



**SIOP EUROPE SUBMISSION TO EUROPEAN COMMISSION CONSULTATION ON THE
FUNCTIONING OF THE “CLINICAL TRIALS DIRECTIVE” 2001/20/EC**

SIOP Europe, the European Society for Paediatric Oncology (SIOPE) would like to thank the European Commission for the opportunity to contribute to the EU Clinical Trials Directive Consultation process, allowing the experience of the several European study groups who have succeeded in launching childhood cancer clinical trials across the EU to be taken into account. SIOPE has responded to each of the five issues and the majority of the specific items discussed in the Consultation paper.

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.

INTRODUCTION

SIOPE agrees with the contention that the Clinical Trials Directive (CTD) has had a negative impact on the conduct of clinical trials. As pointed out in the Consultation, although the objective of the CTD is to standardise the regulation and quality of trials, there is rather a lack of coordination and significant duplication of efforts and resources invested by the clinical trial groups to meet EU CTD requirements. In particular, the CTD has had a disproportionately negative effect on trials in childhood cancer where there has been the greatest variability in national interpretation of the Directive.

Therefore, SIOPE was pleased that the particular issue of clinical research on paediatric medicines was specifically addressed in the Consultation¹. While each major type of childhood cancer is individually rare, 1 in 500 will be affected by cancer during childhood. This represents 1% of all forms of cancer. Despite favourable survival rates, cancer remains the leading cause of death from disease in children and young adults. Therefore, multinational clinical trials are vital to ensure optimal treatment for each young person diagnosed with cancer.

¹ Consultation item no. 14



It is clear that clinical research should not be considered a luxury but rather a necessary tool to combat the burden of cancer. However, the current bureaucratic workload of trial activation is much too high for the many rare diseases that comprise the childhood cancers. Moreover, the rare nature of the disease results in investigator-led trials due to the lack of commercial sponsorship. Indeed, many non-commercial organisations are still unwilling to undertake the role of sponsor at a pan-European level for multinational trials in children.

Response to Consultation item no. 1: Can you give examples for an improved protection? Are you aware of studies/data showing the benefits of Clinical Trials Directive?

Good Clinical Practice/ Good Manufacturing Practice compliance, transparency and better quality research constitute major benefits resulting from the Clinical Trials Directive. In particular, the CTD is important for new EU Member States, where the CTD has pushed authorities to introduce a partial harmonisation of procedures.

However, this positive effect is heavily counterbalanced by significant differences in the implementation of the CTD across Europe, the increase of the administrative burden and related costs, and the negative impact on academic research. In some Member States, the over-interpretation of the CTD is implemented into national laws and the absence of benefits from the CTD compared to the previous GCP has to be considered in the case of non-commercial, academic trials.

While one of the key objectives of the introduction of the Clinical Trials Directive was to guarantee better protection of trial participants, it has in fact been counteractive. Significantly less non-commercial clinical trials were launched after the Directive for the significantly increased bureaucratic burden incurred combined with a significant increase in costs. Yet, the need for investigator-led trials is clear: SIOPE is aware of data from the various tumour and leukaemia groups demonstrating that survival of children with cancer is significantly worse (up to 20%) when treated outside a controlled investigator-led, academic trial. Treating more children outside of controlled trials significantly impairs positive outcomes.

SIOPE Europe deems it necessary to re-draft the EUCTD to dramatically simplify the current regulatory procedures for multinational, non-commercial trials. Such redrafting must take account of the specific issues raised by clinical research for the benefit of children with life-threatening



diseases such as cancer, whose current, suboptimal therapies have significant acute and long-term side effects.

Key issue no. 1: MULTIPLE AND DIVERGENT ASSESSMENTS OF CLINICAL TRIALS

Response to Consultation item no. 2: *Is this an accurate description of the situation? What is your appraisal of the situation?*

The characteristic paediatric oncology trial - an international, academic, non-commercial clinical trial - is much more difficult to get approved by the National Competent Authority (NCA) in comparison to the industry-sponsored trials. The need for a single pan-European sponsor is interpreted differently by national regulatory authorities and has caused severe delays to the launch of new protocols by long-established European collaborative groups.

Focussed upon rules rather than practice, the Clinical Trials Directive has resulted in an inconsistent interpretation of the requirements for sponsors and our experience reflects the findings in the Consultation Paper, i.e. that this characteristic inconsistency of the CTD is causing major problems to established non-commercial academic trial networks in the European Union. The numerous subtle and at times less subtle interpretations of the CTD cause huge administrative burdens for the sponsoring organisations, with many Member States only accepting forms, agreements and contracts in their own nationally-agreed format rather than an agreed "EU Standard".

Example:

Many paediatric anti-cancer trials serve the improvement of treatment concepts and approaches using combinations of authorised medicines which are only available in off-label use for paediatric indications due to the lack of economic interest over the past decades. Paediatric investigator-driven cancer clinical trials are therefore hampered by the definition of an investigational medicinal product (IMP) as about 80% of anticancer drugs are in off-label use. Although first actions have been set to improve drug registration for paediatric indications (Introduction of PIP), regarding the current speed of progress, this will remain a problem over the next decades. As paediatric cancer trials are mostly using drug combinations, most of these drugs are frequently considered as an IMP in the majority of Member States despite being in paediatric use for over twenty years. Some MS consider *all* off-label drugs within a trial as IMPs whilst others restrict this definition to one drug only specifically under investigation within a randomised trial. As a result of off-label use, the majority of multi-drug anti-cancer treatment protocols are regarded as clinical



trials although standard treatment approaches (based on off-label use) are used. Relatively few paediatric cancer trials are performed within the framework of marketing authorisation whilst this amounts to 60 to 80% in adult indications.

All this impacts on a different understanding if a GCP-conformed clinical trial is required to run a common standard of care approach with frequent and necessary off-label drug use, i.e. taking on the full burden of a complete clinical trial authorisation, insurance (the insurance needs of clinical trial participants) and trial management issues such as the degree of adverse event reporting (SUSARS) as well as rules of inspection of clinical trial sites.

Response to Consultation items no. 3: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

Differences in interpretation of the Directive by national regulatory authorities have had a disproportionate effect on trials in children, highlighted by differences in what is deemed an 'investigational medicinal product' when paediatric use of an old drug is outside its licensed indication. Insurance costs have increased a 100-fold with no increase in actual risk between consecutive trials from the same study group.²

As a result, paediatric cancer patients are not offered the maximum opportunity to participate in relevant clinical trials that aim to improve optimal treatment for all children.

Clearer definitions of a clinical trial and an IMP, coupled with the responsibilities of the international sponsor, need to be provided, to cover trials where the standard arm includes long-standing use of cytotoxics outside of their labelled indications. Many drugs used to treat childhood cancer do not have a marketing authorisation for paediatric use, even though such use in multi-agent regimens is considered 'best standard of care' and has clinically-proven efficacy. For phase III trials, such interpretation of the need to declare multiple IMPs, even in the standard arm, has caused the paediatric oncology community to face significant increases in bureaucracy and obligations in terms of pharmacovigilance reporting, insurance and the provision of free drugs.

² Pritchard-Jones K, SIOPE Europe. Clinical trials for children with cancer in Europe - still a long way from harmonisation: a report from SIOPE Europe. Eur J Cancer. 2008 Oct; 44(15):2106.



Response to Consultation item no. 4: *Can you give indications/ quantifications/ examples for the impact of each option? Which option is preferable? What practical/ legal aspects would need to be considered in further detail?*

SIOPE supports Option (b), where authorisation of a clinical trial for the entire Community is performed by one body at Community level in close co-operation with the EMEA and MS. This one-stop-shop for clinical trial authorisation would greatly improve the current situation as state resources are currently not used efficiently, with multiple assessments of the same information undertaken in the various Member States resulting in an enormous increase in costs for staff and administrative tasks. Ultimately, this results in bothersome conflicting responses, highlighting the need for better common guidelines for judgements ideally implemented through a new European Regulation than a Directive.

Example:

Since 2003 for example, when the CTD was implemented into national law, Polish clinical trialists were neither able to introduce the new international clinical trial which became available for Hodgkin Lymphoma patients, the EuroNet-PHL-C1 trial, nor the HR-NBL1-SIOPEN for neuroblastoma sufferers.

Response to Consultation item no. 5: *Can you give indications/ quantifications/ examples for the impact of each option? Which option is preferable? What practical/ legal aspects would need to be considered in further detail?*

The concept of a 'one-stop shop' for the submission of an assessment dossier to the Ethics Committee (Option 3.4.1) would undoubtedly improve clinical trial procedures and reduce the administrative burden of multiple submission of information to separate actors. Clinical trialists are struggling unnecessarily with the current multiple levels of submission and complicated procedures.

Given the diverging cultural viewpoints of Member States, this option may be neither feasible nor desirable. However, for paediatrics in particular there is a real need for Ethics Committees in Member States to develop specific expertise and share best practices on how to deal with ethical issues for paediatric trials. Such sharing of best practice, which could be through the development of 'lead' Ethics Committees to review such trials, should improve the current severe delays in clinical trial activation which is denying potential participants the benefits of participating in clinical research. Thus strengthening networks of national Ethics Committees involved in



multinational clinical trials (Option 3.4.2) would be an important step forward in improving the efficiency of the current procedure.

Key issue no. 2: INCONSISTENT IMPLEMENTATION OF THE CLINICAL TRIALS DIRECTIVE

Response to Consultation items no. 6 and 7:

6: Is this an accurate description of the situation? Can you give other examples?

7: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

Indeed, there is a great variation nationally in onward reporting requirements for SUSARs. SIOPE agrees with the two weaknesses specified:

As there is no common understanding between the MS regarding the definition of SUSARS and SEAs, an enormous amount of over-and under-reporting is observed. As the understanding on what amount and type of information is needed a significant increase of unbalanced SAE (SUSAR) information between MS occurred. SUSAR reporting has become so complex and bureaucratic as to be almost meaningless and real SUSARS risk being missed in the enormous paper burden and amount of information required. This ultimately may lead to insufficient patient protection. Essentially the result of the CTD is an increase in the bureaucratic workload several-fold with no apparent benefit to patient safety; indeed the continuing confusion about interpretation of “local rules” is likely to pose more of a risk to patients than pre-CTD. **Efforts should be made immediately to harmonise rule interpretation and create a more simplified process to ensure efficiency.**

Response to Consultation item no. 8: *Can you give indications/ quantifications/ examples for the impact of each option? Which option is preferable? What practical/ legal aspects would need to be considered in further details? In particular, are the divergent applications really a consequence of transposing national laws, or rather their concrete application on a case-by-case basis?*

SIOPE agrees fundamentally with the argument to adopt the text of the Clinical Trials Directive in the form of a Regulation (Option 4.3.2); however this can only take place if it reflects the particular needs of paediatrics, as outlined in this document. Preferably a re-drafting of the CTD which includes the needs of paediatrics is required.



Key issue no. 3: REGULATORY FRAMEWORK NOT ALWAYS ADAPTED TO THE PRACTICAL REQUIREMENTS

Response to Consultation item no. 9 and 10:

9: Can you give examples for an insufficient risk-differentiation? How should this be addressed?

10: Do you agree with the situation? Can you give other examples?

SIOPE agrees that the risk for a clinical trial varies but currently the CTD adopts a 'one-size-fits-all' approach. The risk-benefit for childhood cancer patients needs to be taken into account, specifically their need for treatment for their life-threatening disease and the fact that best practice is generally viewed as enrolment into a multinational trial, where available.

In addition, the CTD requires a clinical trial to have a single sponsor that has overall responsibility for the trial process. While this is not necessarily a problem for trials of new drugs that are organised and funded by commercial companies, it is a problem for non-commercial, multinational trials. Academic/ non-commercial sponsors find the diverging and unfamiliar national health systems particularly challenging. With regard to co-sponsorship, there should be a limitation on the level of responsibility of the co-ordinating sponsor at European level.

Example:

In the UK, an academic institution can participate in a clinical trial through a direct co-sponsorship agreement between the UK national sponsor and the main co-ordinating sponsor in another country, without the need for that sponsor to accept direct responsibility for ensuring all aspects of trial compliance in the UK. In Germany, however such a model is not accepted and it has therefore only been possible for Germany to easily join multinational trials where a German institution is the lead European sponsor. This has had a direct effect on the number and ease with which pan-European trials for childhood cancer have been rolled out to German centres.

Response to Consultation item no. 12: *In what areas would an amendment of the Clinical Trials Directive be required in order to address the issue? If this was addressed, can be the impacts be described and quantified?*

SIOPE Europe recommends the following amendments:

- Clearer definition of an interventional clinical trial
- Clearer definition of a sponsor and a co-sponsor
- Clearer definition of a paediatric IMP
- Promotion of appropriate expertise to evaluate the appropriateness of new drug trials in children



- Insurance: if insurance is mandated, it should only cover potential additional risk; a sensible approach to calculating risk is required as access to new drugs for children with this high-risk disease is crucial.

Response to Consultation item no. 13: *Would you agree to this option and if so what would be the impact?*

The exclusion of clinical trials of “academic” sponsors is not a positive option. Investigator-led, non-commercial trials are of a very high standard and should not be excluded; however the bureaucratic characteristics of the CTD need to be adapted on reflection of the risk involved.

Key issue no. 4: ADAPTATION TO PECULIARITIES IN TRIAL PARTICIPANTS AND TRIAL DESIGN

Response to Consultation item no. 14: *In terms of clinical trials regulation, what options could be considered in order to promote clinical research for paediatric medicines, while safeguarding the safety of clinical trial participants?*

SIOPE agrees that the EU CTD needs to be modified to reflect the distinctive features of paediatric clinical trials. The Consultation does specify the measures taken by the introduction of the EU Paediatric Regulation (Regulation (EC) No 1901/2006) as well as the recent EMEA strategy. While SIOPE recognises that these actions have helped to increase interest of the pharmaceutical industry in performing clinical trials in children, unfortunately it does not go far enough. Access to new drugs for children with cancer is often only offered on an investigator-led basis for the clinical trial, sometimes after the adult indication has been granted a marketing authorisation. The significant financial support required to run such investigator-driven clinical trials, which are nearly all multinational under the current implementation of the Directive, limits the number of improvements in therapy that can be made available to patients. SIOPE requests the immediate re-drafting of the CTD to ensure that efficient and results-oriented clinical trials can take place.

As regards safeguarding the safety of clinical trial participants, SIOPE considers that for children with life-threatening diseases such as cancer, the additional risk of being on a trial is limited if not zero; in fact the outcome is usually better as there is increased adherence to the treatment protocol.



In fact, for paediatric oncology, there is no evidence that children with cancer are better protected than prior to the introduction of the Directive and plenty of evidence of the decline in the number of phase III clinical trials that are available for children. As a result of the Clinical Trials Directive, the paediatric oncology community is facing a period of sometimes a few years where there is no frontline phase III trial open for certain diagnostic groups.

Key issue no. 5: ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICE (“GCP”) IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

Response to Consultation item no. 16: Please comment? Do you have additional information, including quantitative information and data?

SIOPE considers it important to enhance regulatory frameworks and capacity-building in order to work more closely with our Developing World partners. Oversight of third countries, particularly those that do not have a quality research culture, is undoubtedly positive.

Indeed, while external inspection and adoption of GCP rules is essential, the governments in these third countries need to identify research participation as a managed priority open to assessment by agencies such as the EMEA. However, the greatest emphasis must be placed upon self-regulation linked to performance management, which requires a strengthened culture of national and international transparency and published results of scrutiny where it occurs. The European Union should recognise the positive results of potentially organising investigator-led clinical research with third countries.

Response to Consultation item no. 18: What other aspect would you like to highlight in view of ensuring the better regulation principles? Do you have additional comments? Are SME aspects already fully taken into account?

The administration costs of Good Clinical Practice are very high and have been imposed with inadequate compensatory government funding in many Member States.

Example:

Very few Member States have provided sufficient financial support to clinical trialists. A positive example of state initiatives includes those created in the UK. Costs for Good Clinical Practice in R&D dramatically increased in the UK. This coincided with a wholesale change in the funding strategy for clinical trials which has been very positive, as it has focussed upon the need to support clinical trials so that the UK can accommodate an expanded and target-managed clinical



trials programme as a service-wide strategy for enhancing quality of care and dissemination of new practice.

Most recently in the UK this programme has positively encouraged combining resources to support both investigator-led and commercial trials in hospital and community trials' programmes. Separate assessment procedures in the UK are being harmonised by creating research passports for investigators permitting them to work in multiple NHS institutions and also combining IT-based ethical and R&D assessment processes for new trials approval.

These advances in practice have been introduced successfully by creating national targets and the administrative chaos has been reduced by this concerted shared objective approach with government/national research backing and ring-fenced money.

Indeed, the experience in the UK is that target-setting and competition/comparison between regions are massively effective in changing practice with enthusiasm. If there was a method of harnessing this type of motivation across Member States it would be preferable as it would allow local workers to use their knowledge of the local system to achieve the declared result. Simultaneously, it is crucial that such a process is delivered within a robust ethical environment as the performance management of research creates a tension between the target and the rights of the patient being offered recruitment to a trial.



REFERENCES:

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ABOUT SIOPE EUROPE

SIOPE Europe (SIOPE) is a European organisation promoting optimal standards of care for children and young people with cancer. It is the only multidisciplinary, pan-European organisation dedicated to childhood cancer. SIOPE focuses on making a difference and improving the quality of life of young cancer patients. To do this, SIOPE supports the pooling of initiatives and expertise of multidisciplinary stakeholders in paediatric oncology, building their common experience into a positive force and creating a brighter future for young people with cancer.

Established in 1998, it collaborates closely both with SIOPE (the International Society of Paediatric Oncology) and the European Cancer Organisation (ECCO). 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.

For more information on SIOPE, please visit our website, www.siope.eu or contact Edel Fitzgerald at edel.fitzgerald@siope.eu.

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