IN COLLABORAZIONE CON

INTERNATIONAL PAEDIATRIC TRIAL DAY 2017

Helping children create lives they deserve

MINUTES

Milan – May 9, 2017

Ospedale San Raffaele

Sommario

1. Executive Summary

This document contains the minutes of the International Paediatric Clinical Trial Day, held in Milan (Italy) on May 9th, 2017 at the San Raffaele Hospital.

The meeting provided an overview on the current European scenario of the Paediatric Clinical Trials, describing the issues, the needs and the gaps existing in paediatric medicine research. Moreover, the reasons of the delays and the strategies to overcome them have been explained in detail.

2. Speakers and Chairs

PARTECIPANT	INSTITUTION
Antoinette van Dijk	AICRO
Alessandro Aiuti	Ospedale San Raffaele
Donato Bonifazi	Consorzio per Valutazioni Biologiche e Farmacologiche
Elisabetta Riva	Ospedale San Raffaele
Mark Turner	University of Liverpool
Adriana Ceci	Consorzio per Valutazioni Biologiche e Farmacologiche Gianni Benzi Pharmacological Research Foundation
Marek Migdal	Paediatric Intensive Care Unit in the Children's Memorial Health
Alessandro Aiuti	Paediatric Immuno-Hematology Unit at Ospedale San Raffaele
Annagrazia Altavilla	Espace Ethique Méditerranéen-Aix-Marseille University
Pier Adelchi Ruffini	Dompé Farmaceutici SpA
Martine Dehlinger-Kremer	Global Medical and Regulatory Affairs at SynteractHCR European CRO Federation (EUCROF)
Paolo Rossi	Italian Network for Paediatric Clinical Trials
Joana Claveral Torres	Clinical Research Unit Manager at Hospital Sant Joan de Déu
Claudio Fracasso	Pfizer Paediatric Global Centre of Excellence

3. Discussion

Antoinette van Dijk and **Alessandro Aiuti** for the first Session**, Donato Bonifazi,** and **Elisabetta Riva** for the second Session, opened the meeting welcoming all the participants and highlighting the reasons and the aim of this International Paediatric Clinical Trial Day.

Although we are assisting to a biological and technological revolution in the drug development process, a relevant delay in transferring these innovative technologies into the clinical trials performed in children has been observed. In the last years, some efforts have been done in Europe and currently many paediatric research activities exist but are dispersed. So, now it is necessary to develop a well-organized system to put together all these resources and experiences. The development of specific Networks and Research Infrastructures may be the ideal way to target this purpose.

3.1 Session I

3.1.1 How will the paediatric scenario change with the Collaborative Network for European Clinical Trials for Children: the Enpr-EMA perspective.

The first speaker of the seminar, **Mark Turner**, Enpr-EMA chair and Lecturer at the Liverpool University, opened the discussion providing an overview on the benefits that the European Network of Paediatric Research (Enpr-EMA) at the European Medicines Agency is offering to the management of paediatric clinical trials and drug development process.

He reminded that the professionals involved in clinical trials for children have to face several issues in all phases of the trial management and drug development process. For example, one of the main problems is that the medical product for children, usually studied for adult patients, needs to be adapted with respect to different aspects such as formulation, dose target, indication and safety. In this context, he highlighted the importance of sharing and integrating information about clinical studies data as well as regulatory and HTA data within a well-organized network. This integrated system can help overcoming the fragmentation and the inefficiency characterizing the paediatric clinical trials. So, he showed one of the most visible result of Enpr-EMA: in UK the percentage of studies recruiting paediatric patients increased from 30% to 80% in 2013/2014 both in industrial and public field.

He moved the discussion to another field of clinical investigation: rare diseases and disease subsets. In fact, the paucity of clear and not-redundant information and the lack of coordinated data communication characterizing paediatric trials can be found also in the drug development process for these targeted diseases. Moreover, he explained that the study of these diseases has to handle a high disease heterogeneity and variability. For all these reasons, EFPIA (European Federations of Pharmaceutical Industries and Associations) Companies, Regulators and Investigators expressed the desire to change the old and not well organized approach, favouring a coordinated system able to guarantee clinical trials reliability. This need was satisfied by the IMI2 call (Innovative Medicines Initiative) aimed to create a European initiative that promotes the rapid delivery of paediatric drug trials through improved uniform processes in a coordinated, sustainable network that is widely accessible. He also provided the details of some WPs of the project:

WP2 foresees the organization and governance of the pan European Paediatric Clinical Trials Network by:

- building a main central coordinating organization to steer the network
- establishing a single point of contact for entering the network for all kind of sponsors
- developing a transparent process and criteria for selection of studies to be performed by the network
- building quality management processes to ensure all network activities are in compliance with common research standards and (inter)national regulations for the conduct of clinical trials

WP4 deals with the scientific advice, feasibility and innovation through:

- the set-up and maintenance of groups of scientific experts to trigger innovation developing and implementing innovative methods (dose selection, biomarkers, endpoint and/or study design)
- the set-up of processes to allow patients/parents representatives to give input to new innovative study design and to participate in evaluation of feasibility, design, risk-benefit paediatric study protocols.

WP5 aims at:

- establishing procedure and systems/tools to monitor performance metrics in all network trials
- promoting shared definitions of terminology enabling uniform process for collection and storage of clinical data
- contributing to common program/process to allow electronic storage and archiving of study related documentation.

Finally, he presented a proposal which has been submitted for an Applicant Consortium to IMI2 Call called CONECT4Children: a Collaborative Network for European Clinical Trials for Children. This consortium that includes members from EU and not EU countries is aimed to:

a) improve availability of information about medicines used by children

b) promote the delivery of high quality trials of medicines for children by supporting:

- trial implementation through resources shared between the studies

- trial design using a combination of information about natural history, feasibility and expert opinion

3.1.2. The roadmap for a new Paediatric Research Infrastructure: gaps analysis and feasibility

Adriana Ceci, TEDDY Network Scientific Coordinator, described the current conditions and the big gap faced by the paediatric medicine research. Firstly, she presented the data collected in the European Paediatric Medicines Database (EPMD), promoted by the TEDDY Network, showing that only one third of the medicines on the market are approved for the children and that this gap is distributed among all paediatric ages and all ATC (Anatomical Therapeutic Chemical) groups. Moreover, she underlined the lack of innovative drugs and advanced therapy in the paediatric medicine. She also explained the reason why this big gap exists in paediatric medicines. In fact, there are no proper methods and technologies that enable to perform all the correct trials needed. Moreover, it is necessary to face two main difficulties that characterize paediatric clinical trials: a) children are a “small population”; b) children are not little adults.

She described the meaning of the first statement, showing that the paediatric population recruited for a specific clinical trial is usually splitted at least into five sub populations, so that in each site there will be a very little proportion of the children population. Moreover, the golden standard RCT (Randomized controlled trial) used for the adult patients may be not feasible. Finally, she highlighted that children are not little adults, because their physiologic characteristics are different from the adults and extremely variable by days, months and years of age.

She underlined that although we are assisting to a biological and technological revolution in the drug development, a relevant delay in transferring these innovative technologies into the clinical trial performed in children has been observed.

Fortunately, in the last years some efforts have been done in Europe and several useful initiatives (network initiatives, FP7 projects, IMI2, etc.) have been carried out even if the paediatric research activities still remain very dispersed. So, now it is necessary develop a well-organized system to put together all these existing resources.

She proceeded the presentation analysing the importance of the research infrastructures (RIs) to reduce this gap in the paediatric medicine. RI refers to facilities, resources and related services used by the scientific community to conduct top-level research in their respective fields. A European Research Infrastructure can be an ideal research instrument for facilitating the joint establishment and operation in case of complex and multidisciplinary research activities. She highlighted that in EU there is no Research Infrastructure dedicated to promoting paediatric research. For this reason, on March 29th, 2017 a proposal for designing of a pan-European Infrastructure (EPTRI – European Paediatric Translational Research Infrastructure) to promote technology-driven Paediatric research has been submitted within the Infradev-1 call (Horizon 2020). She underlined that EPTRI is aimed to design a virtual space for sharing of facilities, resources and related services and is supposed to be complementary to the existing Biomed RIs (and in particular BBMRI, EATRIS and ECRIN). In conclusion EPTRI will possibly represent a "one-stop-shop" and a paediatric common service integrated with three already established RIs to harness efficiency and delivery of paediatric research and to strengthen collaboration within the scientific paediatric community.

3.1.3 The Paediatric Regulation ten years after its implementation

The discussion proceeded with the contribution of **Marek Migdal**, member of the Paediatric Committee (PDCO) of the EMA, who provided a snapshot of the current regulatory aspects of the paediatric medicine. He explained why we need to get the paediatric regulation and stated that up to 1997-2000 the majority of medicines used in children was not studied and approved for the paediatric use and the paediatric clinical trials were really rare. To demonstrate that, he provided the example of thalidomide, a drug authorized in German and considered safe for both adults and children. Later on, thalidomide was found teratogenic and it caused developmental malformations in more than 10.000 children e highlighted that the paediatric regulation is necessary to increase high quality and ethical research into medicines for children and guarantee their health and safety. He also provided several dates referring to the milestones in the development of the Paediatric Regulation, such as:

- 26 January 2007, entry into force of the Paediatric Regulation.
- 26 July 2008, European Commission established that applications for Marketing Authorisation (MA for new products) should contain results of studies conducted in compliance with agreed PIP (Paediatric Investigation Plan).
- 26 January 2009, EU commission established that the same obligation is extended to applications for new indication, new route of administration or new pharmaceutical form for authorized "patented" products.

Moreover, he explained that PIP is a research and development program which collects all the data and conditions necessary to generate a product that may be authorized for the paediatric treatment. He also reminded the difference between the PIP and the single trial that is a part of the PIP. He also clarified that the PIP includes details of the timing and the measures proposed to demonstrate quality, safety and efficacy.

He gave some indications about the PIP aspects mainly evaluated by the PDCO EMA and in particular, for "whom" (age groups) and for "what" (indication) the product is addressed.

He also explained that, according to the Article 50 of the Paediatric regulation, EMA is obliged to prepare an EC report every 5 years, which shows the progress of paediatric medicine, and in particular some significant data about:

- the number of agreed PIPs, submitted modifications of agreed PIP and agreed full waivers
- the therapeutic areas addressed by PIPs
- paediatric clinical trials by year of authorization (EudraCT)
- the number of children to be enrolled in clinical trials (EudraCT)
- the impact of the Paediatric Regulation in EU compared to US, Japan and Canada.

Finally, he highlighted the importance and the positive impact of Enpr-EMA, the European Network of Paediatric Research at EMA. In fact, this Network allowed to increase the dialogue between different stakeholders, regulators, academia, industry, patients and policy makers.

He concluded his presentation, underlining the future challenges of the clinical trials in paediatrics, including:

- the change of medical knowledge and needs
- the use of the pharmacogenomics
- development of a major active pharmacovigilance
- development of a network dedicated.

3.1.4. Advanced therapies for genetic diseases: from paediatric clinical trials to approved drugs

Alessandro Aiuti, described his experience as Principal Investigator (PI) of ADA-SCID, WAS and MLD gene therapy clinical trials sponsored by the GSK pharmaceutical company. These trials are testing new gene therapies for specific genetic diseases. He showed that gene therapy methods can be divided into ex vivo (through gene addition or genome editing of isolated cells) and in vivo (through systemic delivery) approach. Moreover, he explained that these innovative treatments still present several issues, such as the need to overcome the biological barriers to engraftment and regeneration as well as the immunological barriers to transplant of cells, or also the limited comprehension of stem cell biology and some safety issues (insertional mutagenesis). For this reason, he underlined that it is necessary to have dedicated clinical research units for ATMP (Advanced Therapy Medicinal products) and validate new tests and analytical methods in order to reach the drug large-scale production according to regulatory quality standards. To show the benefits of the gene therapy approach, he gave the example of the autologous transplant of gene corrected hematopoietic stem cell (HSC) for the treatment of specific immune diseases. This method foresees an autologous transplant of gene corrected HSCs. Since in this approach the donor is the patient, the risk of rejection, toxicity, morbidity and mortality is decreased.

He continued the disclosure providing an overview of the San Raffaele Hospital (OSR) and the SR-TIGET organization. As he explained, OSR is a multispecialty center with 1357 beds and a research institute with around 1500 scientists, whereas SR-TIGET is a joint venture between Telethon

Foundation and OSR, which is equipped with a TIGET clinical trial office (TCTO). After this brief introduction, he showed the ongoing clinical trials at the TCTO, such as the clinical trial for ADA-SCID treatment (Gamma – RV – GT). ADA-SCID is a metabolic disease characterized by the accumulation of toxic metabolites and that affects several organs and causes immunodeficiency and autoimmunity. As he highlighted, Gamma-RV-GT for the treatment of ADA-SCID is an example of the power of collaboration. In fact, the cooperation between authorities and experts of clinical trials (also supported by GSK) and regulatory activities allowed the approval in EU of the treatment in 2016. In conclusion, he provided an overview about the current situation, the studio design, the results and the timing of the other clinical trials ongoing at TCTO, such as the trial for the treatment of Metachromatic Leukodystrophy (MLD), in phase I/II, and an innovative therapy for beta-thalassemia (phase I/II).

3.1.5 Children are not little adults: put the child in the heart of the EU clinical trial ethical and legal framework

Annagrazia Altavilla, lawyer specialized in Health Law and Biomedical Ethics, proceeded the discussion with an overview on the ethical and legal frameworks in the clinical trials. First of all she reminded that, according to the main ethical guidelines, research has to adhere to three ethical principles: respect for persons, beneficence/non-maleficence and justice. Moreover, research has to respect fundamental rights such as dignity, right to life, physical and mental integrity, self-determination and protection of personal data. But she also highlighted another principle universally recognized that needs to be taken into account in the clinical trial process: "the evolving capacities" of the child. In fact, the child is not a single, fixed and universal experience, and at different stages in their lives, children require different degrees of protection, provision, prevention and participation. Later, she showed a list of documents and ethical and legal guidelines to consider in order to conduct a clinical trial, such as:

- Declaration of Helsinki
- Clinical investigation of medicinal products in the paediatric population (ICH E11)
- CIOMS/WHO guidelines
- Convention on Human Rights and Biomedicine (Oviedo Convention, 1997)
- Additional Protocol to the Oviedo Convention on Biomedical Research (2005)
- Directive 2001/20/EC repealed by the EU Regulation 2014/536 on clinical trials

As she underlined, all these guidelines require and guarantee the autonomy of the children through the informed consent/assent and agree on the fact that the research should not start or be discontinued if the child raises objections or resistance.

Furthermore, she proceeded the discussion with an explanation of role of the Ethics Committee (EC), that acts in agreement with Good Clinical Practice (GCP) and gives opinion on trial protocol, suitability of the investigators, adequacy of facilities, methods and documents for informed consent, in order to protect rights and safety of the human subjects. She showed that within the TEDDY network, an inventory of all Ethics Committees at national level of the European countries has been developed, identifying1007 ECs in 29 countries with different composition and function.

Regarding the new EU Regulation on Clinical Trials, she highlighted a new risk-based approach that refers to a "Low-intervention clinical trial". Moreover, concerning the assessment procedures, she explained that the new EU regulation splits the assessment approval into two parts: the risks-benefit approval and ethical aspects assessment. The first part has to be evaluated by a reporting Member State, the second one has to be carried out by each Member State involved in the clinical trial. The new EU Regulation also distinguishes trials with direct benefit for the minor and trials with some

benefit for the population represented by the minor. In the last case, CTs have to pose only minimal risk and minimal burden in comparison with the standard treatment of the minor's condition.

She also explained that there are some ambiguities and a lack of consensus about the interpretation of the term "minimal risk". In fact, there is an absolute interpretation that considers *a **risk** as **minimal** "if the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (45CFR 46.102*) that in some cases could not be protective enough for the children and a relative interpretation considering *a **minimal risk** if, having regard to the nature and scale of the intervention, it is to be expected that it will result, at the most, in a very slight and temporary negative impact on the health of the person concerned*, that is linked to the health of the child and addressed on a case-by-case basis but permits to conduct research with higher risks in sick children.

Finally, she showed another important point included in the European recommendations: e.g. the insurance issues. In fact, insurance companies' contracts should not waive liabilities regarding long-term effects or limit the liability period. Moreover, regarding the data protection, she explained that medical records should be protected by the privacy requirements of the applicable national laws in order not to pose a risk of labelling individuals with pre-existing conditions by insurance companies.

3.1.6. Cooperation between industry and academia in performing paediatric clinical trials

The last speaker of the first session was **Pier Adelchi Ruffini**, who described the benefits of the collaboration between industry and academia in performing paediatric clinical trials. Firstly, he provided an overview of the main problems of the medicines for paediatric use, underlining that, although all the medicines used to treat paediatric conditions have been rigorously tested before their marketing authorization, not all of them have been tested and licensed specifically for their use in children. Additionally, the off-label use is large in paediatric patients.

Gabapentin is a clear example of this issue. He explained that Gabapentin is a drug approved for the treatment of partial seizures both in adults and children and for the treatment of peripheral neuropathic pain in adults. He highlighted that there is also an off-label paediatric use because of the absence of paediatric studies. In this context, he introduced the GAPP project, a project funded by the EU-FP7 with the aim to improve the quality of life in children affected by chronic pain. As he explained, the participants have planned controlled clinical trials investigating dosage, efficacy and safety of gabapentin for the treatment of paediatric pain in children from 3 months to less than 18 years. He stressed that the GAPP initiative has seen the collaboration of several consortium members with different competences and has involved also private companies, such as Dompé -a pharmaceutical Industry- and PHARM, the Sponsor of the 2 clinical trials. In fact, he underlined that the partnership between academia and industry is the most sensible way to address unmet needs in rare conditions where the conduct of large international clinical trials is challenging.

Finally, he gave a brief presentation of the two clinical studies (GABA-1 and GABA-2 studies) foreseen in the GAPP project.

GABA-1 study:

- Is a randomized, double-blind, double dummy, active controlled, multicentre non-inferiority phase 3 study to evaluate pharmacokinetics, efficacy and safety of gabapentin liquid formulation

- Aims to assess the efficacy of gabapentin compared to tramadol for the treatment of moderate to severe chronic neuropathic pain or mixed pain in children from 3 months to less than 18 years of age.

GABA-2 study:

- Is a randomized, double blind, placebo controlled, multi-centre superiority phase 2 study to evaluate the safety, pharmacokinetic and efficacy of gabapentin liquid formulations as add-on to morphine in children from 3 months to less than 18 years of age experiencing severe chronic neuropathic or mixed pain.
- Aims to evaluate the efficacy of gabapentin as adjunctive therapy to morphine assessed by the difference in average pain scores at the end of the treatment period.

Moreover, he showed the clinical sites that are conducting the studies, located in several countries (Italy, France, Germany, the Netherlands, Greece, Albania) and some new countries are now being selected.

3.2. Session II

3.2.1 A global view of paediatric clinical trials from a CRO's perspective

Martine Dehlinger-Kremer, connected via videoconference provided an overview on paediatric clinical trials from a CRO's perspective. She started her intervention showing the current issues of the clinical trial conduct and underlining that 19% of paediatric trials are discontinued early, 30% of completed paediatric trials remain unpublished in the medical literature several years later and the delay in the drug development process cost billions of dollars per year. She presented the results of a survey launched by EUCROF (European CRO Federation) demonstrating that the main constraints in paediatric clinical trials are the patients' recruitment and the legislation issues (for Industries) but also financial concerns and Ethics Committee approval (for Academia). Moreover, she highlighted that, although the number of trials in EU has increased of about 19% in response to regulations and incentives, there is still a relevant gap between the number of paediatric and adult randomized trials. This is due to some challenging characteristics of the paediatric clinical trials such as the behavioural and emotional conditions, the child's age and developmental stage, the limited number of children with specific diseases and the fear of parents to let their child participate.

She also highlighted the importance to have an optimal and proper paediatric development plan (PIP), that has to specify investigators, sites, networks, parents' representatives, patients and scientific consultation as input for proposed studies.

Among all the trial documents, she preferred to focus her attention on the informed consent form that has to be prepared using understandable terminology, an optimal risk/benefit wording and by consulting Young Person's Advisory Groups. Moreover, she underlined that the process to get assent from children has to be conducted at the same time of obtaining consent from parents/legal guardian. Moreover, she specified that there is no unique information method for every paediatric study. In fact, it is necessary to consider many variables such as indications, age at diagnosis, stage of disease, country involved. For this reason, it is fundamental to establish a trust relationship with the child and the parents. As she showed, there is a lack of homogeneity among the laws about the consent/assent both in EU and US countries. This is confirmed by the surveys performed in two different years (2014 and 2016) in 27 European countries by the Enpr-EMA Ethics working group and the Paediatric

working group of EUCROF, showing that there is no harmonization about, for example, the legal age of independent consent or also the age groups for assent and the signature of parents (one or both).

Moreover, she gave some advices about the trial site identification, which is another important issue in the clinical trial conduct. As she explained, the centres are often eager to participate, because they suffer a lack of treatments available, but it is necessary to look at their real resources provided, in order to avoid waste of time and delays. For example, the center should have a proper network-based nurses to assist with trial procedures and an optimal data collection system to allow form completion and data submissions.

She concluded her speech presenting some surveys about the communication between Industry and Paediatric Network that showed some interesting data:

- Usually, Companies have more experience in paediatric clinical trials (phase I-IV) rather than in epidemiological trials or registry based studies
- Only 32% of Companies have already worked with a research network (Enpr-EMA or other networks)

3.2.2. The Italian Network for Paediatric Clinical Trials: a survey for mapping the potentialities of the Italian clinical sites

Paolo Rossi, provided an excursus of the current potentialities of the Italian clinical sites and showed a list of some relevant issues characterizing paediatric clinical studies, such as the need to develop paediatric research infrastructure, the paucity of patients available for the study and the lack of adequate funds to deliver both industry-sponsored and academic sponsored clinical trials. He explained that IMI2 call for proposals made possible the creation of a Pan-European paediatric clinical trials network, called conect4children: collaborative network for European clinical trials 4 children. As he showed, C4C consortium is composed of national hubs, disease specific networks, research networks and largest departments of paediatrics. The Italian hub in C4C is INCiPiT (Italian Network for Paediatric Clinical Trials). The mission of this network is to:

- improve the availability of information about paediatric medicines in multiple countries and sites;
- promote the delivery of high quality trials of medicines using resources and information shared between the studies.

He also provided an overview of INCiPiT, the network composed by the main Italian Children's Hospitals, the largest Departments of Paediatrics as well as national and international paediatric therapeutic Networks coordinated by Italian Institutions. The mission of INCiPiT is to foster and support the planning, conduct and completion of all types of clinical studies conducted in Italy in the paediatric population. He listed some INCiPiT activities such as the survey to map INCiPiT potentialities, and expertise, the creation of SOPs and models to harmonize CTs in Italy and its participation in European and national projects.

In addition, he explained more in depth the survey conducted by INCiPiT to map the potentialities of the Italian clinical sites, explaining that the survey was composed of 60 questions grouped in sections and agreed with several stakeholders at EU level (such as Enpr-EMA). The questions have been sent to all INCiPiT Partners to identify the level of expertise in paediatric clinical research. The results of the survey highlighted some interesting data, such as:

- 8/13 of partners have a dedicated Clinical Trial Centre
- 5/13 of partners have experience in paediatric clinical trials in almost all therapeutic areas

- 11/13 of centers established collaborations with patients associations and Young Persons Advisory Groups (YPAGs).

He concluded that overall the evaluation of the potentialities in paediatric clinical research in Italy showed great results but also some space for improvement.

3.2.3. The voice of patients in paediatric Innovation: the experience of the KIDS Barcelona

Joana Claveral Torres presented the KIDS Barcelona group that has the vision to improve the patient advocacy in research and innovation. In fact, as she explained, since patient recruitment is a challenging issue in the clinical trial conduct, this initiative aims to work on patient and child motivation and active participation. The main pillar of this initiative is the partnership between patients and doctors, researchers and other staff. Firstly, she explained that an YPAG is a group of young children who want to learn more about health and clinical research and participate in monthly meetings with researchers and experts in the delivery of health research. She also described the methodology they used to train the children. In fact, these meetings foresee the direct involvement of patients and non-patients (CYP), who, along with facilitators and investigators, are skilled in all phases of health research (from the introduction of the biomedicine meaning to the clinical trial process).

She stressed the need to consider further issues such as school work and time commitment, family dynamics, pregnancy testing or alcohol/smoking/recreational drugs use that can impact on recruitment and retention of CYP.

Moreover, this initiative wishes to overcome the patient recruitment difficulties through the active involvement of CYP from the beginning. She underlined, in fact, that the children know well the protocol design, timing of visits, relevant endpoints and data collected. To obtain the full involvement, it is important that information sheets are concise and age appropriate and that the commitment is clear from the beginning (frequency and length of visits, diaries, Quality of Life questionnaires and potential side effects). In order to stimulate the curiosity and the motivation of young people, she suggested to highlight and make more clear to them the results of the studies and their fundamental help for the future generations. Finally, she showed some educational resources they use to interact with the children, such as some comics explaining what a clinical trial is or another interactive tools used to describe the clinical trial phases.

3.2.4. Industry funding of clinical trials: benefit or bias?

The last presentation of the day was provided by **Claudio Fracasso** with the aim to give some explanations about the importance of industry as a partner in paediatric clinical trials. First of all, Claudio suggested that the paediatric community look beyond industry as a funder of research, and instead as a critical partner in research that brings news treatments and vaccines to children. In fact, he highlighted that the best way to act is to work together (Companies and Academia) as resulted in IMI-2 EUPCTN, a Pan-European Paediatric Clinical Trials Network. He explained that EUPCTN is a European initiative that has fostered the development of next generation medicines for children, by promoting more rapid delivery of paediatric drug trials through improved uniform processes in a coordinated network.

Moreover, he described the Pfizer Paediatric Center of Excellence (PedCoE), a group of experts with the mission to improve the health and well-being of children through science, operational excellence,

by aligning resources and providing unified voice for the needs of children. He highlighted that this group understands the importance of collaborating with other academic groups with the same mission.

He concluded his presentation by noting that the changing environment is stimulating members of the biopharmaceutical industry to assess their organizational resources, to share knowledge, and to support external initiatives. In particular, Pfizer has been working to optimize its internal processes by attempting to create a paediatric internal website to share all the experiences and knowledge, preparing a new paediatric-specific protocol template and also participating in many external initiatives and forums (IMI2, EFGCP, CRIG...).

4. ANNEX 1 – Meeting Agenda

INTERNATIONAL PAEDIATRIC CLINICAL TRIAL DAY 2017
Helping children create lives they deserve

Milan – May 9, 2017
Ospedale San Raffaele
Via Olgettina, 60

Scientific Programme

09:30 Participants registration

CHAIRMEN: Antoinette van Dijk, Scientific Director AICRO and **Alessandro Aiuti,** Ospedale San Raffaele

10:00 **How will the paediatric scenario change with the Collaborative Network for European Clinical Trials for Children: the Enpr-EMA perspective**
Mark Turner, EnprEMA Chair, Senior Lecturer at the Liverpool University, United Kingdom

10:30 ***The roadmap for a new Paediatric Research Infrastructure: gaps analysis and feasibility***
Adriana Ceci, TEDDY Network Scientific Coordinator, Italy

11:00 **The Paediatric Regulation: ten years after its implementation**
Marek Migdal, Deputy Head of the Paediatric Intensive Care Unit in the Children's Memorial Health Institute, PDCO EMA member, Poland

11:30 **Advanced therapies for genetic diseases: from paediatric clinical trials to approved drugs**
Alessandro Aiuti, Head of Pediatric Immuno-Hematology *Unit at Ospedale San Raffaele, Vice Director SR TIGET, Italy*

12:00 ***Children are not little adults: put the child in the heart of the EU clinical trial ethical and legal framework***
Annagrazia Altavilla, Lawyer specialised in Health Law and Biomedical Ethics (Espace Ethique Méditerranéen - Aix-Marseille University), former PDCO EMA member, France

12:30 ***Cooperation between industry and academia in performing paediatric clinical trials***
Pier Adelchi Ruffini, Chief Medical Officer at Dompé Farmaceutici SpA, Italy

13:00 BUFFET LUNCH

CHAIRMEN: Donato Bonifazi, Chief Executive Officer CVBF and **Elisabetta Riva,** Head of Clinical Research Office at Ospedale San Raffaele

14:30 **A global view of paediatric clinical trials from a CRO's perspective**
Martine Dehlinger-Kremer, Vice President of the Global Medical and Regulatory Affairs at SynteractHCR, President of the European CRO Federation (EUCROF), Germany
(Connection via video conferencing)

15:00 **The Italian Network for Paediatric Clinical Trials: a survey for mapping the potentialities of Italian clinical sites**
Paolo Rossi, Italian Network for Paediatric Clinical Trials, Italy

15:30 **The Voice of patients in paediatric Innovation: the experience of the KIDS Barcelona**
Joana Claverol Torres, Clinical Research Unit Manager at Hospital Sant Joan de Déu, Spain

16:00 **Industry funding of clinical trials: benefit or bias?**
Claudio Fracasso, Global Paediatric Medical Director, Paediatric Center of Excellence, Pfizer Italia, Italy