SIOP EUROPE RESPONSE TO THE REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC CONCEPT PAPER

SIOP Europe, the European Society for Paediatric Oncology (SIOPE) would like to thank the European Commission for the opportunity to contribute to the consultation process of the EU Clinical Trials Directive revision, 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.

It is important to point out that this response was collated by the SIOP Europe Board and office after extensive consultation with the chairs of the European clinical trial groups and national societies.

SIOPE is a specialised network of health professionals working in the field of childhood and adolescent 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 EU Clinical Trials Directive (CTD) (2001/20/EC) has had a negative impact on the conduct of clinical trials in Europe. As widely discussed, although the objective of the Directive is to standardise the regulation and quality of trials, there is in fact **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.

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. Over the last 40 years, academic research within the paediatric oncology community in Europe has made significant process in increasing patient survival rates of up to 80% from previously less than 10%. This was only achievable through close collaboration in multinational consecutive trial strategies, building on the growing experience and expertise from running such trials. Further improvement in outcome particularly in poor-risk groups with less favourable perspectives clinical trials is essential. Indeed it is important to point out that despite favourable survival rates overall, 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 and to enable further advancement in improving outcomes.**

Multinational clinical trials remain vital to ensure further optimisation of outcomes after treatment for each young person diagnosed with cancer and to sustain the momentum of progress developed over the past 40 years. In the eyes of patients and clinical staff in this field of practice, clinical trials and research are not considered a luxury, rather an essential component of the fight against cancer in children and young people. The need for research and trials is clear therefore, its practical delivery, however, is impeded by the lack of commercial sponsorship of trials in rare, and therefore economically low-priority diseases, by the pharmaceutical industry and secondly the bureaucratic burden for investigator-led trials. The need for a non-commercial sponsor especially has inhibited many countries from opening any such trials in children and young people, since it was introduced in EU CTD legislation.

In summary, while clinical research is a necessary tool to combat the burden of cancer **the current bureaucratic workload of trial activation in Europe is much too high for many rare diseases including childhood cancers. As a consequence of the rare nature of the disease, investigator-led trials suffer from a lack of commercial sponsorship.** Thus, many non-commercial organisations are still unwilling to undertake the role of sponsor at a pan-European level for multinational trials in children.

From the outset, SIOPE wishes to draw attention to three areas of particular importance when performing academic research in children:

1) **<u>Waiver policy for IMP definitions and requirements in rare disease (and thus paediatric cancer) paediatric cancer trial settings</u>**

   Rare diseases and paediatric cancer both lack commercial interest and hence lack appropriate drug development. **Thus, the only way currently to treat patients is to utilise drugs in off-label or off-license status, many of which already have an off-patent status.**

   Indeed, the **definition of an IMP** and its full scope of current implications represent a major burden within academic multi-agent phase III trial settings, as various combinations of licensed, but off-label drugs, are tested for their efficacy in defined combinations rather than aiming to register a single drug. Many of these drugs are in use for over 20 years in consecutive trial settings and are the back-bone of many **standard treatments** for our young patients with cancer.

   SIOPE agrees with the contention of the European Science Foundation[1] that mechanisms need to be in place to encourage sponsors to formally share responsibility for trials and identify dynamic ways of addressing pan-European sponsorship of IMP trials.

   The SIOP Europe community recommends that the European Commission consider the concept of a **'waiver decision process'** that can limit the full scope of IMP requirements for drugs in off-label or off-license use in these rare disease indications. In such a case,

[1] European Science Foundation, 2009. *Forward Look: Investigator-driven Clinical Trials*, p.14

an exempted drug should have a long and successful history of usage in published trials[2].

It is clear that there is a real need to continue the use of these drugs that have been administered for the past 20 years in future paediatric oncology trials. However, as there is neither commercial interest nor resources in academia nor relevant public funding to change their off-label status in the reasonable near future, we urge the European Commission to address this matter with the relevant regulatory bodies without delay.

Standard treatment schemes are the basis of current success rates for children with cancer. We suggest therefore considering the following for academic trials in paediatric oncology:

- The current requirements for an IMP should be limited to drugs in unlicensed drug status or licensed drugs when used in doses or dose intensity that is very different to everyday use.
- Off-label drugs being used in clinical trial settings for indications outside their license status, i.e. different disease, different patients and/or age group, should be allowed as auxiliary medications without being forced into IMP status when already in use in standard routine practice in at least one Member State or as the standard arm in a Phase III trial and with a record of relevant publications.
- When running multi-agent, approved standard treatment paediatric oncology trials, a waiver should be in place for the needs of IMP drug supply in public or charity-funded studies.
- Marketed drugs provided from routine hospital or clinic supplies should be exempted from the same requirements for labelling and accountability in the pharmacy as non-marketed IMPs (even if not used in the licensed indications).

2) Risk-based approaches:

The paediatric oncology community would like to see a risk categorisation that is based on **relative risk** as not all childhood cancer trials should automatically be categorised high-risk if the disease itself is high-risk.

Risk-assessment of the therapeutic strategies for childhood cancer should be based on current survival success rates. The major risk comes from the underlying cause: cancer in young people is an aggressive and life-threatening disease. Hence, **treatment-associated risks should be proportionate to this underlying cause**. Low-risk categorisation of established cancer treatment standards should be allowed in children even if off-label drugs are part of these trials.

The concept of risk-evaluation in childhood and adolescent cancer is an issue that is actively being pursued by the European paediatric oncology community. As part of the recently-funded EU Seventh Framework Programme (FP7) project, ENCCA – the European Network of Cancer research in Children and Adolescents, risk-based approaches are currently being determined and expect to be finalised by late autumn of

[2] Examples of drugs that are commonly used and are key life-saving treatments for young people with cancer include vincristine, cyclophosphamid, ifosfamid, doxorubicin, cytarabin, cisplatin and carboplatin. This list is only an example of off-label drugs that are often utilised.

2011.[3] SIOPE and the ENCCA Management Team keenly anticipate working with the European Commission on these proposed solutions to assessing risk.

Potentially, a 'scoring system' could help to address this issue, not only to take accepted and defined trial associated risks into consideration, but to counterbalance these by the underlying disease risk. This would allow for standard cancer treatments to be considered in low-risk trials.

Most importantly however, trials in children should not be excluded from any type of "low administrative burden" regulation just because the drug(s) in question is not licensed for the age group or the indication.

3) Challenging the single sponsor role: Defined roles for a 'Coordinating Sponsor' and a 'National sponsor'.

As rare diseases, the majority of childhood cancer trials enrol patients in more than 10 European countries and even up to 20 countries can participate in academic, non-commercial trials. However, many barriers affect the running of paediatric trials in relation to sponsorship: (a) the legal and language diversity between Member States, (b) the fragmentation in the duties and liabilities of the different Member State trial participants, coupled with (c) the concern by academic institutions to participate in such a costly and bureaucratic non-commercial trial deter research. Solutions other than the current situation of single sponsorship need to be created to address these challenges.

We propose to create the following roles with a defined task profile:

- **Co-ordinating Sponsor**: this is the central contact point to be addressed for key trial queries and results, hence controlling the integrated data of the whole multinational trial.
- **National Sponsor:** the first point-of-contact for country-specific questions and responsible for ensuring conformity at national level of the regulatory and good clinical practice (GCP) issues.

This ensures an efficient and successful trial as country-specific issues are dealt with at national level: a sponsor of a trial involving 20 Member States will be under severe pressure otherwise due to legal and cultural variations.

In relation to this proposal, the paediatric oncology community has already started developing contracts on the co-ordinating sponsor/ national sponsor concept, and this solution has been validated in practice[4]. Please find attached draft template contracts, which provides a first insight into our proposal of co-sponsorship.

[3] The newly-created European Clinical Research Council (ECRC) for Paediatric Oncology, a body set up by the ENCCA project, is being consulted on the most appropriate solutions to deal with risk and risk evaluation of paediatric oncology clinical research. Members of the ECRC include the chairs of both European clinical trial groups and national societies.

[4] The Children's Cancer Research Institute (CCRI) in Vienna, Austria, can provide examples of clinical trials that functioned efficiently using the co-sponsorship system.

Finally, it is essential that the revised EU Clinical Trials Directive forges an environment for creating innovative medicines. **Red tape is the enemy of creativity**. The EU Clinical Trials Directive in its current form allows no room for curiosity-driven research in a clinical setting. As evidence shows, multinational collaboration is vital in particular in view of the more personalised medicine approaches being developed. However, at this point in time, rather than encouraging innovation, current research funding in paediatric oncology is rather funding insurance companies.

We wish the European Commission success in analysing the responses to the Concept Paper and warmly welcome the opportunity to discuss the issues raised in this response in greater detail.

REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC
CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

1. COOPERATION IN ASSESSING AND FOLLOWING UP APPLICATIONS FOR CLINICAL TRIALS

1.1. Single submission with separate assessment

Consultation item no. 1: Do you agree with this appraisal? Please comment.

Yes, a single submission will greatly reduce the administrative work and time currently required for approval of an academia-sponsored multinational trial. However, a reduction of the administrative work expected with this procedure only be achieved if the number of required documents does not exceed the current requirement.

Consultation item no. 2: Do you agree with this appraisal? Please comment.

Yes, a separate assessment would only maintain all the current obstacles facing the paediatric oncology community and would not address the divergence at local level. It is also not clear from the Concept Paper how this system coordinated by the European Medicines Agency (EMA) will deal with the different legislative stipulations and requirements from the various MS and current differences in interpretation. This should be explained and thereafter verified by the clinical trial community.

1.2. Single submission with subsequent central assessment

Consultation item no. 3: Do you agree with this appraisal? Please comment.

Yes, a centralised assessment at EMA of all clinical trial applications is neither appropriate nor feasible.

Given the current differences in interpretation, as well as the contrasting cultural and social aspects between MS and the current lack of harmonisation in the interpretation of the Directive, we do not foresee that a single submission with a subsequent central assessment is a workable strategy in the near future.

In particular only representatives from Member States where the trial is active should be involved. While it may be true that few clinical trials are rolled out in more than 6 MS and almost never in 27, this often takes place in paediatric oncology. We do not envisage EMA or a similar structure being able to manage the new heavy workload. This is evident when one considers that there are approximately 4000-6000 clinical trials active annually in the EU/EEA[5] whilst EMA currently coordinates approvals for around 90 drugs annually. Timely reviews and approvals would be at risk and there would be unnecessary delays with this process.

[5] These figures were specified in the EU Commission's Concept Paper 2011, on which this document is based upon and responding to (see 'Annex-key figures', p. 18).

The action, whatever is finally agreed upon, needs to be simple and straightforward, with a clear understanding by those involved in advance of what documents are required and a defined timeline provided.

1.3. Single submission with a subsequent 'coordinated assessment procedure'

1.3.1. Scope of the CAP

Consultation item no. 4: Is the above catalogue complete?

Firstly, it is clear that a single submission with a subsequent coordinated assessment procedure (CAP) involving only Member States concerned with the clinical trial will reduce administrative work, speed up timelines and encourage harmonisation at the EU level alleviating the current obstacles faced in transposing the Directive in each MS.

Scope of the CAP:

a) Risk-benefit assessment: Off-label medication needs to be acknowledged in relation to risk-benefit assessment, when one considers that off-label use has become daily standard practice in paediatric oncology clinical trial settings. In fact, 80% of drugs prescribed to children and adolescents with cancer are off-label.

   This is due to the historic lack of interest by the pharmaceutical industry and poor action at political level: neither politics nor industry have undertaken adequate financial measures to bring the full scope of paediatric drugs needed to an approved 'in-label' use or create a new legal interpretation for drug use in children with life-threatening cancer.

   Although admittedly the EU Paediatric Regulation ((Regulation (EC) No 1901/2006) was warmly welcomed, the opportunities to advance have not truly been fostered since its inception, with relatively poor drug development for children. Only when off-label-use has been resolved can the major inequalities for children with paediatric cancer and other rare diseases be improved.

   It is important also to reiterate that the risk of receiving treatment for childhood cancer must be considered in proportion to the risks from the underlying, life-threatening disease itself, which is uniformly fatal if not treated.

b) Ethical aspects related to informed consent, recruitment and reward: While the SIOP Europe community recognises that ethics and ethical committees are not included in the CAP, we still consider it vital to emphasise the point here that there should only be one ethical voice per Member State. The ethical obligations, particularly when dealing with multiple ethical committees per Member State, are completely inefficient and cause major and unnecessary time-delays.
   It may be considered that the ethical review of the protocol design and methodology in relation to quality of the research question and hence patient safety and utility of the trial, should be performed once at a European level, whereas the processes for approving information and consent and capabilities of the local team are national issues.
   Whilst the CA focuses on the product, which is essentially the same across Europe, the ECs would focus on the protection of participants, including information and informed consent, personal data protection, the investigation site and investigator capabilities

c) Local aspects related to suitability of sites, the investigator and national rules: The consortiums, ITCC- Innovative Therapies for Children with Cancer and EBMT- the European Group for Blood and Marrow Transplantation, have created efficient tools to address the delays in approving centres. In order to deter the huge workload of assessing local level sites, these consortiums have already accredited centres to ensure high-quality standards and suitability of the investigators. We consider that the European Commission should follow such an example in addressing delays in the future. A central capture of eligibility of trial sites with reasonable updates would help to relieve this burden.

Consultation item no. 5: Do you agree to include the aspects under a), and only these aspects, in the scope of the CAP?

a) **Risk-benefit assessment:** Yes, the scope of the CAP should certainly include the items outlined under a). In principle the concept of a reporting MS to lead the CT assessment is welcomed by the SIOPE community. However, a particular challenge for our community as mentioned previously is the varying interpretation of an **Investigational Medicinal Product (IMP)**. The current varying IMP interpretations represents a major risk when taken within the CAP procedure led by a single MS **because the leading MS then imposes its respective definition or interpretation of an IMP on all the other participating MS.**

It is unfortunate that for paediatric oncology all standard treatment is under the extensive rules of manufacturing labelling and extensive costs in multinational trials. This is a real problem and needs to be given thought and consideration. It would suffice that comparison of accepted standard treatments in Member States does not trigger the rule of IMP definition. This is paramount.
Without a harmonised understanding of the IMP definition, the paediatric oncology community will continue to face major challenges with the CAP procedure. Therefore a crystal clear **definition of an IMP leading to a harmonised and common interpretation within the European community is essential**.

b) **Ethical aspects related to informed consent, recruitment and reward:** We wish to point out that ethical aspects need to be more harmonised on the European level, particularly in relation to consent and the scope and type of consent provided. Childhood cancer patients and families are in very stressful and tense situations dealing with a traumatic situation and an overwhelming amount of information that is naturally burdensome and difficult to comprehend. There is an absolute need to develop straightforward procedures for patient consent, as the scope and level of information has grown considerably in recent years, which has been destructive rather than constructive.

c) **Local aspects related to suitability of sites, the investigator and national rules:** National expertise should not be covered within the scope of the CAP. However, only one evaluation or approval should be provided for each MS.

1.3.2. Disagreement with the assessment report

Consultation item no. 6: Which of these approaches is preferable? Please give your reasons.

Yes, an individual Member State should be allowed to opt out if there are differences in the assessment and no agreement can be reached, which can occur due to national specificities or particular sensitivities regarding a specific trial. However, this should not block the Member States to go on with the trial- those in consensus should carry on participating in the trial. Indeed, it is the SIOPE's opinion that MS would only agree to such a procedure; MS would not agree to the other options outlined.

The Commission or relevant Agency should not possess a role in this situation. As both bodies are not involved in the clinical trial authorisation process, they would neither have the relevant knowledge nor experience nor competence politically to deal with such an issue and it would undoubtedly lead to delays for the trial in question.

1.3.3. Mandatory/optional use

Consultation item no. 7: Which of these three approaches is preferable? Please give your reasons.

The CAP procedure must be mandatory for all multinational trials: otherwise the SIOPE community will have gained nothing from the revision of the Clinical Trials Directive. However, the IMP definitions will thus need to be clarified.

There is no need for a coordinated assessment for a single Member State trial. The administrative and regulatory work for a national trial should not be multiplied here and the central authority workload is already heavy organising the administration for multinational trials.

Potentially, there could be a short 'optional' phase to assess whether the procedure is working efficiently and to prove the concept of the CAP to all concerned. However, it is important that the CAP procedure should not lead to further delays in the authorisation for a trial to commence. Efficient timelines through a professional infrastructure such as the CAP proposes will ensure no delays as is the current case where a trial can begin relatively quickly in the Member State where the first submission is requested and this must not be delayed by the new CAP procedure.

1.3.4. Tacit approval and timelines

Consultation item no. 8: Do you think such a pre-assessment is workable in practice? Please comment.

The concept of shorter timelines for low-risk trials would of course be greatly appreciated. The '60 days' rule of the current Directive should remain.

The definition of a type-A trial needs to be refined however. Certainly a trial cannot immediately be considered ineligible to be a type-A trial only because it involves the treatment of children or treatment outside of the licensed indication – these paediatric oncology trials are using standard procedures at every stage.

It is important to underline the fact that all trials should be assessed individually and there should not be more than significant additional risk related to the disease and standard practice of this disease in a Member State; for example, an additional bone-marrow puncture for a child with leukaemia is acceptable, but not for a child without a bone-marrow disease.

2. BETTER ADAPTATION TO PRACTICAL REQUIREMENTS AND A MORE HARMONISED, RISK-ADAPTED APPROACH TO THE PROCEDURAL ASPECTS OF CLINICAL TRIALS

2.1. Limiting the scope of the Clinical Trials Directive

Consultation item no. 9: Do you agree with this appraisal? Please comment.

We are strongly in favour of a risk-adapted approach (as per Consultation item no. 8) since the current Directive has had a major negative impact on academic research.

The current definition of a non-intervention trial remains very narrow and of course includes only in-label medication, which is not ideal for the paediatric oncology community.
We do agree that rather than excluding non-interventional trials from the scope of the Directive, it would be more appropriate to create harmonised and proportionate requirements which could apply to all CTs.
Extending the definition of non-interventional trials should be considered, particularly as the current definition limits any type of epidemiologic research. . An epidemiological study should have a protocol describing the research and standard diagnostics and treatments; these are very beneficial particularly in ensuring the standard of care in rare diseases. Epidemiologic research, registries, standard of care research, treatment optimisation trials testing treatment strategies, non-drug approaches and risk stratification would also benefit in an extension of the definition of non-interventional trials.

2.1.2. Excluding clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive

Consultation item no. 10: Do you agree with this appraisal? Please comment.

Creating a separate Directive for academic trials is not the appropriate solution as it will lead to major complexities- there will be significant differences in interpretation between Member States on specifically defining 'academic', 'industry', 'commercial' and 'non-commercial trials'.

However the Directive should in some way recognise the nature of academic, investigator-led clinical trials. Indeed, specific paediatric issues need to be addressed more clearly to avoid the current inequalities for children in acquiring adequate cancer care.

Harmonised and proportionate requirements for clinical trials could possibly be achieved through risk-adopted approaches taking into account in particular the risk of the disease for the subject on trial.

2.2 More precise and risk-adapted rules for the content of the application dossier and for safety reporting

Consultation item no. 11: Do you agree with this appraisal? Please comment.

Yes, in principle **we approve that precise risk-adapted rules should be applied for the application dossier and the safety report**: this procedure would be very helpful.

Consultation item no. 12: Are there other key aspects on which more detailed rules are needed?

Modifying reporting requirements for safety based on risk and clinical relevance would be helpful. The risk of a clinical subject clearly needs to be defined in particular with reference to normal clinical practice and the risks of the underlying disease Detailed rules for the trial classification according to the risk should also be outlined.

Protocols generally include interim evaluations and may have 'stopping rules' on important toxicities. This per se is a scientific approach to safety analysis. Statisticians should be consulted on how to make safety reporting more informative and less cumbersome.

The current mass of information on safety that is required to be collated and reported to CA by sponsors is burdensome. We strongly recommend that expected toxicity data should only be captured within a given trial setting or environment and their appropriate databases as this is where the underlying disease and acceptable treatment toxicities are understood and where appropriate 'stopping rules' would impede the continuation of the trial. However, related to the above (where immediate action is needed), much of the information given within expedited reporting rules to CA, remains undervalued. Hence it is questionable whether the analysis of this mass of information given to CA is optimal: the enormous paperwork involved is not improving the safety of patients as the information is superfluous.

Thus, it would be helpful if ONLY SUSARs would needed to be reported to CA for late phase trials or those involving marketed agents used according to their licensed indication or according to standard regimens in common use for diseases such as childhood cancer where many drugs are used off-label. All other serious toxicities could be recorded on the case report forms and summary information could be provided at the end of the study or at predefined intervals to authorities within a given trial setting and not be required to be reported as individual serious events. Investigators could have the option to specify particular serious adverse events that they wish to monitor in real time during the trial, but even in these cases of known toxicities, the reporting could be simplified compared to the current requirements for SAEs. Naturally, due to the severity of the disease, side effects from such strong complex medication are common and expected – the burgeoning paperwork for every side-effect is unhelpful. Moreover, when required, the EUDRAvigilance database does not completely allow investigators to search for possible side-effects.

2.3. Clarifying the definition of 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products'

Consultation item no. 13: Do you agree with this appraisal? Please comment.

It is true that currently, a medicinal product tested or used as a reference is still too narrowly defined for the needs of the European academic community.

- In a comparative study, the standard treatment should not be referred to as an IMP. When comparing two sets of standard treatments there should be no need to call all the drugs in the two standard treatments IMPs; rather the rule of standard treatment should overrule the definition.
- Related to this, off-label drugs should not be automatically referred to as IMPs.
- We welcome the terminology, 'auxiliary medicinal product'. The definition of an auxiliary medicinal product should be clearly defined in particular in view of the IMPD definitions and the need for the very wide off-label use in the paediatric community. Standard treatments thus should be considered auxiliary with no need for an IMP definition if quality is assured.

In treatment optimisation strategies, it often occurs that even one 'investigational medicinal product' cannot be defined as often authorised products are used in various combinations and these different combinations of drugs include non-drug studies. It would be ideal to not define the treatment arms or individual drugs within a treatment arm as an IMP in a clinical trial but rather to have auxiliary medicinal products only. Auxiliary medicinal products, although used in clinical trials, have to be paid by health care systems including the preparation of the drug in hospital pharmacies and the application to patients.

2.4. Insurance/indemnisation

Consultation item no. 14: Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

SIOPE is strongly supportive of the risk-adapted approach for safety reporting and insurance coverage given that the paediatric community could also benefit from a low-risk categorisation under the special paediatric circumstances as outlined above.
We wishes to point out that paediatric oncology clinical research run by cooperative networks with a strong integration of research and care using standard practices does not per se constitute an added risk. We consider it to be a positive step that the European Commission is keen to address the current excessive costs of indemnity against non-commercial or academic clinical trials.

Prospective non-interventional trials under a widened definition should be allowed in the low-risk category even if these are for children with cancer. The liability for possible injury or death of a trial subject already under immediate threat of death by its acute underlying life-threatening disease needs to be reconsidered and needs to question the needs for insurance in such a setting if no new innovative medical products are under investigation.

We support the removal of the need for insurance /indemnisation in low-risk trials provided that children with cancer can also take advantage of this categorisation under well-defined circumstances and requirements.

Option 2 is very much welcomed, i.e. that Member States should be under obligation to provide for compensation for damages incurred during clinical trials in their country according to their legal system. Indeed, Option 2 is similar to the current situation in the UK where 'Crown

Indemnity' exists for medical practice insurance: the UK Government carries the insurance risk for all clinical negligence including research practice for the public/ common good.[6] Damages arising are very low and there is little burden on the national budget. This policy option to put MS under an obligation to provide for an indemnisation for damages incurred during clinical trials for paediatric oncology would be a major contribution to resolve part of the current inequalities for children with cancer and those who care for them. However, it is important to consider that such optional indemnisation may cause a large heterogeneity of interpretation in the different Member States.

2.5. Single sponsor

Consultation item no. 15: Do you agree with this appraisal? Please comment.

No, SIOPE is of the opinion that multiple co-sponsorship under the governance of a coordinating sponsor through co-sponsorship agreements should be allowed for multinational, academia-sponsored trials. We do not support the concept of a single sponsor as currently proposed as this does not cover the real practical needs of multinational trials.

Currently the single sponsor is responsible vis-à-vis the national competent authority and the ethics committee: This is extremely difficult in the multinational setting and the currently fragmented specific national requirements following the diverse implementation of the Directive into national laws, not counting the numerous language obstacles.

The only way forward is a combined approach of a) an end-responsible European single sponsor, who b) can delegate specific tasks (to be laid down in the protocol and or in contracts) to country-specific national co-sponsors. This delegates the overall responsibility to where it should be, but allows flexibility and makes sure that optimal knowledge on local procedures is guaranteed. Draft template contracts and explanations are enclosed to support this response.

Having a co-ordinating sponsor with a central overview and knowledge of the trial specificities (such as accrual and taking responsibility for adequate reporting of pharmacovigilance issues) is key. The coordinating sponsor should maintain the right to delegate the duties to run the trial on the national level in a multinational context to a national sponsor. This is important in order to share sponsor responsibilities with reference to the medical drug or "IMP supply" and insurance costs as well as costs related to monitoring a trial.

Well-defined contracts can regulate the specific responsibilities. The lack of insight into national law is a further reason to delegate part of the co-ordinating sponsor duties to the national expert. Hence we encourage the notion of a national sponsor with written responsibilities for the co-ordinating sponsor for very practical reasons as encountered in particular in academic, investigator-driven trials.

2.6. Emergency clinical trials

Consultation item no. 16: Do you agree with this appraisal? Please comment.

[6] For more information on this system, click on the link: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4125281;

Yes, we are content that the European Commission is taking action in this area and is in agreement with the proposal set out.

We consider a two-step process to acquire consent during such stressful and traumatic situations to be the best approach, i.e. 1) acquire provisional oral consent with witnesses at the start of the trial and 2) acquire written consent within a specified timeline, once patients and extended family members have had time to ruminate on the issues of this life-threatening illness.

3. ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

Consultation item no. 17: Do you agree with this appraisal? Please comment.

SIOPE is of the opinion that all efforts must be done to ensure all the patients included in a trial have the same standards of research, regardless of the place where they were born. The same standards of research should be enforced in all countries that are participating in a study

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ABOUT SIOP EUROPE

SIOP 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 SIOP (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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