SIOP EUROPE STATEMENT ON THE PROPOSED EU CLINICAL TRIALS REGULATION

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SIOP Europe, the European Society for Paediatric Oncology (SIOPE), representing the paediatric and adolescent oncology clinical research community across Europe, welcomes the proposal by the European Commission for an EU Clinical Trials Regulation, which encapsulates changes that will address many of the concerns and limitations of the EU Clinical Trials Directive (2001/20/EC).

The conduct of collaborative studies across multiple Member States has been seriously impeded by the current Directive and there is real potential for these limitations to be reversed by the Clinical Trials Regulation (CTR).

We particularly support and welcome:

- The introduction of the single Portal for application for clinical trial authorisation;
- The co-sponsorship model;
- The requirement for the establishment of national indemnity schemes;
- The recognition that not all clinical trials pose an additional risk to subjects compared to treatment in normal clinical practice.

However some areas remain a major concern as they put into question our ability to successfully re-build academically-led and sponsored clinical trials for children and young people with cancer.

1. National Indemnity Schemes

We hope that the European Parliament will insist on maintaining the proposed and fundamentally important requirement for the establishment of national indemnity schemes. We are concerned that there maybe considerable opposition from some stakeholders to the revised requirements for provision of clinical trial indemnity, but we believe that the introduction of national indemnity schemes will be a major facilitator for the future growth of non-industry sponsored clinical trials. Academia-driven clinical trials should be encouraged because they serve as fundamental cornerstones to improving standard practice and hence to improve and optimise a patient's treatment and care. National indemnity schemes will be a particularly critical issue for the academia-sponsored trials that are not categorised as low intervention trials and therefore will have an insurance requirement, which is often disproportionate to the risk posed to the patient and/or trial and prohibitively expensive to academic and publically-funded Institutions. **The introduction of the National Indemnity Schemes is a hugely positive initiative.**

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2. Low-intervention clinical trial category

The 'low intervention clinical trial' category in the CTR is a very welcome step forward allowing proportionate application of regulatory control over clinical trials.

In paediatric oncology (and in many rare diseases), the vast majority of drugs involved are used in standard clinical practice outside their marketing authorisation ('off-label use'). We remain very concerned that **in the context of 'off label use' of licensed medicinal products, there will be fundamental differences between Member States in the interpretation of when the 'low intervention clinical trial' category applies**. For example; individual Member States may require different levels of supporting evidence to define a treatment regimen as standard treatment, particularly in the 'off label' drug use setting. To avoid potential diversity in interpretation, we propose:

A: A clear guideline for the CTR definition of standard practice in disease groups, i.e. stating the acceptable level of evidence (to define a drug's use as standard practice) demonstrated either through published treatment guidelines or published results of Good Clinical Practice (GCP)-based academic clinical trials in peer-reviewed international journals.

B: A modification to the text (Article 2 3b) to reduce the possibility of misinterpretation: **'A low intervention clinical trial is where the proposed trial treatment poses no higher risk to the subject than standard medical care and where the use of a medicinal product in an off-label setting is supported by sufficient published evidence and/or guidelines'**

It is recognised that standard treatments are not homogenous across Europe, and adopting this approach will help the acknowledgment that more than one standard practice may apply for the same disease but they all need to fulfil the same basic quality requirements. An additional beneficial outcome may be the facilitation of trials aimed at treatment optimisation; i.e., it may foster the generation of evidence-based definitions of standard practice through comparison of different standard treatments within the low-intervention clinical trial' category. This will contribute to harmonisation of standard practice across Europe.

3. The definition of an Investigational Medical Product

We understand the definition of an Investigational Medical Product (IMP) in a clinical trial is likely to remain unchanged but are concerned that the diversity in application of the definition will continue under the CTR.

In spite of an apparently clear definition of an IMP within the EU CTD, which is now incorporated into the Clinical Trial Regulation, our experience is that the designation of a medicinal product as an IMP or an auxiliary medical product (AMP, previously a non-investigational medical product or NIMP) has varied between Member States. This confusion predominantly arises in trials where the medicinal products in the back-bone therapy are licensed but being used 'off-label' albeit in a standard treatment regimen normally used in clinical practice.

The lack of agreement between Member States on which medicinal products should be defined

as IMPs and NIMPS (now AMPs) has created insurmountable hurdles in collaboration between Member States in non-industry trials.

We seek reassurance that all medicinal products that are used as part of a backbone therapy will be considered AMPs, even if they are being used outside their marketing authorization but as a standard treatment regimen and this will be applied equally in all Member States

In clinical trials where two (or more) standard practice treatment regimens are being compared, the trial does not generate any new safety information about the drugs involved. Nevertheless, under the current Directive and the proposed CTR, all drugs in both arms are defined as IMPs. It is particularly important that this type of trial is categorised within the low-interventional trial category; otherwise there will continue to be a disproportionate burden of drug accountability, safety reporting and insurance needs (although the latter hopefully will be covered through the proposed national indemnifications schemes).

We propose that the CTR should specify that if trial treatment arms do not contain any unlicensed drugs AND ONLY compare standard practice treatment approaches then regardless of whether the drugs are being used off-label, the trial would always be categorised within the low intervention trial category.

4. Annual Safety Reporting

We strongly support the introduction of the ability of the sponsor to define in the protocol the adverse events that need to be reported to the sponsor. This approach will allow proportionate safety reporting and a considerably reduced administrative burden. However, this benefit is lost in the wording of Article 39 (1). There is a great opportunity in the CTR to introduce proportionate safety reporting and reduce unnecessary collection of adverse events data that do not add any useful additional information to the already known safety profiles of the medicinal products.

We propose a modification to Article 39 (1) that the requirement for an Annual Safety Report should not apply to authorised medicinal products used outside their marketing authorization (off-label) if their use is in a low intervention clinical trial.

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BACKGROUND INFORMATION ON SIOP EUROPE

SIOPE is a specialised network of health professionals working in the field of childhood cancers in Europe*. It is the only multidisciplinary, pan-European organisation dedicated to paediatric oncology and it exists to address the main challenges in childhood cancer such as promoting and supporting collaborative clinical trials within Europe, furthering education and training for health professionals, increasing awareness on and around childhood cancers and improving information exchange and dissemination across borders.*

Established in 1998 with an office based in Brussels since 2007, SIOPE is the continental branch of SIOP (the International Society of Paediatric Oncology), a Founding Member of the European CanCer Organisation (ECCO), and a member of Eurordis – Rare Diseases Europe, the European Forum for Good Clinical Practice (EFGCP) and Rare Cancers Europe. Representing multinational clinical trials groups and national childhood organisations, SIOPE develops novel strategies for cancer awareness, cancer diagnosis, and cancer treatment focused on children.

Aware that a highly dedicated multidisciplinary approach to treatment as well as investing in high-quality clinical research can greatly increase survival rates, SIOPE actively encourages greater coordination of clinical trials activity in Europe, as well as supporting education and exchanges between all professionals working in the field of paediatric oncology. SIOPE additionally maintains strong links with national patient organisations ensuring a strong patient perspective is maintained, as well as keenly promoting information dissemination of the latest development in cancer research and EU policy. Moreover, SIOPE leads on the dissemination of the EU-funded Network of Excellence, ENCCA – the European Network for Cancer research in Children and Adolescents.

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For more information on ENCCA, please visit www.encca.eu or email encca@ccri.at.

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