"Second General Assembly" Meeting Minutes

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Paolo Rossi
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Place; Meeting Date; Duration
Rome; 19/12/2016; 8 hours/1 day

Partner in charge
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Author(s)
Lucia Ruggieri

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1. Agenda

8.45 Participants' registration

9.00 -13.30 Clinical research in adult and children: commonalities and specificities (Chairs: A. Ceci - P. Rossi)

9.00 The experience of ISS – Italian Institute for Health in the European Research Infrastructures scenario (G. Migliaccio, EATRIS Scientific Director)

9.15 Research Infrastructures in biomedicine: a system pipeline to support biomedical research (M. Lavitrano, BBMRI-ERIC Management Committee Co-Chair) – intervention not delivered, apologies from M. Lavitrano, absent for unexpected commitments

9.30 The new clinical trials regulation to improve the clinical research in Europe: the ECRIN contribution (J. Demotes, ECRIN General Director)

9.45 Paediatric clinical trials: challenges and opportunities. The contribution of PedCRIN (M. Turner, EnprEMA Chair)

10.00 Scientific expertise and specialty level needed to design scientifically-sounded paediatric trials and research

- C. Giaquinto, GRiP-PENTA
- N. Ruperto, PRINTO
- P. Telfer DEEP
- O. Della Pasqua (Dose selection and innovative study design)
- F. Bonifazi (HTA and disease Registries)

11.15 Q&A and discussion

11.30 Coffee Break

12.00 National networks and initiatives contributing to the European Paediatric Clinical Trial Research Infrastructure (EPCT-RI) (Chair: C. Giaquinto)

- E. Jacqz-Aigrain (INSERM, France)
- P. Rossi (INCiPiT, Italy)
- F. Martinon (RECLIP, Spain)
- A. Godo (Albania)
- M. Migdal (Poland)

13.15 Q&A and discussion

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15.00- 16.00 General Assembly - TEDDY Network activities and plan of action (Chairs: M. Turner - A. Ceci)

- The TEDDY European Paediatric Medicines Database 2016 Report (M. Felisi, TEDDY EPMD coordinator)

- The TEDDY Working Group on Off Label Use in Paediatrics: current status and next actions (S. de Wildt, TEDDY GOLUP Working Group coordinator)
- The TEDDY survey to identify paediatric trials competences and capacities at site level (L. Ruggieri, TEDDY Survey responsible)
- TEDDY Inventory of procedures for obtaining Paediatric Clinical Trials approvals (C. Manfredi, TEDDY Inventory responsible)
- TEDDY contribution to ENCePP- European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (K. Verhamme, TEDDY representative in ENCePP), via teleconference

16.00 General Assembly – Roundtable - Paediatric clinical trials sustainability in the framework of the paediatric regulation (Chair: D. Bonifazi) *Discussants*: A. Altavilla, C. Giaquinto, E. Jacqz Aigrain, M. Mellado, M. Migdal, A. Neubert, S. de Wildt

17.00 General Assembly - TEDDY commitments, membership and boards

2. Participants

Participant	Institution
Altavilla Annagrazia	Espace Ethique Méditerranéen CHU Marseille, Aix-Marseille Université
Bonifazi Donato	Consorzio per Valutazioni Biologiche e Farmacologiche
Bonifazi Fedele	Gianni Benzi Pharmacological Research Foundation
Borgonzi Nicola	Ospedale Pediatrico Bambino Gesù
Ceci Adriana	Consorzio per Valutazioni Biologiche e Farmacologiche; Gianni Benzi Pharmacological Research Foundation
Ciabattini Marco	Università degli Studi di Roma Tor Vergata
Claverol Torres Joana	Hospital Sant Joan de Déu
Como Arjel	Medicine University of Tirana
Copponi Giorgia	University Hospital Bambino Gesù
Della Pasqua Oscar	University College London
Demotes-Mainard Jacques	European Clinical Research Infrastructure Network
Felisi Mariagrazia	Consorzio per Valutazioni Biologiche e Farmacologiche
Ferro Giusy	Università degli Studi di Roma Tor Vergata
Folino Gallo Pietro	Consorzio per Valutazioni Biologiche e Farmacologiche
Fracasso Claudio	Pfizer Pediatric Center of Excellence
Frazzetto Angela	Associazione Italiana di Ematologia e Oncologia Pediatrica
Fulceri Francesca	IRCCS Fondazione Stella Maris
Gazarian Madlen	Faculty of Medicine, University of NSW, Sydney, Australia
Giannini Cosimo	Università degli Studi "Gabriele D'annunzio" Chieti - Pescara
Giaquinto Carlo	Fondazione Penta; Padua University
Godo Lena Anila	Albanian Paediatric Association; University Hospital Center "Mother Teresa"
Guarino Alfredo	Università Federico II di Napoli
Jacqz-Aigrain Evelyne	University Diderot Paris
Johnsson Elin	Gothia Forum, Pediatric Clinical Research Center
Kuli Lito Gjeorgjina	Albanian Paediatric Association; University Hospital Center "Mother Teresa"
Kreka Manika	Consorzio per Valutazioni Biologiche e Farmacologiche – Branch of Albania
Lindfors Rossi Inger	Penta Foundation
Livadiotti Susanna	Clinical Trial Center, University Hospital Bambino Gesù
Lupo Mariangela	Consorzio per Valutazioni Biologiche e Farmacologiche
Manfredi Cristina	Consorzio per Valutazioni Biologiche e Farmacologiche
Mangiarini Laura	Penta Foundation

Martinez Pellicer	Hospital Universitario La Paz
Martinon Federico	Hospital Clínico Universitario de Santiago de Compostela
Mellado Maria José	Autónoma University of Madrid; Hospital Universitario Infantil La Paz Madrid
Migdal Marek	Paediatric Intensive Care Unit Children's Memorial Health Institute
Migliaccio Giovanni	EATRIS - European infrastructure for translational medicine
Moretti Franca	Istituto Superiore di Sanità, EATRIS
Myronenko Sergii	PharmaSich, LLC
Nieto Adela Cañete	Hospital Universitario y Politécnico La Fe
Neubert Antje	Paediatric Clinical Study Centre University Hospital of Erlangen
Odlind Viveca	Gothia Forum, Pediatric Clinical Research Center
Pontrelli Giuseppe	Clinical Trial Center, University Hospital Bambino Gesù
Pugi Alessandra	Clinical Trial Office Azienda Ospedaliero Universitaria Meyer
Puopolo Maria	Istituto Superiore di Sanità
Racaniello Mauro	Farmindustria
Ranucci Giusy	Università Federico II di Napoli
Rojo Pablo	Hospital 12 de Octubre of Madrid
Rossi Paolo	Paediatric Department University Hospital Bambino Gesù
Ruggieri Lucia	Gianni Benzi Pharmacological Research Foundation
Ruperto Nicolino	IRCCS Istituto Giannina Gaslini
Scalera Giselda	Direzione Generale Ricerca e Innovazione, Ministero della Salute
Scattoni Marialuisa	Istituto Superiore di Sanità
Simonetti Alessandra	University Hospital Bambino Gesù
Taruscio Domenica	Istituto Superiore di Sanità
Telfer Paul	Queen Mary University of London; Barts Health NHS Trust
Turner Mark	EnprEMA; Liverpool University
Verhamme Katia	TEDDY representative in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), The Netherlands
de Wildt Saskia	Radboud University Nijmegen & Erasmus MC

3. Discussion

3.1 Clinical research in adult and children: commonalities and specificities – the role of Research Infrastructures (RIs)

Adriana Ceci and **Paolo Rossi** opened the meeting with the starting topic of the event that is the contribution, the roles and the challenges of using RIs in the scientific and medical landscape.

Giovanni Migliaccio introduced the role of EATRIS, the European Research Infrastructure for translation of scientific discoveries into medical products for human use. EATRIS mission is to support researchers from academia, biotech, pharmas and other research organisations in the development of their biomedical discoveries for novel preventive, diagnostic or therapeutic products starting from clinical proof of concept. EATRIS provides infrastructure and expertise service for clients. National nodes of the infrastructure have been built and the Istituto Superiore di Sanità coordinates the Italian one (A_IATRIS).

Jacques Demotes Meinard explained the possible contribution of the Research Infrastructure for Clinical Trials, ECRIN, in the transition to the new Regulation on Clinical Trials in Europe. Despite the Regulation is expected to simplify and promote clinical trials conduction in Europe, a challenging transition phase is expected. In this sense, ECRIN is expected to contribute providing a reliable and updated source of information about the applicable legislative framework and the required documents to get clinical trials approval.

Mark Turner intervention highlighted the need and difficulties in paediatric clinical trials conduction, thus clarifying the challenges and expectations of a paediatric clinical trial research infrastructure as anticipated by the preparatory collaborative work done within the forthcoming PedCRIN project. PedCRIN will establish, in the framework of the European Infrastructure of Clinical Trials, a paediatric branch to create tools and procedures facilitating the performance of clinical trials involving children.

3.2 Clinical research in adult and children: commonalities and specificities – scientific expertise and specialty level needed to design scientifically-sounded paediatric trials and research

Carlo Giaquinto has presented the network Penta-ID and GRiP (Global Research in Paediatrics) project. Penta was launched in 1991 to study HIV in paediatric setting and its activity has been enlarged in 2010 to include studies in other infectious diseases (antimicrobial, antivirals, anti-hepatitis). To date, PENTA-ID activity includes publicly and privately-funded clinical trials, cohort studies collaboration, pregnancy studies and training/educational programmes. GRiP is an EU funded Network of Excellence to facilitate paediatric clinical research and has recently concluded the first international master programme in paediatric medicines development and evaluation.

Nicolino Ruperto has shared some highlights of PRINTO, an international network involving more than 60 countries and 500 clinical centres in Europe and world-wide, for the planning and conduction of paediatric clinical trials in the field of rheumatologic diseases, that are rare, chronic and highly debilitating in paediatrics. After presenting the most relevant achievements of the network, that has 20 years of activity, some of the most

relevant challenges that PRINTO has encountered during its years of activity have been summarised and proposed for discussion.

Paul Telfer introduced the DEEP project for the study of iron chelators in paediatric patients with iron overload as an example of multinational EU/non-EU cooperation to perform paediatric trials To date, a new formulation of deferiprone (syrup) has been produced for the use in paediatrics, data about the PK of deferiprone in patients aged <6 years have been published and the larger Randomised Controlled Trial in paediatric iron overloaded patients in the world is currently ongoing, with 2/3 of patients having completed the study. Moreover, the specific UK experience has been presented, with details about the UK methodological and regulatory requirements. Conclusively, the proposal to setup a large consortium of haematology research centres will be soon launched.

Oscar Della Pasqua highlighted the advantages of quantitative assessment through Clinical Trial Simulation, especially in challenging scenarios, when it is difficult to generate new data through clinical trials. In fact, the quantitative assessment of the benefit-risk balance supporting clinical decisions as performed by Clinical Trial Simulation, can be used to predict aspects that are difficult to observe in clinical trials, to optimise clinical trial protocol, to integrate and synthesise data deriving from previous studies (or high-quality evidence from clinical practice), to develop personalised treatment approaches. A relevant application of simulation is related to dosing issues that can be evaluated and predicted in silico before patients' exposure.

Fedele Bonifazi lectured about the usefulness of Health Technology Assessment (HTA) in the systematic review of existing evidence, providing recommendations on medicines and other health technologies that can be funded/reimbursed. The European Medicines initiatives in the framework of HTA have been presented, with reference to the adaptive pathway approach. These initiatives only recently have been extended to the paediatric medicines and technologies. In this framework, also in the paediatric field the use of large patient registries can be used to have a real-world perspective of the course of the disease, the profile of a medicine or a treatment approach, assumed that registries are properly designed and executed according to high-quality standards. Some examples of registries in the field of thalassaemia have been presented, together with an EMA initiative to improve the exploitation of existing registry and the setup of high-quality new registry to generate post-authorisation data to be used for regulatory purposes.

3.3 National networks and initiatives contributing to the European Paediatric Clinical Trial Research Infrastructure (EPCT-RI)

Carlo Giaquinto chaired the session about the initiatives that have been established at national level to gather the efforts and promote paediatric clinical research. Different countries have been selected, in order to present different development and organisational aspects.

Evelyne Jacqz-Aigrain has introduced the consolidated French experience, with the Paediatric Clinical Investigation Center (CIC) Network, funded in 2000 and currently gathering about 15 research units in France. CIC Network sites have about 140 ongoing trials, with the number of phase I/II paediatric trials constantly increasing in the last years. The reasons at the basis of the creation of a French structural network have been mainly scientific, practical and ethical and are an enduring problem in paediatric clinical research scenario, with limited patients' number and consequent recruitment difficulties being the

most relevant critical aspects. Some collaborative network activities are performed, such as the management of ethical aspects and training. Similarly, collaboration with specialised networks is sought.

The recently-established Italian paediatric network INCiPiT (Italian Network for paediatric Clinical Trials) has been presented by ***Paolo Rossi***, network coordinator. INCiPiT, currently including about 20 centres, coordinated by the Ospedale Pediatrico Bambino Gesù (Rome), has the ambition to build a well-structured research infrastructure to conduct paediatric clinical trials in Italy.

The first activity of the network has been the development of several project proposals submitted to the Italian Medicines Agency (AIFA), where INCiPiT has been included either as a Research Unit or as a support Network.

Another new national network has been presented by ***Federico Martinon***, coordinator of a fully developed and professionalised reference network for paediatric clinical trial units in Spain. Formally, RECLIP network has been built in November 2016, with few months of preparatory activity. It has gained institutional endorsement from several Spanish bodies and has established collaboration with some specialty networks, that are chairing several scientific areas of RECLIP. To enter RECLIP, centres have to indicate a series of information to assess their capabilities and being classified as consolidated, thematic or emerging centres. A plan for integration of new members has been recently defined, with a yearly admission of new centres.

The Albanian situation has been presented by ***Anila Godo***. The Albanian scenario has not a long-standing experience or consolidated network for paediatric clinical research, since the commitment of Albania in clinical trials involving children is quite recent and related to the DEEP project. In the last years, some aspects of the clinical research have been regulated by the Albanian legislation. Shortcomings and available facilities in Albania have been presented, while to improve the Albanian research framework it would be necessary to improve the involvement of universities in clinical trials; to develop strategies to evaluate the impact of research projects; to launch fundraising/application for funding activities and to improve the public awareness about the need for research in children.

Marek Migdal has presented some data about clinical research in Poland, highlighting the reasons for which this country is attractive and active in the clinical research scenario. In the field of paediatrics, most of activity is referring to the Children's Memorial Health Institute that is the largest tertiary care.
With reference to networking activity, formal endorsement has been provided from the Ministry of Health.

3.4 General Assembly - TEDDY Network activities and plan of action

In the afternoon, some relevant aspects related to TEDDY activities have been presented and discussed for further in-depth analyses.

Mariagrazia Felisi has presented some data deriving from the TEDDY European Paediatric Medicines Database (EPMD), including information on paediatric drugs authorised by the EMA under the centralised procedure. EPMD data show that after 10 years from the entry into force of the Paediatric Regulation, the number of paediatric medicines has tripled, but they remain ˜ 1/3 of all the centrally authorised medicines and it still persists a paucity of medicines approved for preterm and term newborns.

However, despite not a clear trend can be observed, in 2016, it seems that a higher number of paediatric medicines has been centrally-approved.
The data show that after 10 years, the principal aim of the Paediatric Regulation is partially achieved, but the inequality between adults and children is still relevant.

Saskia de Wildt spoke about the recent TEDDY Working Group on Off-Label Use in Paediatrics. The group has been established following other initiatives on the issue (i.e. from lobby organisations and industries) that were considered not appropriate in a paediatric setting by many TEDDY members. For this reason, a cross-sectional European working group has been built within TEDDY, to develop a preliminary statement to "Good Off-Label Use Practices in paediatrics". However, a meeting at the European Parliament, involving TEDDY working group, has allowed to a proposal of a common document, integrating paediatric specificities among other general aspects. The draft of the common declaration will be soon circulated among TEDDY partners.
Moreover, a survey about off-label use has been developed, to understand how off-label is regulated at EU level.
An example of regulation is represented by the medicines monographs that are published and updated in the Dutch Kinderformularium. A similar experience has been performed at Italian level, by AIFA Paediatric Working Group and published on the Italian Official Journal.

Lucia Ruggieri presented the key outcomes and partial results of the TEDDY survey to map centres competences and experience for paediatric clinical trials. The survey, developed by TEDDY in collaboration and FINPEDMED and agreed with Enpr-EMA, is being administered at national/regional level, through the collaboration with national representatives. In Italy, the survey has been administered to INCiPiT centres, with a 30% response rate and, besides providing an insight on the national scenario of paediatric clinical research, has allowed to identify the strengths and weaknesses of the survey instrument.

Cristina Manfredi presented the Inventory of procedures for obtaining Paediatric Clinical Trials approvals, a TEDDY initiative aimed at collecting information on the relevant local requirements and procedures for a clinical trial application (CTA) such as: laws governing clinical trials, ad hoc provisions for paediatric trials, details on the ethics committees / national competent authority, type of application / existence of a national website, procedures for compiling the EU CTA form, documents to be submitted and any applicable fees. The inventory will be made available in the framework of the PedCRIN project.

Katia Verhamme has reported about the involvement of TEDDY in pharmacoepidemiologic and pharmacovigilance activities, following the attendance of the EncePP plenary meeting in November. The proposals that have been agreed for the involvement of TEDDY are the following: to register TEDDY in the publicly available register of non-interventional post-authorisation studies (EU PAS Register), to participate in the EncePP Special Interest Groups (SIG) on Pregnancy and to register institutions adhering to TEDDY as organisations interested to participate in EMA tender studies.

3.5 Roundtable - Paediatric clinical trials sustainability in the framework of the paediatric regulation

***Discussants*: Annagrazia Altavilla, Carlo Giaquinto, Evelyne Jacqz-Aigrain, Maria Mellado, Marek Migdal, Antje Neubert, Saskia de Wildt**

During the roundtable, the feasibility of paediatric clinical trials has been discussed, with reference to some key points, introduced by the chairman **Donato Bonifazi**. With reference to the *development of strategies to avoid patients' retention*, the following proposals and reflections have been suggested:

- innovative follow-up, using call phone instruments
- the development of a strict connection between the physician and the patient, in order to establish confidence
- good explanation of the trial before giving consent
- use of registries to collect information on patients and plan clinical trials and enrolment strategies on the basis of data emerging from registries
- choice of clinical settings where it is possible to establish a careful follow-up of patients (in this case, the difference between acute and chronic diseases has to be taken into account in advance)
- where possible, specialists should establish links with primary care physicians
- promotion of the trials among nurses/physicians to get qualified support
- to perform qualitative studies in parallel with clinical trials to analyse all the aspects (economic, social, disease-related) possibly causing patients' retention

All the discussants agreed on the need to develop a patient-tailored approach, involving paediatric patients not only during the trials but also before, in providing advices on the informative material and tools that are developed for patients. In this framework, the importance of Young People Advisory Groups is recognised also to comment on clinical trial design (e.g. patients reported outcomes).

With reference to the *development of a single Clinical Trial Application Package*, it is recognised that it is not straightforward to interact with Ethics Committees and Competent Authorities and in the current framework it is not feasible to develop a general European consent form. The advancements related to the entry into force of the new Clinical Trial Regulation are also debatable. This is also related to the fact that Member States are not prepared to the change in the regulatory framework.
For these reasons, it is important to continue activities to overview and identify the type and the structure of documents that are needed according to the legal framework. Moreover, another agreed proposal is to develop a survey to investigate how the member states are prepared for the entry into force of the new Regulation.

With reference to the *infrastructure/expertise requirements to perform successful paediatric trials*, it is important to have equipped, organised and experienced clinical trial units, for independent studies.
Beside this, a good expertise in Quality Assurance is needed and trial-specific Standard Operating Procedures (SOPs), prepared by experienced researchers, are needed to have good clinical trials.

The roundtable concluded with an insight about the tragedy of thalidomide consequences for children, following the recent recognition by the European institutions of a damage compensation for victims, to remind the importance of develop high-quality and reliable evidence about the safety and efficacy profile of a drug, before administering it to children.

3.6 General Assembly - TEDDY commitments, membership and boards

Donato Bonifazi concluded the meeting, announcing that the following institutions asked to enter TEDDY Network:

- Assiut University, Faculty of Medicine, Egypt
- Centre National de Greffe de Moelle Osseuse, Tunisia
- Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) – Branch of Albania
- Gothia Forum for Clinical Research, Sweden
- Hospital Sant Joan de Déu, Spain
- Hospital Universitario 12 de Octubre, Spain
- Pharmasich Plus, LLC, Ukraine
- Phoenix Clinical Research, Lebanon

Elin Johnsson from Gothia Forum, **Manika Kreka** from CVBF Albania, **Joana Claverol Torres** from Hospital Sant Joan de Déu, **Pablo Rojo** from Hospital Universitario 12 de Octubre and **Sergii Myronenko** from Pharmasich have briefly introduced their Institutions.