SIOP EUROPE

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Comments from SIOP Europe on the European Commission's Public Consultation on Rare Diseases: Europe's Challenges

SIOP Europe is the European Branch of the Société Internationale d'Oncologie Pédiatrique (SIOP) and represents health professionals working in the field of childhood cancer in Europe. While the overall prevalence of childhood cancer is approximately 1 in 600 children before their 15th birthday, each individual type of childhood cancer has a much lower prevalence and easily falls into the category of a rare disease. Indeed, some forms of childhood cancer are so rare that they affect less than 5 children per year in a typical European country.

Treatment for childhood cancer is generally complex and involves input from multidisciplinary sources, often with very specialist expertise in surgery, pathology or radiotherapy. Oncological treatment is generally protocol driven and delivered in specialist centres. Countries vary in how these are networked with the local treatment centres and hence how far patients have to travel for treatment. There is also national variation in robust referral patterns to specialist treatment centres for children with cancer but in particular adolescents.

Progress in the treatment of children with cancer has been largely driven by randomised phase III clinical trials. These are usually investigator led in the academic community using out of patent drugs outside of their licensed indication, since few paediatric studies have been performed for licensing purposes. Due to the rarity of childhood cancer, these trials have necessarily needed a European dimension, with multinational participation. However, the continuation of a comprehensive portfolio of clinical studies across the range of childhood cancers is now threatened by the excessive bureaucracy required to open clinical trials in Europe. This has had a disproportionately negative effect on clinical trials in children, where many drugs are arbitrarily defined as investigational medicinal products (IMPs) because of their off-label use in the paediatric age group. The administrative burden in opening clinical trials in treatment centres has caused a huge disincentive for opening trials for the rarer subtypes of childhood cancer. This therefore threatens the completion of these trials and continued progress in knowledge of the diseases they set out to understand.

Q1: is this current EU definition of a rare disease satisfactory

Probably yes though it is absurd that different countries can have different definitions, particularly if this dictates access to funding.

Q2. Do you agree that there is a pressing need to improve coding and classification in this area?

Yes, particularly in cancers in adolescents aged 15 years and upwards who often have paediatric type cancers yet may be subject to adult type anatomical coding. Also there is an urgent need to improve registration of cancers in the adolescent age group. Some European countries still need assistance and resources to establish population-based childhood registries which are critical for monitoring outcomes and essential research resource.

Q3. Can a European inventory of rare diseases help your national/regional system to better deal with RD?

The Automated Childhood Cancer Information System (ACCIS) project coordinated by IARC in Lyon and the EuroCare studies, both of which had EU support, have been invaluable in analysing differences in incidence and outcomes for childhood cancer in different European regions. Continuation of these networking projects between cancer registries in Europe is essential if we are to monitor those diseases or European Regions where there is the greatest need for improvement in survival. For those countries which are just developing national centres of expertise for treating childhood cancers, again such information is essential for planning services and also monitoring improvements.

Q4.Should the European Reference Networks privilege the transfer of knowledge? The mobility of patients? Both? How?

Online information both for parents and professionals can be extremely important in accessing information on a very rare type of childhood cancer. Access to the "best standard of care protocols" and information for diagnosis and treatment of all childhood cancers should be easily available to both health professionals and patients/parents. There is a large amount of expertise across the field of childhood cancer within Europe. This requires better coordination especially on clinical trials and availability of new agents.

Q5. Should online and electronic tools be implemented in this area

Childhood cancers are increasingly being broken down into ever rarer subgroups according to their molecular biology. Some of these molecular tests are already used for risk stratification and determining treatment intensity; sometimes the clinical impact can be the difference between treatments can be as great as no further treatment versus high dose therapy with stem cell rescue. There is therefore clearly a need to ensure uniform standards and procedures in such molecular testing and to facilitate quality assurance schemes with sample exchange and the development of national reference laboratories.

Q6. What can be done to further improve access to quality testing for RD? and Q7. Do you see a major need in having an EU level assessment of potential population screening for RD?

A minority of children with cancer have a genetic predisposition e.g. leukaemias in Down's Syndrome, Wilms tumour in overgrowth syndromes or children with anairidia or genito-urinary abnormalities. The value of screening for childhood cancer in these conditions is debatable. Where the cancer risk is perceived to be greater than 5%, many geneticists would arbitrarily advise screening. It is difficult to capture these populations to know what

their actual cancer risk is or whether screening, e.g. by abdominal ultrasound, makes any difference to long term outcome. A coordinated approach to facilitating data collection perhaps through web-based international registries, should be considered.

Q8

The solution to the orphan drugs accessibility problem needs to be addressed on an EU scale.

Q9 Should the EU have an orphan regulation on medical devices and diagnostics

Probably yes.

Q10 What kind of specialized social and educational services for RD patients and their families should be recommended at EU level and at national level?

The views of childhood cancer parent's organizations should be taken into account when discussing this issue both at a national and European level.

Q11 What model of governance and of funding scheme appropriate for a registries database and biobanks?

Improvements in the treatment of childhood cancers will increasingly rely on better understanding of the underlying biology. Most of the commoner groups of childhood cancers are now split into ever smaller molecular subgroups according to defined biomarkers. These may be used for diagnostic, prognostic or response assessment purposes. In order to evaluate the true clinical relevance of such biomarkers, it is essential that translational research is facilitated in international clinical trials recruiting patients across Europe, in order for studies to have sufficient statistical power to test the true clinical relevance of a particular marker. In order for these molecular studies to reach their full potential, it is essential that updatable clinical outcome data remains linked to the specimen. Therefore, data protection laws should not be over zealously applied across national boundaries in order to retain the full potential of these valuable clinical trial sample sets.

Registries, databases and biobanks attain 'added value' when they represent a truly comprehensive collection of a rare disease. This inevitably means international cooperation and collaboration which should be encouraged and not hindered by unnecessary bureaucracy or difficulties in obtaining funding that may be spent beyond national boundaries. Hence, governance issues simply need to respect national laws and should not add another level of complexity or demand additional consent or audit trails. Funding schemes should reward and encourage multinational participation and data/sample sharing in truly joint projects.

Q12 How do you see the role of partners (industry and charities) in an EU action on rare diseases? What model would be most appropriate?

Whereas understanding the molecular biology of certain rare diseases has led to important insights into disease mechanisms, clinical research to translate this knowledge into new therapies of benefit to patients has lagged behind. This is largely because developing new drugs to treat rare diseases has less financial interest for industry than investing in common diseases. It is therefore of paramount importance to stimulate partnerships

between academia, industry and patient organisations to ensure that clinical development of new approaches can be properly tested in a timely fashion.

Under the current implementation of the EU Clinical trials directive, with large variations between countries in many aspects of the legislation, it is clinical trials in rare diseases that have suffered most. With many academic centres struggling to find the resources to employ the administrative staff necessary to demonstrate GCP compliance for their larger trials, it is not surprising that many centres choose not to open a trial in a rare disease, particularly when they expect to treat only one or two patients a year. This reduced recruitment then jeopardises the aims of the clinical trial. Part of the action to facilitate clinical research partnerships should focus on simplifying implementation of the EU CTD for rare diseases. For example, it could be specified that for later phase (phase II and III) clinical trials in rare diseases, a single national approval process should be sufficient to open a trial in that country, with a means to rapidly activate/approve a treatment centre when an appropriate patient presents.

An EU coordinated approach to developing national plans for treatment of rare diseases, in particular in relation to supporting clinical trials, should be proposed.

Q13 Do you agree with the idea of having action plans? If yes, should it be at national or regional level in your country?

Rare diseases clearly benefit from coordinated networks and action plans. These need to be at nothing smaller than national level, with international communication and European oversight to ensure that national plans are compatible with implementing international research projects.

Q14 Do you consider it necessary to establish a new European Agency on RD and to launch a feasibility study in 2009?

Probably yes. Research in rare diseases takes a long time due to the small numbers of cases for treatment and the long time frame required to build up suitably sized biological sample banks. These clearly require long term investment to allow research to come to fruition. A feasibility study of how to implement a phase III clinical trial in a rare disease where there are only a handful of cases each year in an average European country would be a challenging pilot – the paediatric oncology community would be pleased to collaborate in such a venture.

On behalf of SIOP Europe

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