"TEDDY General Assembly 2019 Meeting"

Report of the meeting

Ministry of Health, Consumption and Social Welfare, Madrid;
29/03/2019

Report of the meeting

Welcome Address

Adriana Ceci welcomed all the participants to this General Assembly in Spain. The Spanish partners have been involved in TEDDY since the beginning in 2005. The TEDDY Network of Excellence arose from the Task-force in Europe for Drug Development for the Young, a consortium funded in 2005 as a Network of Excellence within the EC Sixth Framework Programme and it represented the first paediatric initiatives at that time. It is a multidisciplinary and international network and it witnessed over the years to the many changes occurred in the paediatric research framework starting from the approval of the European paediatric regulation. It continued its activities also after the funded period on a voluntary basis and recently it was provided with an autonomous legal status.
She then pointed out the main objectives of this General Assembly:

- renewing the interest and commitment of TEDDY partners and participants in TEDDY activities,
- reopening useful discussion on mission, vision and governance model of this first multinational paediatric Research Network in EU into the changed scenario of Paediatric Research.

Session 1 - TEDDY NETWORK ACTIVITIES FROM LAST GENERAL ASSEMBLY UP TODAY

Maria Mellado and Oscar Della Pasqua chaired the first Session of the Assembly welcoming all the participants and introducing the main topic of the session: activities from last General Assembly to today.

TEDDY Scientific activities and tools

Mariagrazia Felisi, Clinical Director at Consorzio per Valutazioni Biologiche e Farmacologiche acting as Coordinator of the TEDDY Scientific Coordination Committee (SCC), presented the scientific activities of the Network, the Scientific Coordination Committee (SCC) activities, the TEDDY participation to EnprEMA, the TEDDY Working Groups (WGs) results and the tools developed within the network.
She first described the network scope, its evolution along the last 15 years and its members and boards. She focused on the aims and activities of the SCC as described in the Statute. The SCC is set up to coordinate the scientific activities of the TEDDY Network and it is currently composed of 6 members appointed by the General Assembly and it has met 5 times since the last General Assembly.
TEDDY is part of the Enpr-EMA, currently as category 1 network, and has been invited to participate to tenth annual workshop (2018) of Enpr-EMA and Coordinating Group meeting, held in London on June 7th and 8th, to the Enpr-EMA Coordinating Group meeting with networks members in 2018 October 22nd and is involved in many Enpr-EMA activities and WGs.
Later on, she moved to the TEDDY Working groups description that were depicted more in depth by the following speakers as WGs chairs. Seven WGs have been established during the last general assembly that are currently revising their mandate: 1) Off-label use in paediatrics, 2) Health data, 3) Active engagement of children and adolescents, 4) Advanced therapies in paediatrics, 5) Ethical issues in paediatric research, 6) Paediatric clinical studies methodologies and procedures, 7) Regulatory & Pharmacovigilance.

She moved then to describe the TEDDY tools available on the official website. The ICH-GCP e-learning course, aimed at providing a guide for all individuals that are involved in clinical research and that need to acquire GCP recognized certification, was developed in the context of the GAPP project and then maintained by the TEDDY Network. The course is accredited by TransCelerate BioPharma. She described the course structure, objectives and contents. The course is available online on a dedicated e-learning platform and all materials can be viewed via web or saved by the user on the computer. At the end of the course, a certificate is released upon the completion of a final test. More than 600 users have attended the course so far.
The second tool described is the European Paediatric Medicines database (EPMD) containing information on paediatric drugs authorised by the European Medicine Agency (EMA) under the centralised procedure and available on the TEDDY official website. It is aimed to create a harmonised, integrated and reliable European source of information on paediatric medicines in Europe and includes many information about the paediatric drugs authorised by EMA, i.e. tradename, active substance, marketing authorization date, ATC code, paediatric indication, orphan MP, etc. The database also includes information about the studies conducted in the paediatric population leading to a centralised Marketing Authorisation, such as study title as stated in EPAR, study code, type of study (based on scope), type of study (based on statistical approach), codification, etc. She also reported some results that have been extracted by the database analysis: centrally-approved medicines, the number of paediatric medicines and the total of medicines approved by EMA under the centralized procedure, the distribution of authorized medicines by ATC and by age. She concluded that, after 12 years, the principal aim of the Paediatric Regulation has been partially achieved underlining the need to increase the efforts to not reduce the Paediatric Regulation's effects. She pointed out the utility of the EPMD in providing useful information to set up new studies and to support the activities of the WG on off-label uses through an integration of the database with the drugs used off-label. She concluded her intervention listing other scientific activities carried out by the network: participation in projects (EPTRI and EJRPD), scouting and applications of new projects, scientific publications, participation to EMA consultations.

Paediatric applications of ATMP

Giovanni Migliaccio, initiator of the TEDDY *Advanced Therapies in Paediatrics* Working Group, held a presentation about *Paediatric applications of Advanced Therapy Medicinal Products (ATMP).* He first introduced the definition of Advanced therapy as reported in the EU regulation 1394/2007 underlining that information about ATMP are particularly relevant in 2 main fields: marketing authorization and clinical trial.
The reasons that led to have a specific regulation about this new class of medicines can be found in the novelty, complexity and technical specificity of advanced therapy medicinal products as well as in political/economical motives linked to the need to ensure access for these products to the market. Moreover, it has to be considered also the issues related to the use of embryonic stem cell (allowed/not allowed).
Advanced therapy medicinal products include the 3 following categories: gene therapy medicinal product (GTMP), somatic cell therapy medicinal product (CTMP), a tissue engineered product (TEP). The inclusion of tissue engineered products introduces a novelty in the definition of a medicinal product since it refers to the concept of regeneration. A tissue engineered product may contain cells or tissues of human or animal origin, or both and is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue. The cells or tissues may be viable or non-viable. The presence of cells allows to identify the product as a "medicinal product" and not a device, i.e. artificial aorta covered in tissue working as replacing system.
Later on, he moved to discuss about other legal definitions related to the ATMP, giving examples about when cells or tissues shall be considered "engineered". For example, it is not considered engineered a cell underwent to a cryopreservation process, but it is considered engineered a cell put in culture for 24 hours.

Regarding the effect of these legislations on ATMP research, he highlighted that for these products a centralized procedure for Marketing Authorization is compulsory. A dedicated Committee for Advanced Therapies (CAT) has been created at the European Medicine Agency and most of the countries have centralised the authorization of clinical trials in the national agency.
Focusing on paediatric, within the 313 applications for ATMP classification at EMA, 19 are for paediatric subjects and most of them are for a genetic disease. Few products are on the market and 4 have been withdrawn. Overall, 2 products were approved for paediatric and one of them has been withdrawn from the market since it was too expensive. Currently only one product is on the market for a rare paediatric disease, Strimvelis, developed by the Telethon foundation and acquired by GSK. It is very expensive but overall cheaper compared to the previous therapies.
In the last part of the presentation, he presented the TEDDY WG on ATMP aimed to spread the knowledge about ATMP manufacturing in the paediatric community, define the specific requirements for paediatric applications, focus on the research in human development underpinning the development of advanced therapies and on the business model required for their application. The WG is currently working on a COST proposal about foetal\newborn application of ATMP (a collaboration with RESTORE project is envisaged) and on consultations on EMA guidelines.

Off-label use in paediatrics

Lucia Ruggieri, held a presentation on *Working Group on Off Label Use in Paediatrics*. The WG has been established in mid-2016 to address the specificities of off-label medicines use in paediatrics. Currently she is leading the WG working to draft a policy statement on paediatric off-label use.
Among the relevant aspects to be considered in paediatric, she pointed out that the scarce availability of paediatric medicines is the most relevant driver for the off-label use in paediatrics. In some subsets (e.g. rare diseases) and for some patients group (neonates) the lack of paediatric medicines is very high and also in US paediatric labelling is still unsatisfactory. She underlined that off-label does not mean lack of evidence and possible evidences might derive from different sources in order to permit the off-label use of a drug. Then she described in a simple way the process: once available evidences are submitted and evaluated by a regulatory agency and included in the drug products characteristic, then the use become in-label. This process should consider different aspects: quality/quantity of available evidence and need to generate new data, type of information required and accepted by regulatory agencies, promptly availability of medicines for children. And benefit-risk evaluation should consider benefits and their uncertainties towards the risks and their limitation.
She underlined that another aspect that has to be considered when talking about off-label is the safety profile pointing out that a high level of uncertainties exists about the relation between off label and adverse drug reactions due to scarce information of the physicians, lack in paediatric labelling, underestimation of the crucial differences in PK/PD, dosing adjustment errors. She then highlighted that further research on this field is needed in particular with large cohort of patients in order to have statistically significant analyses. She added that among the driver-factors favouring the off-label use of drugs in paediatric is key the lack of age-appropriate formulations. Several initiatives (i.e. STEP database) are working to overcome this issue.
Coming back to the WG main activity, the next steps will be drafting and agreeing upon the document among working group members and submitting the documents to the TEDDY SCC for approval. Among other possible activities, she proposed the development of collaborative project proposals and the collaboration with other TEDDY Working Groups. In particular, a collaboration might be sought with the WG on paediatric clinical studies methodologies and procedures and the WG on active engagement of children and adolescents. Within other activities of the WG, she mentioned consultations issued by EMA, European Commission and other relevant stakeholders, scientific events at national/international levels, creation and periodic update of an internal common literature database on the matter. She concluded listing the member of the WGs.

Young Patients Advocacy Groups activities

Gabriele Ciavarella and Antonio Di Pietro, KIDS Bari representatives, along with Nensi Semanaj, KIDS Albania representative, introduced the presentation on *Young Persons' Advisory Groups activities*.
Gabriele Ciavarella provided an overview of the activities performed by KIDS Bari and in general by the Young Persons Advisory Groups (YPAG). He described what a YPAG is, an organization composed of youths, patients, carers, and people interested in a health condition or in research, actively participating as partners, advising researchers and their teams in a full range of activities.
KIDS Bari is the first YPAG in Italy promoted by CVBF and TEDDY Network in collaboration with the Paediatric Hospital "Giovanni XXIII". Many advisory groups have been founded over the last years forming the iCAN (International Children's Advisory Network). He described their experience in the last iCAN summit in Edinburgh and showed a video of KIDS Bari members.
He then gave a general overview about the training program they attended during the first year of KIDS Bari set-up while Antonio Di Pietro went into more details of the 5 pillars of the training program. The Biomedicine pillar gave them the possibility to address some aspects of the biomedicine, finding out for example what is a drug and how it works as well as understanding the difference between children and adults. In the Basic Research pillar, the Kids participating to the training learned how to discover and study a molecule in order to transform it into a drug. In the Clinical Research pillar, they analysed the different clinical research phases and learned how to design a clinical study, faced the important themes of the relationship between the investigators and the paediatric patients, the ethical aspects of the clinical studies and the importance of the informed consent. In the pillar of Innovation and Information they received an overview of the innovative methods in the approach with the patients (design of the more comprehensible informative materials). He finally described what they learned in the pillar related to the Humanization of Healthcare: the rights of children staying at the hospital and how to improve care and quality of life.
Later on, he gave an overview on the KIDS Bari mission and activities they carried out in the last year. They participated to the Rare Disease Day and to the World Kidney Day campaign, they were involved in the revision of the different surveys addressed to children and they participated in the EPTRI General Assembly at the Ministry of Health in Madrid on March 27th-28th, 2019. He finally listed the activities foreseen for the next year such as the development of a serious game, the creation of a web site and a blog, volunteering activities as well as awareness campaigns on health themes.
Nensi Semanaj held the last part of the talk presenting the KIDS Albania activities, the first YPAG in Albania promoted by the Albania Branch Office of CVBF and TEDDY Network, in collaboration with the University Hospital Center "Mother Teresa". It includes 18 members with the aim to advocate young people, patients and participants in clinical trials and to raise public awareness. They met every 4-6 weeks and they followed the same training program described above for the KIDS Bari. They were also involved in the EPTRI surveys in order to translate, revise and make them more suitable for the children and finally disseminate them. During the last year they carried out many volunteer activities (they visited children in thalassemia unit of the hospital), they were involved in awareness campaigns (World Diabetes Day, Rare Disease Day), they participated to the summit in Edinburgh in July 2018. Finally, she listed the future activities foreseen (volunteer activities, awareness campaign, participation in Scientific Meetings) and their social media channels.

WG Health Data Plan of Action

Fedele Bonifazi, initiator of the TEDDY *Health Data* Working Group, held a presentation on its *Plan of Action.* The WG aims to investigate the use of health data to support research in Paediatrics.
He described the work carried out by the WG members within the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and in particular the concept paper "Different strategies to conduct multi-database studies for drug surveillance in real world setting: a reflection on the European model" they contributed to. Later on, he suggested some activities for the

next year: continue to work within the ENCePP WG3, draft of a position paper, participate to public consultations. Going into more details about the ENCePP WG activities, within the review of the studies in the EU PAS register with a special emphasis on multiple database studies, TEDDY *Health Data* WG will contribute to identify studies investigating drugs with a paediatric relevance to be revised. Regarding the position paper foreseen among WG activities, the aim is to discussing paediatric peculiarities in processing data from children. They need to find authors willing to work on this activity. Finally, he suggested to participate to EMA consultation about "Role of big data for evaluation and supervision of medicines in the EU" and also for this activity the WG is looking for volunteers to be involved. He finally showed the list of TEDDY WG Health Data members.

Discussion

Oscar Della Pasqua started a very rich debate asking to Giovanni Migliaccio a question regarding his presentation about ATMPs. In particular he raised the question if we are ready or not to face the technical and scientific challenges that these new advanced therapies are bringing considering the recommendations and legislations that are coming into force in this field. Giovanni Migliaccio answered that this is a complicated question since there are a lot of technologies that are in common at every age but many others are specific for paediatrics, i.e. gene therapy in utero. There are a lot of aspects, among which the ethical one, to be taken into consideration. Oscar Della Pasqua added that, behind the paediatric peculiarity, the advanced therapy is completely changing the whole concept of clinical study, and many aspects, such as safety issues, have to be faced.
Antonio Perez added that ATMP represent a real challenge not only for the future, since it is already present in the therapeutic option available nowadays. Currently industry is leading the field but a collaboration between academy and industry is needed since we still do not know how these innovative therapies would impact the kids. Safety studies are required in the short and long term and a position statement at European level should be addressed.
Stefano Benvenuti joined the debate adding that one of the main issues with ATMP is the authorization of a clinical trial in paediatric population. We are moving from life-threatening or rare diseases to "less rare diseases" or diseases for which other therapeutic options are available, for example thalassemia. The question he posed is to which extent should a parent authorize a therapeutic approach that reduces disease burden but not eliminate it totally. And also, the payment or how we can measure the improvement in life quality are other issues to be considered in order to balance the risk of an advanced therapy.
Adriana Ceci added a comment underlined that currently the advanced therapies in paediatric are increasing, there are lot of gene therapy approaches that have been applied to PDCO, that means they are in the pipeline and for many paediatric diseases we are going into the gene therapy direction.
The session ended with Donato Bonifazi asking to KIDS representatives what they think about how they can continue with their involvement in KIDS activities balancing them with their future study and work. Gabriele answered that he does not see a problem of overlapping in managing these activities, especially if they choose a scientific study. Antonio agreed with him and added that it is possible to manage both activities also if they do not choose a scientific study.

Session 2 - PERSPECTIVES IN THE LANDSCAPE OF PAEDIATRIC MEDICINES - Participation in collaborative projects

Evelyne Jacqz-Aigrain, Professor at Paediatric Pharmacology and Pharmacogenetics, Paris Diderot University and Annagrazia Altavilla, Responsible of international relations at Espace Ethique Méditerranéen/Paca-Corse – APHM/ Aix-Marseille University, chaired the second session of the Assembly welcoming all the participants and introducing the main topic of the session: participation of TEDDY in collaborative projects.

RESTORE: the wider community engagement in the definition of a European large-scale research initiative on Advanced Therapies

Stefano Benvenuti, Global partnerships manager, Fondazione Telethon, held a presentation about RESTORE, a large-scale research initiative on ATMPs. He started the talk reported that Fondazione Telethon joined the TEDDY Network last year and he moved to the description of the RESTORE project. RESTORE is a preparatory action for a large-scale research initiative. Large scale research initiatives are 1-billion and 10-years investment by the European Commission and Member States focusing on specific scientific and technological challenges. The path that led to the RESTORE kick-off started in the 2016 with a public consultation followed by a 2-stages call and the preparatory action that will led in the 2020 to the launch of two large-scale Research initiatives 2021-2030 in the Health and Life science area.
He described RESTORE vision and mission and highlighted the main issues that have to be solved in order to promote the development of advanced therapies in Europe. It is required to overcome the scattered research and development efforts across Europe, to face scientific and technological challenges to take into consideration other aspects such as pricing, reimbursement, ethical issues, educational path dedicated to ATMPs to meet the project objectives. The consortium is led by Berlin Brandenburg Center for Regenerative Therapies (BCRT/Charité), in Germany and is coordinated by Prof. Hans-Dieter Volk and involved 10 partners from different European countries and Israel. Apart these partners, there are more than 200 supporters among which the TEDDY Network.
Later on, he provided an example of ATMP product developed by Telethon, Strimvelis® used to treat a genetic immunodeficiency ADA-SCID. A long time was required from the first patient treated to the market approval and it was a project built together with EMA.
He went back to the RESTORE project pointed out the preliminary work done so far by the project partners in defining Scientific Working Groups that will work on different aspects of the ATMP development. He listed the Scientific Working Groups established linked to different aspects, manufacturing, pre-clinical model system, new clinical applications, clinical research and implementation. The first meeting of these WGs will be in Berlin on the 6th and 7th of May 2019. He finally talked about the expected impact of the Project: make Europe a relevant player in the field and not just a payer of treatments developed in the USA and Asia, develop better treatments for patients with highly unmet medical need, create new business opportunity, bringing innovation in cutting edge fields and shift from chronic treatment to cure of genetic diseases.
He finally listed the events in which RESTORE will be presented.
Discussion: Giovanni Migliaccio asked why among the WGs there is cancer and not paediatric. Stefano Benvenuti answered that it was because of the expertise of the partners and since cancer is one of the most of the field in which the advanced therapy is much applied now. Adriana Ceci asked how the paediatric aspects could be included in the project. Stefano Benvenuti answered that their position is to have paediatric expertise and competences in most of the WGs, especially in the most relevant in the paediatric field, i.e. new clinical application, clinical trial (WG11), implementation into the clinical routine. Oscar della Pasqua suggested that they need more expertise/partners in the drug development process. Antonio Perez suggested a collaboration with European Reference Network and Stefano Benvenuti confirmed that they are already in contact with ERNs.

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

Cristina Manfredi, leader of the TEDDY *Regulatory & Pharmacovigilance* Working Group, started giving an overview on the PedCRIN project. The project is aimed to develop capacity for the management of multinational paediatric & neonatal clinical trials and some pilot of multinational paediatric trials have been conducted. The consortium is led by ECRIN (European Clinical Research Infrastructure Network) and the project is made of 6 Work Packages.
The aim of WP3 is to develop tools specific for paediatric trials or upgrade tools already developed by ECRIN to take into consideration paediatric specifications and then these tools will be disseminated and the members of the consortium will be trained to use them. She showed the task and deliverables foreseen in the project.

The first activity curried on by CVBF in collaboration with INSERM and the TEDDY Network was a survey to better understand the real needs of the scientific and user's community. Analysing the results, she pointed out that, besides the need for financial support to research and innovation in paediatrics, most of the researchers addressed required support in the preparation of the protocols, especially for the application of innovative approached in the design of the studies. Moreover, there is less need for support by respondents from centres belonging to a National Network, with respect to the others centres, and there were no differences between neonatologists and other paediatricians. After the survey, a gap analysis was performed to 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.
Later on, she described the tools developed within the task 3.3 and 3.4. In the ethical and regulatory field, the CAMPUS database has been created as Online database including country-specific information on regulatory and ethical requirements in clinical research across Europe. Since the database did not include information about how the process of informed consent should be carried out in the paediatric population, this information was added such as the legal age of consent, who should sign the informed consent form, if there are specific requirement in the country for paediatric clinical trial…Regarding PV a systematic review was performed to identify the already available tools for AEs/ADRs assessment in the period 1996-2017. Other activities carried out in the Pharmacovigilance field is the certification of centres being able to perform Pharmacovigilance activities in order to include paediatric specific requirement.
She then described the activities carried out in the monitoring and standard values field and a tool for the biosample management whose aim is to produce a checklist as an easy-to-use instrument to properly manage samples and to properly collect and storage data in the context of paediatric trials on the basis of the European applicable rules and legislation. She moved then to describe the certification of CTUs work, with the contribution of INSERM. Clinical Trial Units (CTUs) support investigators by providing statistical, epidemiological, logistical and methodological expertise and help with coordinating multi-centre trials. The work carried out within this activity consists of providing criteria to certify CTUs specialised in conducting paediatric/neonatal clinical research activities.
Discussion: Donato Bonifazi asked which chances the paediatric research community have to valorise these tools developed within PedCRIN projects considering that the project is coming to the end. Cristina Manfredi answered that the new initiatives and projects can have a good occasion to test and valorise these tools such as in C4C and the call launched within the project.

DEEP project: focus on paediatric patients' empowerment

Manika Kreka, Medical Director at CVBF-Albania, held a presentation on "DEEP project: focus on paediatric patients empowerment". She started giving an overview on the DEEP project, that initiated around 2011 and included many centres from EU and non-EU countries. The project aim was to perform paediatric studies on deferiprone and to develop a new liquid formulation specific for the paediatric population in partnership with ApoPharma Inc. Within the project, 2 clinical trials, 1 observational and 1 pharmacoeconomic studies were conducted in order to apply for a PUMA (Paediatric Use Marketing Authorization).
Thereafter, she came to the main topic of her talk highlighting the need to actively involve children in the decision-making process related to a clinical trial as part of the updating guideline 'Ethical considerations for clinical trials on medicinal products conducted with minors' prepared by the European Commission and the Paediatric Committee within the EU Regulation 536/2014. She pointed out that it is universally established that written communication, combined with verbal interaction, may enhance children's understanding of their participation in a clinical research. The contents and styles of documents addressed to children are elements that largely influence their understanding of written documents. It has been also demonstrated that the use of pictures, following appropriate recommendations, improves the quality of communication, especially for patients with very low literacy skills.
After this introduction, she described what have been done within DEEP project to improve patient's empowerment. Three booklets were produced adapted to the participants' capacity of understanding

for three different age ranges. Moreover, 2 ad hoc assent form have been prepared, for the two oldest age ranges. The informative materials produced have been evaluated within the QuBo study through a survey addressed to all the paediatric patients participating in the consent/assent process in order to evaluate how effective the booklets are in communicating key elements of the study, the understanding of the disease and therapy and to assess the acceptance and likeability of the booklet by paediatric patients. The study was conducted in Albania and in Italy and finally demonstrated that the use of informative booklets in the DEEP-2 trial has been appreciated by children and adolescents and has favoured the understanding and participation of children in the clinical trial.
In the last part of her talk she focused on the lay summary of results that will be prepared to reach and inform a large target audience, the lay community, about the results achieved by the DEEP2 clinical trial. The lay summary will include an introduction about what is iron overload, what is iron chelation therapy, which iron chelators are available on the market and why it has been decided to investigate deferiprone, a brief description of the 3 clinical studies and their results. Moreover, it will include a map indicating the recruitment sites and the number of enrolled patients to show to patients the number and the origin of all the children enrolled in the study. The Lay Summary will be prepared in the 6 languages of the project (Albanian, Arabic, French, Greek, English, Italian) and in an appropriate writing style as reported in the guidelines above mentioned.
Finally, she pointed out that as the summary will be addressed to patients and parents, it is important to consider the involvement of Young People Advisory Groups (YPAGs) in the development and/or review of the summary to assess the comprehension and the value of the information provided.
Discussion: Oscar Della Pasqua and Adriana Ceci asked if these initiatives have brought concrete results in term of the efficacy of the trial. Manika Kreka answered that the informative materials improved the acceptability and awareness about the study. Mariagrazia Felisi added that, beyond the positive experience of the QuBo study, it has to be considered that a comparator study would have been added more power to the results. Mariangela Lupo suggested a collaboration with C4C cross cutting theme in order to test the impact of these activities.

Young patients' engagement in the European Joint Programme on Rare Diseases – EJPRD

Mariangela Lupo, leader of the TEDDY *Active engagement of children and adolescents in the themes of clinical research* Working Group, held a presentation about Young patients' engagement in the European Joint Programme on Rare Diseases – EJPRD. She started reporting the following UN Convention on the Rights of the Child statement: "Children and Young People have a right to have their views heard in all matters affecting them and for these to be taken seriously". She also underlined that many challenges have to be faced in this field such as age, background, previous existing knowledge, language, mental state and she stressed the need to engage children early in the research process and to educate them about the importance of participating in clinical research. She highlighted that in order to properly engage young patients, specifically tailored methods should be applied to the training and empowerment process. First of all, she suggested to educate and empower the paediatric patients in the specific topic of the project for which their help is requested. For example, they can help in improving the language, content and format of the assent document. In order to have a dynamic interactivity with them she suggested to use the best methods to collect information such as focus groups, questionnaires or surveys, personal interviews, etc. Going more specifically in the EJPRD, she described the project aim to create a research and innovation pipeline "from bench to bedside" ensuring rapid translation of research results into clinical applications and uptake in healthcare for the benefit of patients. She gave an overview about the project, partners involved and EU contribution. The project is structured in 4 big pillars and 5 transversal WPs. She went to describe more in depth the 4 pillars in terms of aims and main activities foreseen. Then she focused on pillar 3 in which the TEDDY Network is involved. TEDDY is particularly involved in WP15 whose main objective is to address one key component of the EJP on RD that is to improve RD research and innovation and to enhance the uptake of research results by building the capacity of the patient community and other key stakeholders. TEDDY will lead task 15.4 aimed to create educational materials and activities for paediatric patients. The planned activities include short

workshops in collaboration with Fundaciò Sant Joan de Deu, EURORDIS and the eYPAGnet (the European Young Persons' Advisory Group network) for 15 patients' representatives focusing on several areas of interest. At least three Face to Face 'paediatric patient experts training courses' will be hosted in Italy, Spain and France. Moreover, she emphasised that TEDDY is among the few organisations whose members have been considered in the Consortium Agreement as Contributing Entities as EJPRD Linked Third parties and have rights to access to the Background and the Results of the project at the conditions set out in the Consortium Agreement, in the same way as the members of the involved ERICs and ERNs.
She added that TEDDY is also involved in Coordination and Transversal activities and in particular in the communication and dissemination activities.
Finally, she concluded highlighting that TEDDY will play a central role in further engaging and empowering rare disease patients into research and in providing them with the tools required to apprehend and actively contribute to innovation and therapy development.
Discussion: Donato Bonifazi asked how to put together the experience of the KIDS groups and patients' associations considering that these are different organizations. Mariangela Lupo answered that activities foreseen for TEDDY will start in the third year and they are planning to involve both the organizations.

Session 3 – ACTIVITIES AND PROPOSALS FROM TEDDY SPAIN PARTNERS

Donato Bonifazi, Chief Executive Officer at Consorzio per Valutazioni Biologiche e Farmacologiche, and Cristina Calvo, Head Clinician, Paediatric and Infectious Diseases Department, Hospital Universitario La Paz, chaired the fourth session of the Assembly welcoming all the participants and introducing the main topic of the session: activities and proposals from TEDDY Spain partners.

Authorised Paediatric Clinical Trials in Spain

María Jesús Fernández-Cortizo, Head of Service at Spanish Agency on Medicines and Healthcare Products and Spanish PDCO Alternate member held a presentation about "Authorised Paediatric Clinical Trials (CT) in Spain" providing an analysis of the clinical trials with medicinal products including a paediatric population that have been authorised in 2017 and 2018 in Spain. The analysis has been performed using the AEMPS CT database, Spanish Registry of Clinical Trials ("REec") in which clinical trials are uploaded once authorised by AEMPS and the AEMPS 2017 Annual Report. First of all, she specified that paediatric CT also include trials involving both adults and children. She showed that if the numbers of paediatric CT increased between 2014 and 2018, the number of only-paediatric CT is not increasing. She then described the paediatric CT authorised per Age groups. Most of the studies authorised include adolescence and children from 2 to 17 years old. The same trend was observed for paediatric-only CT. Most of the trial are sponsored by a pharmaceutical industry but if you look trials involving neonates (very few trials), you can realize that a majority of them are performed by academic. She showed the number of CT per therapeutic area. The numbers of CT in oncology is huge increasing. Regarding the site and locations involved in paediatric CT, it could seem that they are spread all over the Spain but for certain specific diseases these studies are confined in specific area where the expertise is concentrated. Catalonia and Madrid, followed by Andalusia and Valencia and Santiago the Compostela are the places in which the majority of studies take place. She concluded that the percentage of CT that include paediatric population remains below 15% of the global number authorised. Most of them are mixed trials (enrolling paediatric and adult subjects). The age groups mostly included in the CT authorised in Spain were adolescents and children. The main therapeutic areas investigated in paediatric CT were oncology, respiratory tract

diseases, haematology, neurology and infectious diseases. She finally suggested to reflect about what the national Spanish agency can do to promote paediatric CT authorization and she reported the EMA and EC action plan on paediatrics that foresees the establishment of a framework for exchange information between the EMA/PDCO and of a Clinical trial Facilitation Group (CTFG) to improve dialogue between EMA/PDCO and clinical assessors. At the national level she emphasized the action that has been taken so far by AEMPS: the creation of an office for support of Innovation and knowledge of medicinal products and an Independent Clinical Research Support Office.
Discussion: Cristina Manfredi asked if the last office mentioned by the speakers is based in the national agency. María Jesús Fernández-Cortizo answered that is based in the AEMPS working very closed with the Clinical Trial Unit to help with administrative procedures and how to deal with medical products. Mark Turner asked if there is a balance between individual sponsors and institutional sponsors. She answered that most of the studies showed are sponsored by an institution represented by a physical investigator. Antonio Pérez Martínez agreed adding that he is indeed promotor of independent academic studies. Stefano Benvenuti asked about the Spanish situation related to non-commercial studies since in Italy, as also confirmed by Donato Bonifazi, results from non-commercial studies cannot be used for registrative purposes, unless fees to ECs are payed.

Impact of the Spanish HIV HGM BioBank in the paediatric research

Maria Angeles Muñoz-Fernández, Scientific Director of the Spanish HIV HGM Pediatric BioBank held a presentation on the Spanish HIV BioBank that was set up in 2003. Sixty-four hospitals spreading across Spain participate in this HIV BioBank that is responsible for the preservation and storage of HIV samples from children and adolescents infected via vertical transmission (CoRISpe). She described the organigram of the BioBank that is organized following the present legislation that indicate that the Scientific Director and the Data Manager are the final responsible for this type of infrastructures. Two external Committees, scientific and ethical, assist the Director in the decision-making procedure. Quality and Data Managers are responsible for the day to day functioning of the Biobank and are responsible for the samples and the samples-associated information quality. Sample and Final Products Managers are responsible for sample reception, processing and cryopreservation as well as perform Quality Control Procedures. Training Manager is in charge of keeping the personnel updated on technical procedures. Infrastructure Manager is responsible for the correct functioning of the scientific equipment. New Techniques Manager designs the experiments with the objective to standardize the new procedures. The BioBank collects samples of Vertical transmission HIV-infected patients' cohort (CoRISpe). Researchers can ask samples for HIV infection-related projects. Biobank Personnel are responsible for managing, processing and cryopreservation of the samples.
The biobank has one laboratory for samples processing and two cryopreservation rooms. For patients above 16 years, a model of informed consent has been designed based on the Spanish legislation. For children below 16 or mentally disabled, it is established that the parents or tutors sign the consent and if the child is above 12 and is aware of his/her pathology, she/he should also sign the consent. Regarding the BioBank functioning, a deposit agreement gives directions for sending samples to the BioBank and it is signed by the Biobank Director and CoRISpe coordinators. An initiation kit is foreseen and sent to the clinicians with documents and formats for sample extraction and shipping. A shipping procedure has been defined and the samples are processing to obtain PBMC, plasma, pellet, DNA that are cryopreserved. The BioBank foresees a procedure for data consolidation and sample cession to researches who have sent a request. At the BionBank, all the processes are performed using standardized and validated techniques which ensures the quality, traceability, and homogeneity of the samples giving them a high scientific value. The BioBank is certificate by the Norma ISO 9001 with internal and external controls and collaborates with different projects related to quality control. The BioBank collected so far more than 12.111 samples from HIV children. The required samples have been used for many research projects and the BioBank is participating in many clinical trials with the PENTA Foundation.
Discussion: Cristina Manfredi asked for more information about the consent, if it is requested for a specific research or for the sample. She answered that the consent is for the samples therefore it is

not needed to request it for each project. Stefano Benvenuti asked about how they manage the issue of the consent when the children become adults. She answered that they asked to re-sign the consent as adult.

Cell and advanced therapies for children with cancer

Antonio Pérez Martínez, Head of Paediatric Hemato-Oncology Service of the University Hospital La Paz held a presentation about "Cell and advanced therapies for children with cancer". He started his presentation talking about immunotherapy and how immune system can eliminate tumours cells. He described the main steps forward in the immunotherapy history. He then gave an overview on immune effector cells and in particular the natural Killer cells for cancer cell therapy.
Later on, he focused on cell engineering and how to use a Hematopoietic stem cell transplantation (HSCT) as cell therapy and then he moved to talk about CAR T-cell immunotherapy.
Chimeric Antigen Receptors (CARs) combine specific antigen recognition and T cell activating functions. Although a CAR specificity is often based on antibody single-chain fragment variable regions, Natural Killer cells receptors (NKG2D) have also been used. NKG2D-CAR based therapy has been shown to be effective against different tumour types including ovarian carcinoma, multiple myeloma in vitro and in vivo. His research group has recently shown NKG2D-CAR redirected memory T cells target osteosarcoma cells in vitro and in vivo, while they are innocuous against healthy tissues. Considering that many paediatric tumours express NKG2D ligands, they can be good candidates for NKG2D-CAR cell therapy. They have recently obtained good results with this approach in leukaemia.
Moreover, he added that they are able to produce cells for immunotherapy in the hospital with a very low price since they have developed a protocol of production in house and they have validated the procedure in order to produce cells to be infused to patients.
Finally, he presented his team and unit of research. He concluded highlighted the following points: immunotherapy is now a reality; immune effector cells can be considered new drugs for childhood cancer and hematopoietic Stem Cell Transplantation is evolving in a Cell Therapy approach. For the future he believes that hospital needs transformation towards a Research University Hospital and collaboration between Industry and Academic is required.
Discussion: Mark Turner asked how to promote the transformation of the hospital he mentioned mainly in relation to the funds issue. He answered that they tried to find the funds they need through national and international grant but also pushing the hospital and health institutions through the involvement of patient's association in order to get funds. He added that it is not a problem of money in his opinion, but of how to distribute resource.