"TEDDY General Assembly" Meeting Minutes

Virtual; 22/06/2021

Index

1. Agenda

TEDDY GENERAL ASSEMBLY MEETING

Virtual meeting - June 22nd, 2021

9.00-9.20	Welcome Address and update on the TEDDY activities	A. Altavilla
9.20-9.40	EC Consultation on medicines for children & rare diseases	F. D'Atri
9.40-10.00	Results of the Council of Europe survey in collaboration with TEDDY	L. Lwoff
10.00-10.20	European Paediatric Medicines Database (TEDDY-EPMD) Tool	M. Felisi and M. Toma
10.20-10.40	Innovation in clinical trials methodologies in limited populations	O. Della Pasqua
10.40-10.50	Virtual coffee break	
10.50-11.10	Modelling & Simulation: In silico Methodologies for Drug Discovery in Paediatric Research	C.D. Altomare
11.10-11.40	How to evaluate off-label use of medicines in the paediatric population: International/global perspectives	M. Gazarian and S. de Wildt
11.40-12.00	Data protection issues in paediatric research under GDPR: the roles of codes of conduct	J. Herveg
12.00-12.20	EJP RD training activities for rare and paediatric expert patients	M. Lupo and B. Nafria
12.20-12.40	TEDDY Kids serious game "My Clinical Trial Center"	Kids Bari and Kids Albania
	TEDDY MEMBERS SESSION	
12.40-13.00	TEDDY 2020 Financial Statement, 2021 budget and membership fee	D. Bonifazi
13.00-13.30	Discussions on future activities	All

2. Participants

Annagrazia Altavilla (Espace Ethique PACA/Corse APHM/Aix-Marseille University);
Adriana Ceci, Viviana Giannuzzi, Lucia Ruggieri, Maddalena Toma, Antonella Didio and Franco Bartoloni (Gianni Benzi Foundation);
Donato Bonifazi, Mariagrazia Felisi, Mariangela Lupo, Valeria Pignataro, Giovanni Migliaccio, Maria Cavallo, Cristina Manfredi, Ornela Cullufe, Bonka Georgieva, Arlinda Demeti, Manika Kreka, Ana Dilo, and Galib Ishtiaque (CVBF);
Daniel Torrecilla (RECLIP);
Alketa Hoxha (University of Tirana);
Nicola Santoro (AOUC Policlinico - Bari);
Fabio D'Atri (European Commission);
Saskia de Wildt (Radboud University);
Oscar della Pasqua (UCL);
Madlen Gazarian (University of NSW-Australia);
Jean Herveg (CRIDs University of Namur);
Laurence Lwoff and Natalia Zaytseva (Council of Europe);
Begonya Nafria (Sant Joan de Déu Research Foundation);
Fidelie Kalambayi (Romanian Angel Appeal Foundation);
Toni Irmgard (UKER);
Cosimo Damiano Altomare (University of Bari Aldo Moro);
Marina Brocca (European CMT Federation);
Franck Devaux (HUDERF);
Marios Phylactides (CING);
Sergey Suchkov (MGUPP);
Johan Vande Walle (University of Gent);
Bjoern Burckhardt (Heinrich Heine Universität);
Martine Dehlinger Kremer (EUCROF & PRAealth Sciences);
Savanna Andreou (Cyprus institute of neurology and genetics);
Segolene Gaillard (Hospices Civils de Lyon);
Florence Guillot (ANR);
Beate Aurich (APHP Paris);
Petia Stratieva (ePAG ERN-EYE, Retina International);
Jasmin Albano (Universitätsklinikum Tübingen);
Claudio Fracasso (Pfizer Srl);
Philip Connor (Cardiff and Vale UHB);
Lorenzo Polenzani (ACRAF);
Fiona Rako (Kids Albania);
Valeria Gatti (Kids Bari).

3. Discussion

3.1 Opening of the General Assembly

The TEDDY General Assembly (GA) meeting was held virtual on 22nd June 2021 due to the health emergency caused by the COVID-19 pandemic.
The Chair— Annagrazia Altavilla, welcomed and opened the discussion to briefly update the activities carried out by TEDDY in the last year and plan the next steps. The General Assembly was then followed by discussions on the different topics held by participants.

3.2 Update on the TEDDY activities - Presented by Annagrazia Altavilla (TEDDY Chair)

Annagrazia Altavilla provided the assembly with a brief update on the activities carried out in the last year. She announced the next activities.CVBF will organise a workshop with TEDDY experts entitled "Modelling & Simulation (M&S): Research Methodologies for Small Populations in Rare Diseases" and organised in the framework of the European Joint Programme on Rare Diseases (EJPRD) project. The main objective of this workshop is to facilitate discussion and exchange of knowledge on the M&S methodologies and strategies as innovative facing complex multifactorial or rare diseases and conditions that require highly specialised treatments and resources addressing small population specificities.
Beneficiaries of this workshop are the Rare Disease community, including PhD students, Post-doc researchers, senior scientists, young clinicians, investigators and academics.
Annagrazia Altavilla will develop the new Guide of the Council of Europe on participation of children in decision-making process on matters regarding their health with representatives of the Committee on Bioethics (DH-BIO) and the Steering Committee for the rights of the Child (CDENF) of the Council of Europe.
In this framework, TEDDY will develop new initiatives with the Council of Europe.

The new website for the TEDDY network was also shared. It will be available for everyone very soon.

3.2.1 TEDDY publication activities

Different publications involving TEDDY members were published in 2021—

- Altavilla A, Halila R, Kostopoulou M-A, Lwoff L, Uerpmann K, Strengthening children's participation in their health: the new initiative of the Council of Europe, Lancet Child & Adolescent Health 2021 Feb 10: 1-2. Available at: https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(21)00019-5/fulltext

- Toma M, Felisi M, Bonifazi D, Bonifazi F,Giannuzzi V,Reggiardo G, de Wildt S, Ceci A et al., Paediatric Medicines in Europe: The Paediatric Regulation – Is It Time for Reform? Front. Med., 02 February 2021 Vol.8. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7884470/

In addition, the following work has been submitted in 2021—

- M. Toma, V. Giannuzzi, A. Landi, D. Bonifazi, MG. Felisi, F. Bonifazi, A. Ceci on behalf of TEDDY, "Orphan Paediatric Medicines in Europe."

- M. Toma, MG. Felisi, A. Ceci on behalf of TEDDY, "Paediatric drug repurposing in Europe after the Paediatric Regulation."

3.2.2 TEDDY communication activities

TEDDY disseminates news and valuable information from the paediatric community relevant to the TEDDY partners through the TEDDY newsletter, website, and official social channels.

3.3 EC Consultation on medicines for children and rare diseases- Presented by Fabio D'Atri (European Commission)

Almost three years ago, the regulations on rare diseases and medicines for children had begun to access the strength and weakness of the legislation. Both legislations have been successful— as the number of medicines that have been authorised for children and studied in children has increased, the number of clinical trials involving children has also increased, and there are more published evidence about the use of medicine in children. But, in unmet medical areas, there has been little development. The structure of paediatric investigation plan (PIP) does not comply with one-size-fits-all. The availability and accessibility also varies across Member States and burdensome. So, the revision of the paediatric regulation is proposed which will foster research, ensure availability, provide effective and efficient procedures. However, the core of the existing regulation will not be changed. In PIP, the drug's mechanism of action has also been taken into account, not just whom the drug has been indicated for.

Revision of the orphan and paediatric legislation will be carried out by—

- Impact Assessment
  - Public consultation ongoing till end of July 2021
  - Targeted consultations
  - Interviews
- Legal Proposal(s) in 2022

The pharmaceutical legislation is a set of actions which aims to ensure the access to affordable medicines by fostering innovation, improving security of supply, reducing red tape and adapting to new scientific and technological developments. Revision of the pharmaceutical legislation is ongoing by—

- Roadmap inception impact assessment
- Evaluation and impact assessment (ongoing)
- Public consultations (after the summer 2021)
- Other consultation activities (end 2021)
- Adoption of proposal(s) (2022)

3.4 Results of the Council of Europe survey in collaboration with TEDDY- Presented by Laurence Lwoff (Council of Europe)

Oviedo convention has been a turning point in human rights in biomedicine, but has also raised human rights challenges that need to be addressed. Within this framework, the Strategic Action Plan on Human Rights and Technologies in Biomedicine (2020-2025) prioritises children's participation in the decision-making process regarding their health.
The COE – Committee on Bioethics (DH-BIO), with the support of TEDDY European Network of Excellence for Paediatric Research, released a survey to identify national provisions, guidelines and

practices aimed at strengthening children's participation in the decision-making process in health care, research and more in general in the biomedical field.
The Council of Europe survey was carried out online with the support of TEDDY and released to the main stakeholders (DH-BIO / CDENF delegates, healthcare professionals, Scientific societies, Patients/parents/children, European clinical research network, Research organisations, European Institutions representatives and industry representatives)The survey, composed of eight main questions and sub-questions, was successful. Answers from 36 countries were obtained. The most relevant activities identified from the survey in decision making process within healthcare and research are education for young persons and for parents/family members as well as training of healthcare professionals to better involve children.
The need to work more with a pluridisciplinary approach on this topic as well as the need of stronger engagement and collaboration among all the stakeholders have been pointed out.
The results of this survey will help in outlining best standards and practices and determining roadmap for developing a guide for healthcare professionals, patients/parents' association expected in 2022.

3.5 European Paediatric Medicines Database (TEDDY-EPMD) Tool- Presented by Mariagrazia Felisi (CVBF) and Maddalena Toma (Fondazione per la Ricerca Farmacologica Gianni Benzi Onlus)

This online database creates a harmonised, integrated, and reliable pan-European source of information on all paediatric medicines registered under the European Medicines Agency (EMA) Centralized Procedure. The EMPD database can be accessed at:

http://epmd.teddynetwork.net:8081/epmd2_public/

In the period October 1995 – December 2020, a total of 1280 Medicinal Products and 906 Active Substances have been approved by EMA under the Centralised Procedure

- 452 and 357 of them were paediatric medicinal products and paediatric active substances, respectively (35% and 39%)
- Lower number of medicines refers to neonates and younger children, while this number increases for older children and is the highest for adolescents
- Anti-infectives for systemic use represents the group with the highest ratio
- Genito-urinary system and sex hormones and Cardiovascular system the groups with the lowest ratio
- The recent publication suggested that out of 175 new active substances (from 2007-2019), 6/175 have a PUMA granted, 3/175 are ATMPs, 53 medicines repurposed for paediatric use, 57/175 were orphan and most of them belong to A-ATC (19/57) and L-ATC (12/57) first-level categories.

This report confirms that the expectations of the European Paediatric Regulation (EC) N◦ 1901/2006 have been mainly satisfied and paediatric drug repurposing in Europe seems to be particularly implemented. However, a limited number of studies supports these MAs application, and it is questionable if a special repurposing procedure involving the EMA-PDCO opinion would foster the development of more and high-quality paediatric medicines.

Future activities (by December 2022)—

- Upgrade to EPMD 2.0 with Technical, Graphical, and Additional Information

- A new section of the EPMD will include all paediatric drugs in development, consisting status of the PIP, condition under study, requested studies, age of population under study.

3.6 Innovation in clinical trials methodologies in limited populations- Presented by Oscar della Pasqua (UCL)

Some of the alternative methods for evidence generation are—

- Dynamic Bayesian borrowing (a formal integration of prior knowledge, increased precision)
- Basket designs (multiple diseases for a given marker)
- Real world evidence (pragmatic clinical trials, non-interventional model-based)

However, the biggest barriers for paediatric trials are lack of evidence synthesis, limited data (precision) and uncertainity. Modelling, simulation, and extrapolation can be considered for evidence synthesis. Therefore, a major opportunity lies for cross-fertilisation.

3.7 Modelling & Simulation: In silico Methodologies for Drug Discovery in Paediatric Research- Presented by Cosimo Damiano Altomare (University of Bari Aldo Moro)

Drug design in paediatrics is challenging because of the age-related ADME and metabolism related toxicity. Hence, the necessity of Pediatric Biopharmaceutical Classification System (BCS) has emerged. Active substances, as well as excipients can lead to toxicity. As of today, many computational platforms have been developed for predicting age-related toxicity, such as—

- MetaQSAR database which can predict metabolism
- STEP that is Safety and Toxicity of Excipients for Pediatrics database
- Derivation of new developmental toxicity models (CAESAR) 2.1.7 based on machine learning and artificial intelligence
- Developmental/reproductive Toxicity library (PG) 1.0.0
- Developmental toxicity consensus model by Toxicity Estimation Software Tool (TEST) 4.2.1

3.8 Evaluate off-label use of medicines in the paediatric population; International/global perspectives

3.8.1 Perspective from outside the EU - Presented by Madlen Gazarian (University of NSW)

Key ethical considerations relevant to responsible off-label prescribing—

- Evaluating whether there is sufficient evidence to justify off-label use
- Collecting information and conducting research when there is inadequate evidence about an off-label use
- Informing patients about the uncertainties & potential costs associated with off-label prescribing.

However, off-label prescribing is still not regulated by medicines regulatory agencies and made of variable decisions and recommendations. Hence, the Council of Australian Therapeutic Advisory Groups (CATAG) has identified four priorities—

- A generic information leaflet and consent form for patients/carers

- Education and training tools for prescribers & other decision-makers include improving awareness & knowledge of issues associated with off-label medicines use, as well as developing skills to support evidence-based & ethical decision-making & Quality Use of Medicines (QUM)
- An off-label medicines use the registry to support the generation of "real world" evidence to guide future decision-making better
- Centralised evidence-evaluation (and/or decision-making) process for selected medicines & populations

3.8.2 Perspective from the UE - Presented by *Saskia de Wildt (Radboud University)*

As per Art 68 Medicine Law— Off-label is only allowed when the healthcare community has described its use in guidelines or standards.

Kinderformularium was introduced to perform risk-benefit analyses for drug use in children based on available scientific literature, licensed information, expert opinion. Kinderformularium 2.0 was introduced in 2015, which harmonised drug therapy in the Netherlands, as it is considered an official Dutch Pediatric dosing guideline endorsed by KNMP, NVK, NVZA. Some of the improvement projects are—

- Nefrodose (dose adjustment in renal failure)
- Calculator (a software that helps to reduce calculation mistakes and thereby safer pharmacotherapy)
- Information for parents
- Neodose project
- International (the German Kinderformularium).

3.9 Data protection issues in paediatric research under GDPR: the roles of codes of conduct- Presented by Jean Herveg (University of Namur)

Since 25 May 2018, a new set of common rules in the EU regarding the processing of personal data has been adopted, which is "The General Data Protection Regulation" (n°2016/679) (hereinafter GDPR). The main goal of GDPR is to prevent the misuse of information and therefore regulating the processing of personal data and to support the data subjects' informational rights.

The Code of Conduct (hereinafter CoC) ensures the effectivity of GDPR. The CoC is intended to contribute to the proper application of GDPR, taking account of the specific features of the various processing sectors and the specific needs of micro, small and medium-sized enterprises.

The adherence to a CoC does not presume the compliance of the data processing activities with the GDPR. The CoC must also comply with the applicable national laws.
Contribution to the good implementation of the GDPR rules in a specific sector, means the CoC must increase the compliance with data protection rules and that must be demonstrated, and it must implement the GDPR taking into account the specificities of the sector. It should furthermore increase the confidence of the citizen. They must be approved by the competent supervisory authority (hereinafter SA) and the EU commission can declare some CoC to be applicable in the entire EU.

Codes of Conduct can be, national (one EU MS), translational (several EU MS) or codes of conduct with provisions regarding the transfer of personal data outside the EEA/EU zone

Drafting will be done by an association or organisation representative of categories of data processors or data controllers. The language of draft will be the language of the competent SA, also in English for Translational CoC.

Importantly, in paediatric research, the following aspects need to be taken into account —

- Information to be imparted to patients/children and families
- Data Subjects Participation
- Exercise of Data Subjects' Rights (e.g. access to data)
- Issues related to incidental Findings
- Issues related to Processing Genetic Data

TEDDY could play an important role in this field.

3.10 EJP RD training activities for rare and paediatric expert patients- Presented by Mariangela Lupo (TEDDY) and Begonya Nafria (Sant Joan de Déu Research Foundation)

The need to include children in drug development programs has been largely recognised over the past few decades, and stringent legal and regulatory frameworks have been established all over the world with significant but insufficient results.
To enhance this engagement, training is required for young patients which will educate them on rare diseases, medicines development, and clinical research. Due to the paediatric specific developmental characteristics, specifically tailored methodology should be applied to the training and empowerment process of paediatric patients.
Within the task 15.4 of the European Joint Programme on Rare Diseases (EJPRD) project, short workshops will be organised under the coordination of the TEDDY Network in collaboration with EURORDIS and the Sant Joan de Déu Research Foundation (FSJD) addressed to 15 paediatric patients for each of the three years 2021-2022-2023.

- Online pre-test of participants to verify their knowledge
- 3 annual workshops in 2021, 2022, 2023 in different countries, workshop will be 3-days course
- The workshop in 2021 is going to be online because of pandemic
- Workshop will be held at the partner premises, or location identified by TEDDY and FSJD
- Each course will train 15 participants
- Participants must be pre-adolescence and adolescence, aged 12-18 years with chronic rare disease
- Educational webinars
- Short assessment questionnaire
- Interactive methodology
- Performed in English

A program committee has been set up and will—

- Be in charge of the developing the training plan
- Revise materials for each workshop
- Approve panel of proposed speakers
- Update training plan as per the results of workshop survey
- Consists of—
    - Task Leader- Mariangela Lupo (TEDDY)

- One representative from TEDDY (Annagrazia Altavilla), FSJD (Begonya Nafria), and EURORDIS (Virginie Bros-Facers)
- One representative from paediatric patients organisation— Ketotic Hypoglycemia International (Danielle Drachmann)
- One representative from c4c (Becca Leary)
- One representative from EPTRI (Adriana Ceci)

Young program committee is foreseen and will consist of—

- One kid from KIDS Albania (with McCune Albright syndrome)
- One kid from KIDS Bari (with Mainzer Smaldino syndrome)
- One kid from KIDS Barcellona (with Spinal Muscular Atrophy)

Training plan tailored for young people is under finalisation. It will consist of—

- Common module (about rare diseases, orphan drugs, ethical/legal aspects, patient advocacy)
- Scientific content (will be adopted each year in areas, such as oncologic diseases, metabolic diseases, haematological diseases).

3.11 TEDDY Kids serious game "My Clinical Trial Center"- Presented by Fiona Rako (KIDS Albania) and Valeria Gatti (KIDS Bari)

The TEDDY Kids serious game was presented by the Kids Albania and Kids Bari young members. Since its establishment in 2017 as YPAG (Young Persons Advisory Groups), Kids Albania and Kids Bari have been making contribution to research on the health and well-being of children and young people. YPAG continues to help researchers design clinical trials, improve communication with children as well as their families, and suggest methods for disseminating the results of the most effective studies. Different YPAGs around the world have constituted iCAN— the International Children's Advisory Network. The TEDDY Kids serious game— "My Clinical Trial Centre" has received iCAN approval and been developed to explain to children in a fun way what clinical trials are, how they work and why they are so important to developing drugs suitable for children. The game is extremely informative, as game-players will learn about clinical trial, study protocol, informed consent and assent in children, phases and procedures of clinical trials, data collection, and pharmacovigilance. The game is available in Android and iOS, and developed by Hero— an innovative start-up. Currently, the game is available in English but very soon— it will be available in Italian and Albanian.

3.12 Approval of the financial statements- Presented by Donato Bonifazi (CVBF)

Donato Bonifazi provided a quick overview of the TEDDY Network administrative situation. The Network started in 2005 as an FP6 project coordinated by CVBF and involving several research Institutions from all over Europe and some neighbouring countries (Israel). The funded period ended in 2010 but TEDDY never stopped its activities, growing up to over 50 members from more than 20 countries. The TEDDY Network became an autonomous legal entity in July 2017 and started participating in EU funded projects: EPTRI since January 2018 and EJPRD since January 2019, leading specific tasks in the networking and training activities, that are particularly relevant in the two projects.

The 2020 financial statement was characterized by a positive balance of 2 thousand euros after covering the total costs of 61 thousand euros, based on just one employee and few more expenses, while the main incomes are from the participation in the two projects:

- European Paediatric Translational Research Infrastructure, just ended;

- European Joint Programme on Rare Diseases, which will continue up to the end of 2023.

The budget for the current year is aimed to exactly replicate the 2020 result, with a very slight increase of both incomes and expenses.

Finally, with regards to the membership annual fee, he proposed to confirm the 50 euros fee for all the categories of members, while the supporting Institutions are of course allowed to make higher freely contributions, and he said that it was decided not to ask for the fee during the 2020.

The assembly approved:

- the financial statements, with a positive result of 1.802 €,

- the 2021 budget with expenses for 70 thousand € and a positive result of 2.000 €, and

- the membership fee of 50 € for the year 2021.