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Report from the 2020 annual meeting of the members and Coordinating Group of the European network of paediatric research at the EMA (Enpr-EMA)

Date: Monday 28 September 2020

In 2020 the annual meeting of Enpr-EMA was held virtually and restricted to the Coordinating Group (CG) and Enpr-EMA members rather than a wider workshop in view of the Agency's business continuity planning related to the COVID-19 pandemic. The meeting saw an update by the European Commission on the evaluation of the Paediatric and Orphan Regulations, as well as on the EU Pharmaceutical Strategy. In addition, the meeting focused on the impact of COVID-19 on the paediatric population and facilitated a dialogue on overcoming the challenges caused by the pandemic on clinical trials including children, and learnings for the future.

Chairpersons: Pirkko Lepola, Gunter Egger

Morning Session

Report from the Coordinating Group

Pirkko Lepola, the chair of the Enpr-EMA CG, summarised the activities of Enpr-EMA. Activities included publication of the document on "Preparedness of medicines' clinical trials in paediatrics. Recommendations by the Enpr-EMA working group on trial preparedness", consolidated Enpr-EMA responses to public consultations initiated by the EC and FDA, representing Enpr-EMA in scientific meetings/conferences, sharing centrally distributed regulatory and registry related up-to date information, as well as issuing support letters to various paediatric research activities.

Pirkko thanked everyone, particularly the participants of the various working groups, for their contributions and all the work involved.

Presentation: *Update on Enpr-EMA activities 2019-2020 (P. Lepola)*

Adoption of update to CG mandate

The mandate was adopted without comments.

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Update on EU evaluation of Paediatric and Orphan Regulation

Fabio D'Atri of the European Commission's DG SANTE presented an overview on the evaluation of the Orphan and the Paediatric Regulation.

The presentation focused on how the two regulations have worked and fulfilled their intended objectives, together and on their own. Fabio informed participants that a short paper (inception impact assessment) presenting options for solutions for the identified shortcomings would be published for public consultation in the autumn. This would be followed by a full impact assessment of the options.

Presentation: *Evaluation of the legislation on medicines for children and rare diseases (F. d'Atri)*

Update on EU pharmaceutical strategy

Antonios Rodiadis of the European Commission's DG SANTE introduced the Pharmaceutical Strategy for Europe. The strategy covers the whole life cycle of medicines development, including lessons learned from the COVID-19 pandemic, highlighting the need for a future-proof and crisis-resistant system. Ensuring access to affordable medicines, ensuring sustainability of health systems, preventing shortages, enabling sustainable innovation (including for unmet needs) and supporting EU influence and competitiveness on a global level are the main pillars of the strategy. Feedback received from the public consultation on the Roadmap and an open survey to the Pharmaceutical Strategy, as well as from a stakeholder workshop will feed into the Commission Communication which will include legislative and non-legislative measures for the short, medium and long term.

Presentation: *Pharmaceutical strategy for Europe (A. Rodiadis)*

Key points raised during the ensuing discussion on the ***role of paediatric networks to contribute to the pharmaceutical strategy, and interactions between Enpr-EMA and the EC:***

- Paediatric research, including clinical trials with children, is not yet completely accepted by everybody. Awareness must be raised on the need for financing paediatric research and specialised infrastructure for the action plan of the Pharmaceutical Strategy and the implementation phase.
- Enpr-EMA has a great pool of experts to collaborate not only through provision of consolidated comments to public consultations but also through targeted consolidations on specific issues, such as unmet medical needs, both in the assessment and the implementation phase.
- Enpr-EMA network members are interested in building a closer relationship with policy makers to provide input on policy needs, so that any changes (legislative and non-legislative) bring the result required.
- The need for better incentives for medicine development related to patients' needs was highlighted as e.g. for purely paediatric rare diseases neither the Orphan nor Paediatric Regulation offer sufficient incentives.

Afternoon session:

EU-Initiatives progress update:

Conect4children (c4c)

Mark Turner explained the collaboration between c4c, the European Paediatric Translational Research Infrastructure (EPTRI) and the European Joint Programme on Rare Diseases (EJP RD). c4c promotes efficient and high-quality design and conduct of paediatric clinical trials, while EPTRI facilitates collaboration on preclinical aspects, biomarkers and formulations in preparation of clinical trials (see following section).

C4c has made good progress: national hubs in 20 countries are operational, offering national single points of contact for industry and providing links with research sites. Three non-industry proof-of-viability (POV) studies have been selected and funded, two being ready to start enrolment in October 2020. One industry-sponsored POV study has been selected for c4c support, others are in preparation. Nine requests from industry partners for advice have been completed by expert advisory groups in various therapeutic areas. So far, no request for expert advice has been received from academics; extending advice even beyond c4c will be explored in the future. The voices of families and young persons are represented in all strategic feasibility advices. An educational portal has been set up with several online courses available. A Core Common Paediatric Data Dictionary is under revision in collaboration with the Clinical Data Interchange Standards Consortium (CDISC) and others. A confidentiality disclosure agreement template was agreed by four companies for industry proof of viability studies. The planned multi-stakeholder meetings are currently delayed due to COVID.

Presentation: *c4c update for Enpr-EMA (M. Turner)*

European Paediatric Translational Research Infrastructure (EPTRI)

Donato Bonifazi presented the concept of EPTRI**,** proposed as a new infrastructure to aggregate a large research community focused on basic, preclinical and translational research for paediatric medicines. The design phase has been concluded funded within the H2020-INFRADEV-01-2017 programme and is now starting the preparatory phase to reach ERIC (European Research Infrastructure Consortium) status.

330 research units from 259 Institutions from 29 EU / non-EU countries are willing to act as EPTRI providers to develop services related to paediatric drug discovery, paediatric biomarkers, developmental pharmacology, paediatric formulations and medical devices. Results of EPTRI's work are intended to underpin paediatric clinical studies via collaboration with EnprEMA, c4c, ERNs and other relevant paediatric initiatives.

EPTRI applied for inclusion in the European Strategy Forum on Research Infrastructures (ESFRI) Roadmap 2021 to be officially recognised as a biomedical research infrastructure.

Presentation: *European Paediatric Translational Research Infrastructure (EPTRI) (D. Bonifazi)*

European Reference Networks (ERN)

Luca Sangiorgi presented the ERN rare diseases research coordination and support action (ERICA), a proposal submitted to the EC, to build a platform which will integrate all ERN's research and innovation capacity through knowledge sharing, engagement of transdisciplinary research groups working across the global health spectrum. ERICA's objective is to ensure access to safe and efficient therapies for the benefit of patients suffering from rare diseases. ERICA is also linked to the EJP RD and the

International Rare Diseases Research Consortium (IRDiRC), the research infrastructures, with biobanks, EMA, and industry. One of the proposed work packages, i.e. the work package "Clinical Trial Support", aims to map, integrate and link ongoing activities with regards to facilitating Europe-wide multicentre clinical trials. In this context, connection with currently on-going paediatric initiatives will be established via c4c and EPTRI.

Presentation: *ERICA - ERN Rare disease research coordination and support action (L. Sangiorgi)*

Global initiatives progress update:

Multi-Regional Clinical Trials (MRCT) Center

Dominik Karres provided an update about the MRCT initiative on promoting global clinical research in children, based in Boston, involving health authorities, academic medical centres, patient advocacy groups, industry, trade and professional associations. MRCT aims at identifying current initiatives to improve paediatric research globally, challenges related to decision making by and on behalf of children, meaningful ways to engage patients/families/community members, proposing solutions to regulatory, ethical, and operational challenges and using the COVID-19 pandemic as a lens through which to examine opportunities for innovation in the conduct of paediatric clinical trials.

Three thematic working groups have been established: 1) Decision making for children's participation in biomedical research, 2) Benefit/risk considerations for pediatric research, 3) Challenges in implementation of global pediatric clinical trials. Planned deliverables include educational materials/brochures, publications, structured recommendations to regulatory agencies and ethics committees. In addition, collaboration with existing networks is planned to develop a "Preparation Plan for Pediatric Clinical Research during Public Health Emergencies".

Complementary Enpr-EMA activities related to the planned MRCT deliverables were highlighted:

- published tool kit on assent/consent requirements in Europe
- ongoing work on assent/consent guidance for paediatric clinical trials in Europe
- patient/parent engagement activities led by Enpr-EMA networks and EMA
- published recommendations by the Enpr-EMA working group on trial preparedness
- international environmental scan of ethical and regulatory requirements for clinical trials

During the discussion, it was noted that the MRCT initiative aiming at global representation, has a US focus, despite some Enpr-EMA representatives being involved. Enpr-EMA networks hence raised the question if there is still an opportunity to engage and were encouraged to reach out to the MRCT Center, with the aim to further strengthen the representation of the European perspective by sharing existing expertise in support of the project deliverables, and to help avoid potential duplication of work. It was stressed that Enpr-EMA input and contributions should be acknowledged in any outcome deliverables supported by Enpr-EMA members.

Interested Enpr-EMA members are invited to reach out to Dominik.Karres@ema.europa.eu

Presentation: *Multi-Regional Clinical Trials (MRCT) Center and its initiative on promoting global clinical research in children (D. Karres)*

Report from the Working Groups (WG):

Working group on research staff

Previous activities of the WG aiming at identifying needs related to training for paediatric clinical research nurses across EU Member States resulted in a questionnaire-based study to learn about the roles and training needs of paediatric research nurses (https://bmjpaedsopen.bmj.com/content/1/1/e000170).

In carrying out the study the WG found that research nurses would benefit from enhancing connections. Consequently, the WG managed to bring together European network by identifying key research nurse groups in paediatrics across Europe. A total of 40 groups / clinical centres expressed an interest in working with Enpr-EMA. It was agreed that a research nurse group under the umbrella of Enpr-EMA could provide a useful central resource for sharing information between interested parties at a European level. Yet, the COVID-19 pandemic necessitated re-distribution of resources and reprioritisation. The WG plans to move forward 1) by liaising and seeking close alignment with the c4c Nurses Group to avoid duplication, and 2) to start implementing recommendations from the previous survey, such as promoting the role of clinical research nurse/coordinators in countries where the role is still being developed, determining nurse retention strategies, to perform either another survey or group calls with existing research nurses to determine current career pathways/ opportunities in each Enpr-EMA member country, similar to the survey conducted by Irish Research Nurses Network (IRNN) in Ireland.

In order to increase involvement of nurses in the WG, all Enpr-EMA network representatives are encouraged to "spread the word" and contact details of the WG leads!

Presentation: *Working group on research staff (V. O'Mahony, P. Dicks)*

WG on clinical practice evidence in the labelling

Even to date about half of all medicinal products with a marketing authorisation (MA) and being on markets in Europe are prescribed to children without having a paediatric indication in the Summary of the Product Characteristics (SmPC). This WG aims at building a case to search for new ways and potentially for changes in legislation at European level to make it possible to update the SmPC of products with a European MA in adults by using published clinical and other research and registry data developing criteria to ensure that they provide appropriate evidence to support the medicine's safety and efficacy in the paediatric population.

To this end a statement paper is being prepared with the aim to present selected products as examples with high medical need, to present existing data sources to support risk-benefit analyses for the paediatric population, and to discuss potential solutions to provide physicians with best-evidence dosing information while striving for the highest possible level of evidence to support uptake of paediatric indications in SmPCs.

During the discussion it was learned that recently a survey was conducted in Japan on a different approach using automatically generated data from numerous hospitals; more detailed information will be provided. Japan was invited to collaborate in the WG.

Presentation: *Working group on clinical practice evidence in the labelling (S. de Wildt)*

WG on international collaboration

This WG was established with the aim to identify and address cross-jurisdiction challenges in the conduct of global paediatric clinical trials in order to boost international collaboration. Representatives from regulatory authorities and national networks from the following five regions are part of this WG: USA, Europe, Canada, Australia and Japan. The first task, an environmental scan to be answered by both the regulators and the networks, has been completed and Thierry Lacaze presented the results.

The environmental scan is divided into 4 categories: Paediatric Clinical Trial Regulatory Requirements and Incentives, Paediatric Clinical Trial Submission Process, Paediatric Clinical Trial Review Process, Ethics and Other Requirements and Processes for Participation as a Paediatric Clinical Trial Site.

Tables comparing paediatric clinical trial regulatory requirements in the five jurisdictions, as well as on ethics requirements for participation as a paediatric clinical trial site have been developed.

The next steps will be to prepare one or more manuscripts for submission to a scientific journal.

Clinical trial authorisation during a pandemic (CTFG perspective)

This topic was cancelled due to Ann Marie Janson Lang not being able to attend the meeting.

COVID-19 impact on paediatric clinical trials, how to overcome the challenges. Can some new approaches be taken forward for future paediatric trials?

Gunter Egger highlighted the guidance on the management of clinical trials during the COVID-19 pandemic, which was jointly published by the EMA and the Heads of Medicines Agencies (HMA) acknowledging the impact of the pandemic on clinical trials and trial participants.

Update from Europe:

Italian sites of the **European Reference Network for rare bone diseases** established a Helpline providing high-quality care remotely to patients with rare bone diseases during the COVID-19 pandemic. The experts involved in the helpline were health professionals (doctors, nurses, physiotherapist, etc.) with extensive experience in rare skeletal diseases. The service was free, provided to health care workers and patients, could be reached 24/7 and was provided in Italian in order to avoid a language barrier. The Helpline initiative received more than 200 calls and messages asking for information and advice.

In some cases, patients were followed remotely, putting patients at home in contact with regional and/or local institutions, checking daily developments and/or supporting general practitioners in the decision to refer (or not) patients to the COVID-19 departments.

Lessons learned: Although social media and chats are most commonly used in offering remote care, a telephone line has allowed all patients to communicate directly, quickly and without any digital barriers (especially for older patients).

Presentation: *Care for patients with Rare Bone Diseases during COVID-19 pandemic (L. Sangiorgi)*

The Business Continuity Planning (BCP) developed by c4c using a template for country readiness and site readiness was presented. The business continuity planning was geared towards analysing critical activities in order to avoid major delays/disruption, identifying activities to maintain at low

priority, activities that can be paused and resume and activities that can continue. Mitigation plans and communications were established, with monitoring who will do what when.

Lessons learned: The consortium had some difficulty moving from planning as usual to business continuity planning. Most members of c4c did not have any prior experience with BCP so were not initially familiar with methods of planning and risk assessment that distinguish between business as usual and business that is conditional on potential, or real disruption. It is important to train for BCP.

Presentation: *Business continuity planning in conect4children (M. Turner)*

Update from North America:

The **Institute for Advanced Clinical Trials for Children** (i-ACT) conducted a survey to evaluate the impact of the COVID-19 pandemic on clinical trial sites. All sites surveyed noted that some aspect of clinical research activities was reduced or suspended during the COVID-19 pandemic. However, multiple accommodations were made to allow for some research activities to continue and 92% of sites were able to complete start-up activities for new studies. Solutions to manage the many challenges, included use of telecommunication applications to complete study visits remotely, use of a rota schedule for research staff to monitor adverse events and other safety parameters, use of electronic gift cards for participant reimbursement, and use of virtual platforms for patient visits.

Lessons learned: Widespread reliance on "traditional" processes (e.g. paper study documents, lack of e-consent guidelines) created initial problems but COVID-19 spurred increased acceptance and uptake of new processes: sites adapted to virtual and telehealth platforms, created new plans, processes and revised SOPs to limit future disruption.

The **Maternal Infant Child and Youth Research Network** (MICYRN) in Canada surveyed their members regarding COVID impact on their research centres. Most research units allowed research visits within hospitals for COVID-related studies or in cases where patients were already coming in for standard of care visits (essential visits only). Sites reported that, on average, 50-60% of studies were progressing. Research staff are encouraged to work from home whenever possible. On-site patient visits require personal protective equipment and social distancing measures being in place. Verbal and e-consent has been allowed at most institutions, virtual visits are increasing through use of secure telecommunication platforms and telehealth systems. Some institutions have allowed for home visits and study drug delivery to patients' homes.

Processes expected to stay in place post pandemic include expedited intra-provincial ethics reviews, virtual and electronic consent and telehealth and remote visits of patients (when possible).

In May 2020 Canada's Minister of Health enacted the Interim Order Respecting Clinical Trials for Medical Devices and Drugs Relating to COVID-19, which introduces flexibilities in how Health Canada authorizes trials over their lifecycle and reduces reporting requirements to lighten administrative burden on sponsors.

Presentation: *COVID-19 and clinical research in Canada (T. Lacaze)*

Update from industry/CROs

Industry representatives reported that ongoing clinical trials faced challenges related to operational aspects (e.g. lack of resources at sites, difficulties to access sites) but also to a lack of validated age-appropriate endpoints for remote data collection. Many companies had to put their trials on hold to avoid having to change endpoints. Examples were presented how industry was adapting by moving

towards decentralised clinical trials (DCTs), ensuring participants' safety while enabling them to participate remotely in trials through telemedicine and wearable technology.

Another option highlighted were trials with a combination of home and site visits. Positive effects included reduced study fatigue, elimination of parents' fear to travel to sites during the COVID-19 pandemic, no missed visits, and a positive impact on patient retention. However, not all sites allow home health care when the medicine is to be prepared by a hospital pharmacy. Other limitations observed at some sites were poor availability of accessible electronic medical records, limited equipment (e.g. webcam availability) at the site, limited availability of site staff due to the emergency status.

Positive aspects of remote monitoring included freeing up time for data review, and a reduction in trial costs due to decreased travel costs.

The presentation ended with suggestions for new operational approaches that could/should be taken forward in the future post pandemic. Such a shift will necessitate endpoints to be adapted for remote monitoring and regulatory pathways adapted to the use of technology in paediatric clinical trials.

Presentation: *COVID-19 impact on paediatric clinical trials, industry perspective (C. Ollivier and M. Dehlinger-Kremer)*

The meeting ended with two presentations from the paediatric medicines office at EMA on **Multi-system inflammatory syndrome in children (MIS-C)** and **Preparedness for paediatric COVID vaccine trials.**

Multi-system inflammatory syndrome in children (MIS-C)

MIS-C is less frequent than COVID-19 disease but can be very severe. Meta-analyses of studies on MIS-C show that up to 71% of children with MIS-C need intensive care as compared to 3% of children infected with COVID-19. Different from COVID-19, the main causes of admission of MIS-C patients to intensive care units are shock and aneurysms besides the need of mechanical ventilation. It was flagged that at present two different definitions of the condition are used in different geographic areas and it would be important to harmonise terminology for data collection purposes.

Presentation: *Multi-system inflammatory syndrome (L. Fregonese)*

Enpr-EMA members were informed that PRINTO has started an international registry to better characterise this new clinical phenotype (MIS-C). So far, 87 paediatric centres worldwide had reported 475 cases of this new clinical phenotype. (https://www.printo.it/projects/ongoing/31)

Preparedness for paediatric COVID vaccine trials

The presentation on COVID vaccines development provided an overview of vaccines in the late development phase, and the development timelines during a pandemic. The focus was then on development requirements from international regulators. Before initiation of Phase IIb/III studies, safety data from early phase trials need to be favourable and preliminary relevant immunogenicity data must be available to support selected doses and vaccination schedules. Furthermore, it was stated that the International Coalition of Medicines Regulatory Authorities (ICMRA) recommended to characterise immune response from animal models, including potential enhanced disease (ED). The primary endpoint for Phase 3 studies is laboratory-confirmed COVID-19 of any severity.

As currently a third of new infection clusters occur at schools and universities, the role of children in the transmission of infection is increasingly discussed. The importance to plan for assessment of

paediatric safety and effectiveness of new vaccines was stressed. The EMA has put in place a process for rapid assessment of paediatric investigation plans for COVID-19 related indications.

Presentation: *Preparedness for paediatric COVID-19 vaccine trials (L. Fregonese)*

The meeting was closed by the chairs thanking all participants for their contributions.

Speakers:

- Donato Bonifazi, European Network of Excellence for Paediatric Research (TEDDY, EPTRI)
- Fabio D'Atri, European Commission (DG SANTE)
- Martine Dehlinger-Kremer, European Contract Research Organisations Federation (EUCROF)
- Saskia de Wildt, Medicines for Children Research Network Netherlands (PEDMED-NL)
- Pamela Dicks, Scottish Medicines for Children Network (scotcrn)
- Gunter Egger, co-chair of Enpr-EMA, European Medicines Agency (EMA)
- Irmgard Eichler, European Medicines Agency (EMA)
- Collin Hovinga, Institute for Advanced Clinical Trials for Children (i-ACT)
- Laura Fregonese, European Medicines Agency (EMA)
- Ann Marie Janson Lang, Clinical Trials Facilitation and Coordination Group (CTFG)* not present
- Dominik Karres, European Medicines Agency (EMA)
- Thierry Lacaze, Maternal Infant Child Youth Research Network (MICYRN)
- Pirkko Lepola, chair of Enpr-EMA, Finnish Investigators Network for Pediatric Medicines (FinPedMed)
- Cécile Ollivier, European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)
- Vincent O'Mahony, Irish Paediatric Clinical Research Network (IPCRN)
- Antonios Rodiadis, European Commission (DG SANTE)
- Luca Sangiorgi, European Reference Networks (ERN)
- Mark Turner, conect4children (c4c)