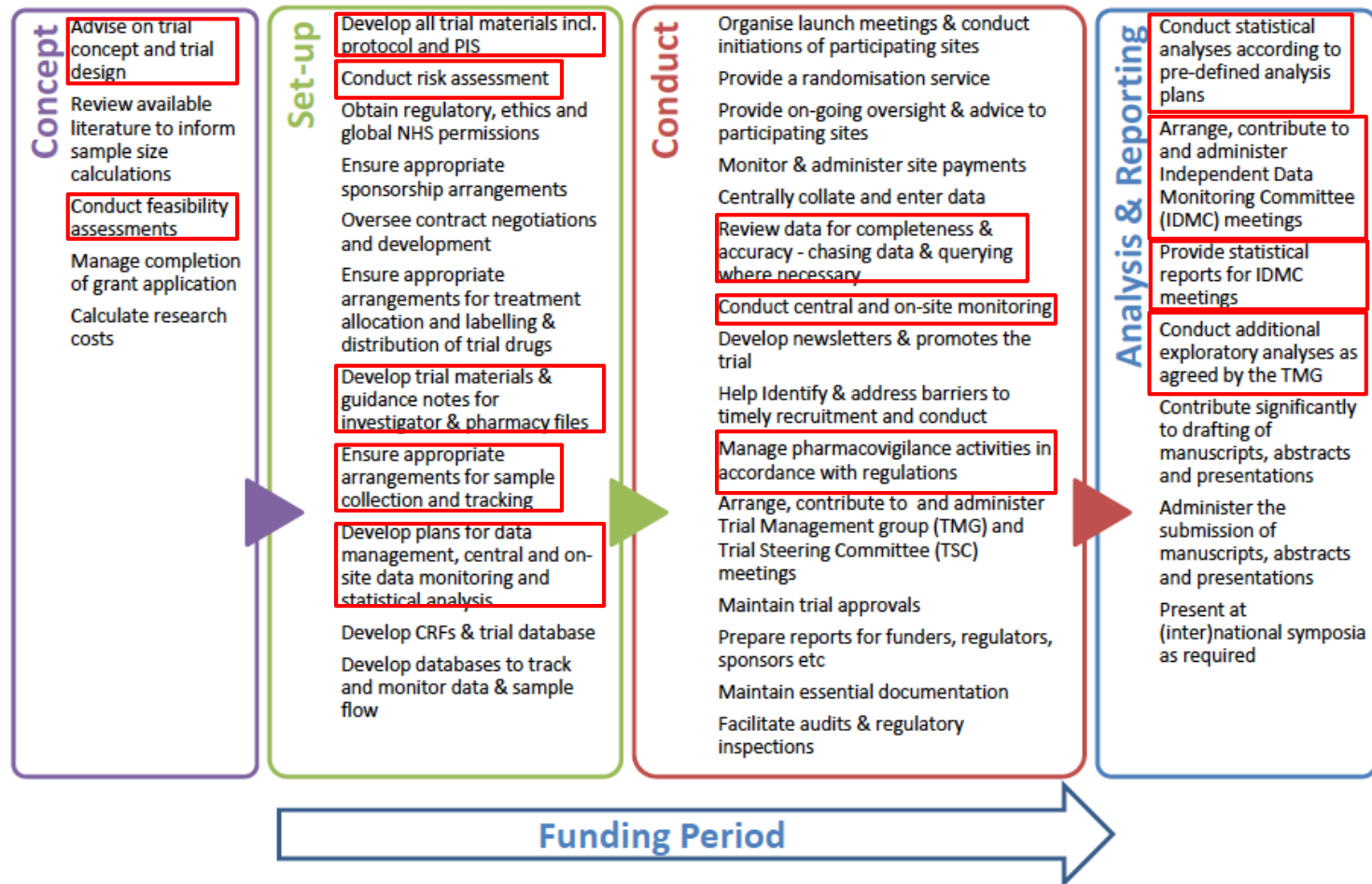
Easy-to-use instrument

- Properly manage samples
- Properly collect and storage data in the context of paediatric trials
- On the basis of the European applicable rules and legislation

Topic 1 - Consent and assent			
Item – measure - procedure	YES	NO	Location/comments
Aspects to be detailed in the information sheet and consent form for parents/legal representatives			
a) biological material handling and use including possible storage for future uses			
- the initial purposes of the processing of samples and data and the future purposes (where applicable) and adequate legal basis;			
- the conditions applicable to the storage of samples and data;			
- any relevant conditions governing the use of samples;			
- the period for which the personal data will be stored, or if that is not possible, the criteria used to determine that period;			
- the applicable safeguards (appropriate technical, organisational and de-identification measures) to be applied during the storage period <u>taking into account</u> the nature, scope and purposes of the processing or categories of processing;			
- the transfer policies according to local and national laws;			

CERTIFICATION OF CTUs

Clinical Trial Units (CTUs) support investigators by providing statistical, epidemiological, logistical and methodological expertise and help with coordinating multi-centre trials¹



¹ Gale C, Juszczak E. A paediatrician's guide to clinical trials units. Arch Dis Child Educ Pract Ed. 2016 Oct;101(5):265-7.

CERTIFICATION OF CTUs

- ▶ To help the selection of clinical trials units (CTUs) specialised in conducting paediatric/neonatal clinical research activities
- ▶ **Methods:**
 - Literature review: papers regarding Clinical Trials Units, GCP in paediatrics population, national regulatory agencies, EMA guidelines, etc.
 - Assessment PedCRIN task 3.1 –Survey on users' needs among the paediatric community + task 3.2–Gap analysis
- ▶ **Domains:**
 - activities of the CTUs
 - CTU's organisation, structures & processes
 - personnel and scientific expertise
- ▶ **Output:**
 - List of criteria (required and optional)

PERSONNEL AND SCIENTIFIC EXPERTISE	
Required	Full time pediatrician and neonatologist
X	Methodologist
X	Statistician
X	Full time study Coordinator
X	(Clinical) pharmacologist / Pharmacist
X	Quality assurance person
X	Data manager
X	Regulatory affair expert
X	Administrative / financial competences
X	Verification / updating of staff training (GCP, GLP, CRF development...)
X	Conflicts of interests for members of the team declared
Optional	Full time research nurses
X	Psychologist and counsellor, ethicist
X	Cultural mediators available on request

HIGHEST NEED REVEALED FROM THE SURVEY

Area of interest	Identified Need	%	Implementation planned in PedCRIN	
1	Application of innovative study design (e.g. modeling&simulation and extrapolation tools/approaches) from adults to children and from older children to neonates	81%	Yes	Task 3.3 and Task 3.4 – Methodology guidelines for trials

2 Identification of relevant calls for funding paediatric trials at EU/international level and support for project application

78% Potentially

Is a new guidance needed? → Hypothesis under evaluation

1	Design protocols for paediatric interventional clinical trials (PK, PK/PD, efficacy and/or safety, other)	76%	Potentially
3	Interaction with national/European regulatory agencies	76%	No

METHODOLOGY GUIDELINES FOR TRIALS

Deliverable 3.5 Tools for the set up of neonatal trials:

- **Pharmacokinetic studies (3)**
 - Study procedures
 - Innovative population PK: scavenged samples
 - Population PK and extrapolation
- **Methodological aspects of neonatal clinical studies (14)**
 - Feasibility assessment:
 - Study population
 - Selection of centres
 - Defining the target population:
 - The definition of standard age groups
 - Data collection
 - Data analysis
 - Controls in neonatal trials: Patients and drugs
 - IMP – GMP: Formulation and excipients
 - Information of parents: Discussion process & enrolment improvement
 - Drug safety and protocol development: Points to consider
 - Statistical methodology in neonatal trials & challenge of small sample size
 - Statistical methodology in drugs safety data analysis
 - Inclusion & exclusion criteria & patient safety
 - Neonatal PK studies: Points to consider
 - Involvement of parents in neonatal studies
- **Design aspects of neonatal studies (1)**
 - Design of neonatal studies: classical & innovative designs
- **Neonatal patient-centred outcome measures (3)**
 - Neonatal patient centred outcome measures: - Neonatal trials: what should be collected
 - Short-term outcome in neonatal trials: Points to consider
 - Long-term outcome in neonatal trials: Points to consider



METHODOLOGY GUIDELINES FOR TRIALS

Deliverable 3.5 Tools for the set up of neonatal trials:

- **Pharmacokinetic studies**
 - Study procedures
 - Innovative population pk: scavenged samples
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 - Long-term outcome in neonatal trials: Points to consider

Deliverable 3.7 Tools for procedures for the management of neonatal trials:

- **Clinical trials from adults to neonates**
 - Clinical trials from adults to neonatal – Specific criteria to be considered
- **Biosamples in neonates**
 - Blood sample types in the neonatal population
 - Blood/ biological sample volumes for research in neonates – EU guidelines and recommendations
 - Biosample management: collection, storage, shipment etc.
 - Biobanking and neonatal samples
- **Monitoring plan**
 - Serious adverse events in neonatal care and implications in clinical trial conduct
 - Guidelines for clinical trial monitoring in the neonatal population from theory to application
 - Patient transfers in neonatal trials: Points to consider for data collection and analysis
 - Training trial monitors for neonatal studies: Points to consider
- **Neonatal pharmacovigilance**
 - Data Safety Monitoring Boards: Points to consider
 - Guidelines for pharmacovigilance: Points to consider for the neonatal population
 - Methods for causality assessment in neonates
 - Neonatal diseases and complications: Incidence and clinical implications during trial conduct
 - Serious adverse events in neonatal care and implications in clinical trials
 - Biological parameters – normal values for neonates
 - Evaluation of pain related to trial procedures
 - Severity assessment in neonatal trials
 - Targeted follow-up forms for serious adverse events: Points to consider
- **Neonatal clinical trial conduct according to GCP and guidelines**
 - Case report forms: Points to consider
 - Points to consider for the data management of safety data
 - Statistical methodology in drug safety data analysis (as above)
 - Explaining benefit-risk to parents/ legal guardians
- **Training**
 - Drug safety in neonatal clinical trials
 - Drug toxicity stratified by age
 - Drug safety and pharmacovigilance in specify trials
 - Neonatal clinical trials and GCP

OTHER POSSIBLE TOOLS

Possible update/upgrade of tools developed within paediatric projects/networks

- Evidence and consensus-based guidance for the design of paediatric clinical trials
- An evidence and consensus-based tool for harmonization of information given to parents and patients in the recruitment process
- Harmonisation of 6,500 concepts and terms relating to paediatric research posted on web-based resource for utilisation
- A guidance-based tool for the ethics review of paediatric drug trials
- Recommendations for modelling and simulation
- Review and summary of recommendations on the requirements for the use of non-linear mixed effects modelling as a primary method
- Recommendations for innovative design to be adopted in an agreed PIP
- Comparisons of the relative performance of different paediatric trial designs by means of PK-PD based clinical trial simulation
- Development of web-based tool for the sample size calculation in paediatric randomized clinical trials with a superiority design
- Development of an evidence-based tool to justify comparator arm selection in paediatric clinical trials
- Development of models, tools and strategies for innovative approaches on paediatric CTs

OTHER POSSIBLE TOOLS

Collaboration with **INSERM**, leader of the task 3.4, to identify tools that are being developed for neonates within task 3.4 and that can be upgraded also to the paediatric population

Statistical methodology in drug safety data analysis
Defining the target population definition of standard age groups data collection
data analysis
Neonatal patient centred outcome measures: what should be collected
Short-term outcome in neonatal trials: points to consider
Long-term outcome in neonatal trials: points to consider
Guidelines for clinical trial monitoring in the neonatal population from theory to application
Training trial monitors for neonatal studies: points to consider
Severity assessment in neonatal trials
Neonatal clinical trials and GCP
Statistical methodology in neonatal trials & challenge of small sample size
Neonatal PK studies: points to consider

THANK YOU



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