

Minutes of the SIOE Europe Clinical Trials Group meeting

Thursday May 26th 2005, Sheraton Hotel, Schipol Airport, Amsterdam

Chairmen: Guenter Henze & Kathy Pritchard-Jones

All the major groups running international clinical trials in paediatric haemato-oncology were invited to send a representative to this meeting. Nearly all groups were represented (see list of attendees) and the minutes will be circulated to all those invited, with a copy to the chairs of national childhood cancer groups, where they exist.

Apologies were received from Ewa Koscielniak (CWS group), Odile Oberlin & Dieter Korholz (European Hodgkin's consortium).

The meeting was opened by Professor Guenter Henze, President, SIOE Europe. He explained the main aims of this meeting were to:

- Provide a forum where the major clinical trial groups active in clinical trials in paediatric haemato-oncology in Europe could share their experiences, particularly in relation to meeting the requirements of the EU Clinical Trials Directive (hereafter abbreviated to EU CTD).
- To identify common problems/issues to be raised with the regulatory bodies
- To speak as one voice in lobbying the European Commission regarding implementation of the EU CTD
- To discuss the responsibilities of SIOE Europe in relation to clinical trials

Kathleen Vandendael, Executive Director of FECS (Federation of European Cancer Societies) gave the first presentation. She summarised the results of a survey undertaken by FECS to analyse the provisions implemented in the national laws to take into consideration the specificities of academic research and to look at the impact of the EU CTD on non-commercial or academic clinical trials in oncology (copy attached). FECS, which represents more than 18,000 experts in cancer, drafted in consultation with the EORTC, a questionnaire which was broadly disseminated to its members. To date, replies have been received from 21 countries, from either the national competent authorities (11) or from trial investigators (from 16 member states). In countries where many replies had been received, there was sometimes a discrepancy between answers.

Issues raised included:

- **Sponsorship** – there was national variation in the requirement for a single sponsor for a national trial and for a single EU sponsor for a multinational trial.
- Investigational medicinal product (IMP) – there was national variation in the interpretation of the **definition of an IMP**, and therefore in the workload involved in preparing the IMP dossier (IMPD) (fortunately

some countries accepted the SmPC) and the requirement for the IMP to be supplied free of charge.

- **Pharmacovigilance** and **GCP monitoring** – there was national variation in the practical requirements to implement these and in free access to necessary supporting information (e.g. MeDRa code).
- **Scope of CTD**- some countries planned to extend the requirements of the EU CTD to all interventional clinical trials, eg radiotherapy and surgery trials.
- **Regulatory and ethics committees** – there is huge national variation in the costs, paperwork requirements and timescale to obtain approval
- **Insurance/indemnity** – data from EORTC showed huge variation in requirements such as need for ‘no fault’ compensation, duration of compensation, costs of premiums etc. Also, major misunderstandings by ethics committees about requirements was leading to long delays.

The conclusions of this survey were:

- CTD is a legislation designed for large, essentially multinational and industry sponsored trials
- The administrative requirements are not adapted to many academic trials (including some very valuable small trials, e.g. trials on rare diseases or subgroups)
- There is a significant increase in cost, resource, and technical expertise providing a new barrier to investigators
- Supportive approach by most authorities but still divergent approaches and different perception of administrative constraints
- No easy access to validated information for investigators (especially for multinational issues)
- For no clear benefit (perceived) versus previous GCP

A Clinical Trial Facilitation Group has been formed in the EU under the umbrella of the Heads of Agencies organisation. Their mandate is to coordinate the implementation of the EU Clinical Trials Directive across the member states at an operational and national level. To discuss issues that arise from this and to communicate to other groups that are involved in this area but with a different function. This group will be chaired by a representative of the MHRA, Dr Martyn Ward. The Commission will also produce specific guidance for academic trials, as announced in the Good Clinical Practice directive. There is also a question and answer document linked to the Notice to applicant, which clarifies the issue of sponsor and for non commercial trials with involvement of industry (e.g. simple provision of drug free of charge). Kathleen recommended that academic oncology needs to speak with one voice and to feed in to the group drafting the guidance, to ensure that all our areas of concern are addressed. She emphasised that the Clinical Trial Facilitation Group will expect a coordinated approach from clinical investigators working in cancer research and would not appreciate individual approaches from individual clinical trial investigators or even groups. She therefore recommended that paediatric haemato-oncology needed to agree a list of common issues that should be fed back to her at

FECS to be incorporated into information to be passed onto the Clinical Trial Facilitation Group. The Board of SIOPE Europe agreed to draft a list of common problems for circulation to all those present and to be discussed with their national PHO bodies and to be sent to all other countries not represented today.

Action: Kathy Pritchard-Jones to draft and circulate list on behalf of SIOPE Europe Board.

Jeremy Whelan gave the second presentation summarising the **EURAMOS** experience in initiating an international randomised trial for the treatment of osteosarcoma. This involves collaboration between established sarcoma groups in Europe (COSS, EOI, SSG) and the Children's Oncology Group (COG) of North America, covering a total of 14 countries. The trial aims to recruit 1400 patients over a 4.5 year period and contains two therapeutic randomisations, according to histological response to induction chemotherapy. While the main aim is to improve survival in osteosarcoma, the trial also aims to create an international framework to allow large randomised trials to be undertaken in an achievable timeframe, to develop common understanding and methodologies for staging, pathology etc and to facilitate biological research and the identification of novel therapeutic strategies.

The trial was first conceived in Sept 2001 and has just entered its first patients in May 2005. The trial organisation consists of a trial management group, a trial steering group (independent, to advise the management group), an IDMC and separate discipline panels (eg pathology, surgery etc). There is a single safety desk, based at the University Hospital Münster, Coordinating Centre of Clinical Trials (KKS Münster) and a single protocol, which has an international appendix and group specific appendices. Each trial group will have its own data centre that will feed into a single coordinating data centre based at the MRC Clinical Trials Unit in London. Participating institutions will be accredited and have initiation meetings. There will be onsite data monitoring as this was a requirement of the grant awarded to this trial from the European Science Foundation. There is additional national funding in some countries and some of the IMPs are being supplied free by the manufacturers. However, there is no pharmaceutical company acting as sponsor. While the MRC is taking on the sponsor's responsibilities for pharmacovigilance, other responsibilities are being met at the national level. Sponsors have been established in several but not all countries. Mostly these have been academic institutions.

The key to success in getting this trial off the ground had been shared goals and a scientific consensus, albeit that the latter had required compromise by all concerned, committed leadership and good fortune in obtaining significant funding. The bureaucracy had been helped by the fact that the participating groups already had rules for intergroup collaborations. The additional expense in meeting the new standards set up for this trial was recognised. There were still problems in some countries regarding insurance and sponsorship. The pharmacovigilance aspects of this study had yet to be tested in practice.

Further information is available at the trial website: www.euramos.org

Julie Hearn, senior research manager for clinical trials, **Cancer Research UK**, presented the results of a national survey to look at the impact of the EU CTD on academic clinical trials. The majority of the results of this survey were broadly applicable, even though they related to specific UK organisational structures.

She explained how the Department of Health in the UK had created the National Cancer Research Network (NCRN) in April 2001 to improve the infrastructure for clinical research in cancer (www.ncrn.org.uk). Along with equivalent bodies in Scotland and Wales, this initiative had succeeded in doubling recruitment to adult cancer clinical trials to just over 10% of all cases. This infrastructure included 26 trials units (both MRC and Cancer Research UK) of which 8 are currently accredited. There is oversight of the clinical trial portfolio by 21 Clinical Studies Groups. She summarised the results of the impact assessment after the first 12 months of trial units having to meet the requirements of the EU CTD as follows:

- Major drop in opening of new trials (except for the 'first in man' studies run through the CRUK's Drug Development Office and studies run through the UK Children's Cancer Study Group, where sponsorship issues had been largely resolved through the National Health Service).
- Overall patient recruitment down from 10.5% to 9%.
- International collaborative trials had virtually stopped.
- Costs of non-pivotal phase II/III trials had doubled.
- Increased staff resources to open and run trials to comply with the bureaucracy involved in obtaining a clinical trial authorisation, ensuring pharmacovigilance and appropriate trial management. 63% felt these had made no difference to trial quality and 50% no difference to trial safety.
- There were indirect adverse effects on other aspects due to a climate of 'risk aversion'.

Possible solutions at a national level were:

- To have a single source of information for academic clinical trialists with a dedicated contact at the national regulatory authority (MHRA) – the NCRN is creating a 'regulatory team' for this purpose.
- To pursue reciprocal sponsorship agreements with EMEA to avoid duplication and excessive bureaucracy
- To ensure funding for a minimum core staff for all new clinical trials, to consist of contracts officers, administrative posts, IT programmer, quality assurance manager, medical time for review of serious adverse events.
- Provision of training for investigators.
- Central liaison with participating institutions' review and approval procedures, to prevent individual hospital's lawyers amending individual clinical trial agreements.

A useful resource is the Clinical Trials Toolkit, www.ct-toolkit.ac.uk, which offers practical help for investigators in the UK in meeting the requirements of the UK Medicines for Human Use (Clinical Trials) Regulations 2004, and contains useful information for all investigators involved in clinical trials in Europe.

Gilles Vassal described a European consortium for Innovative Therapies in Children with Cancer (ITCC, www.itccconsortium.org). This is a network of clinical and translational researchers that aims to run early phase clinical trials of new drugs in children with cancer. There is also a biology section comprising tumour-specific biology labs for expanded preclinical evaluation of new agents in childhood cancers. As an example, he described the Phase I studies of TarcevaTM (erlotinib hydrochloride, OSI-774) as a single agent in children with refractory or relapsed malignant brain tumors and in combination with irradiation in newly diagnosed brain stem glioma. This trial will open at 11 centres in 4 European countries. It is being sponsored by an academic institution (Institut Gustav Roussy, IGR) in partnership with Roche. IGR will act as the co-ordinating sponsor and will be responsible for obtaining the Eudract number, producing the IMP dossiers, a 'sponsor dossier' and for overall pharmacovigilance. Each participating member state will require its own national sponsor. They have set up the pharmacovigilance reporting so that all serious adverse events must be reported within 24 hours to the pharmacovigilance unit of IGR who will decide if it is related to the novel treatment agent and whether it is a SUSAR (suspected unexpected serious adverse reaction). IGR will be responsible for reporting SUSARs within the timelines required by the EU CTD to the national sponsors who will be responsible for timely reporting to their national regulatory authorities. All SAEs that are not SUSARs will be collated for monthly reports to the trial co-ordinators and annual reports to the appropriate national authorities. There is ongoing discussion as to the need for all SAEs to also be reported directly to the national sponsor or whether they can be filtered through the single international pharmacovigilance unit.

The ITCC has not yet obtained EU funding but will be applying in the most recent call of the framework 6 programme, under the specific call directed to paediatric oncology.

Yves Benoit presented the experience of working with **EORTC** on clinical trials in childhood leukaemia (www.eortc.be). He emphasised how the EORTC is a 'not for profit', academic organisation that is well set up to comply with all the requirements of the EU CTD. In particular, it is able to provide sponsorship for all of its approved trials in any European country. Clinical trials are run by the disease oriented groups who receive support from various EORTC Data Centre Units – Disease oriented units as well as specific units including the Safety Desk (compliant with new regulations for pharmacovigilance), Regulatory Affairs Unit (submission of new trials and amendments to existing trials to regulatory authorities and ethics committees), Quality Assurance Unit (performs internal and external data quality audits), Operations Unit (supervises practical organisation of trial including budgets,

resource management), the Intergroup Office (facilitates the set up of trials between EORTC and other groups) and several other units. He gave examples of costs of an EORTC trial compared to two national multicentre trials, showing costs in the range of 150 to 400 Euro per patient per year. (see attached presentation for further details).

There was discussion from the audience about the resources available to EORTC and whether it would be in a position to be involved in a comprehensive portfolio of clinical trials in childhood cancer, including those where smaller institutions might only see a few eligible patients per year. Further comments were made about the flexibility and timeliness of the trial approval process, which Yves Benoit felt was less of an issue. It was recognised that EORTC were the only European organisation set up at present with the structure to meet all of the requirements of the EU CTD. However, there was uncertainty about their willingness to engage with all of the activities in paediatric oncology. It was agreed that a formal request to establish their interest and capabilities in the field of paediatric oncology should be made on behalf of the assembled company.

Action: SIOP Europe Board

Comments from individual trial groups and other representatives

I-BFM, Martin Schrappe

They feel inhibited by the new legislation. The Interfant study was initiated 5 yrs ago. It did not define a sponsor etc as it was not required at the time. More recently, EsPhALL, submitted before legislation finalised, was implemented after 1 May 2004. It has taken 2 years to open the protocol even though it was agreed in one day! Their experience is that inconsistencies in national interpretation of the EU CTD is causing huge delays in opening protocols

I-BFM would like to contribute to the process to take this forward, to address the correct people who will lobby for the needs of academic, non-commercial trials in parliament and will understand the problems.

NHL, Catherine Patte, Alfred Reiter & Angelo Rosolen

The European group for NHL is an informal group of 9 study groups and 14 countries. They have two open phase III trials – lymphoblastic lymphoma and ALCL. Both were opened prior to May 1st 2004. They would like to open two new trials for relapsed patients:

- Rituximab in relapsed B NHL. The protocol is ready, helped by Roche, but is only open in France so far, because of the EU CTD making it too much work for too few patients
- Treatment of relapsed ALCL. Currently, there are highly divergent recommendations in the literature for treatment of these patients (ranging from weekly vinblastine to allogenic BMT!). Numbers of eligible patients per country for a trial are extremely small. Yet if we are not allowed to run trials in these patients, we will never learn.

The question was raised whether single arm studies could be regarded as therapeutic guidelines with a registry rather than a clinical trial? This may be possible in Germany. Sue Ablett, UKCCSG commented that the UK has defined the term 'trial' if randomised, 'study' if not, yet bureaucratic process is the same (ie onerous!).

EWOG-MDS, Charlotte Niemeyer

This group is an offshoot of BFM. Again, they work with very rare scenarios. In order to be eligible to apply for funding, they required a study question. Therefore they incorporated a biology question into a clinical study. They have succeeded in having an approved trial and the University of Freiburg has agreed to be sponsor for the whole of Europe. However, the Italian authorities did not want a German sponsor!

The work of this group has also highlighted the difficulties surrounding how to develop transplant protocols within a reasonable timeframe within the current legislation. The German authorities have suggested writing such protocols as guidelines, including a recommendation for bone marrow transplant, but to collect the data as an epidemiological study. The therapeutic recommendations are placed in the introductory section! Swiss members of the group want to use the protocol and reference morphology service but don't want to put it through their ethics as it costs them too much.

EuroEWING, Uta Dirksen

The Euro-EWING 99 trial started well before the EU CTD. It is recruiting ahead of target. In Germany, they need to write a new protocol very soon because the funding is finishing and will only be continued if linked to a new clinical trial. This highlighted the problem in some countries of being forced to write new protocols, before the results of the previous trial are available, just in order to sustain key staff and resources.

EpSSG, Gianni Bisogno & Michela Casanova

The European paediatric soft tissue sarcoma group is a recently formed Intergroup between CWS (Germany), SIOP (MMT trials) and the Italian STS group. Their first trial (includes a randomised question) for the treatment of rhabdomyosarcoma was finished in Dec 2004 and is in the process of obtaining ethical approval. The group has had to leave it to each country to deal with their own problems. Each national group has to define their own method to get national ethical approval. Italy & France have succeeded in opening the trial, the UK is nearly there. Germany estimate they may need another 2 years to get through the whole process. The EpSSG have also written a protocol for treatment of non-RMS tumours, which contains single arm recommendations, many for very rare tumour types.

Kathleen Vandendael commented that the EU CTD already stipulates that national ethics committees have a maximum of 60 days within which to reach a decision about approving a clinical trial and that they are only permitted a single request for additional information. She recommended that the German investigators, who were having the greatest difficulty in this area, should use

this to query the length of time it was taking for their national approval processes.

CWS Study Group, Ewa Koscielniak

Written comments were received from Ewa Koscileniak, who was unable to attend in person. She commented on the problem of the different modes of implementation and legislation with regard to the EU CTD in each EU country. This has made it impossible to have exactly the same common RMS protocol in Germany compared to Italy and France since the requirements are very different in the different countries.

She also raised the question of the definition of a clinical trial and whether there could be another form of clinical study defined and accepted by all paediatric groups in Europe, suggested name: 'Non-interventional trial', "Observational study" "Optimisation Study". How would such studies get financial support? The German Cancer Aid Foundation is reluctant to support such studies. However, she is convinced that we need two different formats of study: "standard therapy" protocols without randomised questions based on common agreement by experts (who would form a study committee). Written consent would be needed for data collection only. Such studies are the optimal basis for additional biological or other research projects. In very rare diseases, like some soft tissue sarcomas, even a single arm, common European therapy concept is scientifically (and clinically) interesting. The other format would be the "true" GCP study with a randomised (or other new drug) question. Each study group would need both "observational studies" and GCP studies. We will have to overcome a lot of obstacles but she is convinced that a common European initiative is essential for success.

E-SIOP Neuroblastoma group, Ruth Ladenstein

The current high risk neuroblastoma trial has funding from the EU under the framework programme 5. However, the group needs to identify a backup partner as they are not a legal body and hence cannot take on responsibility for indemnity, insurance, sponsor etc. She highlighted the need to define what is a clinical trial and the responsibilities of the sponsor. Differences in interpretation in each country could lead to some countries being unable to join a trial because of lack of national solutions and insurance.

The group were also concerned about patients being treated according to their protocols but patients were not being registered in the trial. In Austria, if you register a patient with the data centre, they are automatically in the trial, whether they accept randomisation or not.

This led to a discussion about the responsibilities of sponsors of trials and the worry that the generic use of a protocol that has been published without the side effects being clearly defined, could lead to the trial organisers being prosecuted. There was a discussion that in fact, none of the clinical trial groups were a legal body and therefore could not be considered the trial sponsors or be eligible to take on the responsibilities of a sponsor.

Kathleen Vandendael commented that from her recent meeting with the European Commission representative, the legal status of the responsibilities of the overall sponsor are unlikely to be defined or clarified further. Lawyers from pharmaceutical units might be able to give advice on specific scenarios.

Finn Wesenberg commented that this had been discussed in the Nordic countries with the advice that the national law will always be highest in priority. Hence, each doctor is responsible for the treatment he delivers.

Kathleen Vandendael commented that the whole EU CTD had been drafted with the idea of development of drugs in mind. The sponsor was responsible for proper management of trials and to take the decision to stop the trial if it becomes too dangerous. They were not responsible for individual patients.

Jan de Kraker asked about the role of SIOP Europe. He feels there is a role for SIOP Europe in all this. The EU CTD means order from an authority - which authority? He feels that SIOPE should be one of the authorities. He would like to see one voice speaking for paediatric oncology on these issues and prefers SIOP Europe to be that voice. He raised the question of the involvement of SIOP Europe in the sponsor responsibilities for SIOP studies.

SIOP Nephroblastoma group, Jan de Kraker

The current SIOP WT 2001 enrolled its first patient in 2001. It includes several national groups in Europe and also the Brazilian national WT group. The trial has no sponsor. It has been running for over 4 years and has randomised 250 pts. He is worried about the lack of sponsor.

Sue Ablett, UKCCSG, commented that the EU CTD had been implemented differently in different countries. In the UK, open studies such as SIOP WT 2001 had to find a national sponsor. In many other EU countries, this did not apply to the SIOP WT 2001 trial.

SIOPEL, Joseph Zsiros

SIOPEL trials have been running since 1988 for the treatment of a rare childhood cancer. Two trials have been finished and three trials are open. They use both registered and unlicensed drugs. SIOPEL trials are conducted through the UKCCSG data centre. The group feels this ensures high data quality but means the group functions as a network of individual institutions who all have to meet the requirements of the UKCCSG. Due to small numbers of patients, the group requires wide international collaboration, including countries outside the EU. They want to ensure that laws do not exclude the participation of countries outside the EU as their participation is very important. They see the need for an umbrella/common voice for paediatric oncology to raise our common issues, including need for funding, and to solve these.

SIOP Brain tumour trials, David Walker

This group deals with ~25% of childhood cancers, making it only slightly smaller than I-BFM. They work with a very varied membership, including surgeons, neuropsychologists etc, who have all valued the environment

fostered by the link with SIOP. Studies are now open in virtually all brain tumour types. Arrangements for running trials are diverse, with individual trials run by different data centres in different countries (Italy, UK, Sweden, France).

The question of what is needed to enable them to move forward more rapidly was discussed at a recent debate in Edinburgh, attended also by members of the relevant COG groups. It was recognised that success had come about because of the commitment of individuals to science and to children with brain tumours. There was a need for more funding in order to start to move more rapidly. The group also wished to point out that there should be no upper age limit for clinical trials of tumours that occur in childhood, as these were unhelpful to making progress.

LCH study group, Andreas Zoubek

This was founded in 1985. Since 1991, it had initiated two studies, then in it opened the LCH III trial. There were subgroups in UK, USA, Canada, Argentina, Spain, Germany, Italy, etc. LCH III had enrolled 475 pts, of which half were from the German, Austrian and Swiss group. They had plans for a new study for 2007. China, Japan, Israel and Russia wanted to join. There was no sponsor for their current trials and they highlighted increasing lack of funds. In 2003, their income had been 105,000 Euro and had come largely from parents' groups and private donations (80%). In 2004, only 20% of their income of 124,000 Euro had come from this source, with the remainder being found from research funds participating institutions.

European New Agents in Leukaemia Group (ENAIL) Michel Zwaan

Their issues in meeting the new regulatory requirements had been covered by the presentation of Gilles Vassal.

International Clinical Trial statistical support, Maria Valsecchi

The statistician's role is to ensure good trial design, good data quality and proper analysis of results. Central monitoring of data quality at the Trial Data Centre is essential and is often the current standard for academic trials involving licensed drugs. Central monitoring can identify the need for on site monitoring/help for poorly performing centres. Whether this approach is sufficient under the EU CTD is still unclear (and may depend on the type of trial). She suggested that the statistical community discusses a general framework of what is essential for trial monitoring. In general, it is felt that the EU CTD this requires additional resources.

She was interested in Kathleen Vandendael's comments on the 'room for manoeuvre' in national implementation of the EU CTD. In Italy, a new definition of non commercial trials was made this year. This could be put forward as an example for other countries to consider and submitted to the Clinical Trial Facilitation Group for consideration in drafting their guidelines.

International trial data centre (UKCCSG data centre), Sue Ablett

The UKCCSG data centre functions as an international data centre for a few trials. They have received very patchy funding for this activity and have taken on trials in a 'spirit of optimism' because they are not always sure of grant

funding when they agree to take on a trial. She emphasised the need to work together and to work with adult colleagues in addressing the EU CTD. We need to emphasise the special problems of small numbers in childhood cancer. We must ensure that requirements of GCP are applied sensibly. In the UK, the EU CTD has not stopped opening of new trials but has required more work. The UKCCSG has sorted out the issue of sponsor in England and Wales for all of its trials (but Scotland is still under discussion). This has involved a university hospital trust (part of the National Health Service) taking on some of the responsibilities of the sponsor in a co-sponsorship model with UKCCSG. They will provide indemnity and the UKCCSG data centre will continue to do the rest – protocol review and approval, SAEs etc.

The UKCCSG had submitted an ‘umbrella protocol’ for single arm studies in rare tumours to their national ethical system but this approach had not been accepted.

Remote data entry (RDE)– the UKCCSG has experience of three different systems. It is difficult and inefficient to work with three different systems, both for the treating centres and for the trials unit. There is a need for future rationalisation. She described her recent visit to the Children’s Oncology Group in the USA and how efficiently they work. Virtually all protocols are their own (ie no intergroup trial design!), they have a single RDE system. They are able to open 50 protocols a year and each finished and approved protocol takes a maximum of 2 weeks to open! She emphasised the huge effort that had already been made to standardise trial templates, forms, databases etc at a national level in the UK. While recognising the needs of different languages, she felt there was an opportunity to collaborate and share in advance this work for design of new trials.

NOPHO, Finn Wesenberg

NOPHO comprises five national groups and covers 24 million people and 6 million children. In implementing NOPHO clinical trials, national regulations take precedence over EU rules. Several Nordic protocols predate May 1 04. Denmark only wants one sponsor per trial, Norway will accept several.

Baltic Society for Paediatric Oncology and Haematology (BSPOH), Lina Rageliene

The Baltic society was founded in January 2005. It has 35 members to date, who treat approximately 200 children with cancer per year. They aim to improve professional training and research and to participate in protocols with NOPHO and SIOP. They want to integrate more with SIOP Europe. They will organise meetings and plan to develop in each country a common register. They plan to organise joint scientific projects in epidemiology. Their first scientific conference will be held in Spring 2006 with the theme ‘solid tumours’.

Summary of round table discussion

There was agreement that the overall quality of care for children with cancer in Europe was good and that this had been achieved partly by enrolling the

majority of children into trials that had led to improvements in therapy. One of the priorities of all groups was therefore to keep children in protocols and to ensure that we do not have to spend years on the process to renew each protocol.

It was agreed that this forum provided the opportunity for a 'single voice' to represent the concerns and needs of clinical trials in paediatric haemato-oncology. Participants were happy that SIOP Europe should lead in providing a platform for continued discussions. Common issues for all trial groups were identified. These are listed in the attached appendix and will be circulated for comments prior to submission to Kathleen Vandendael, FECS. She will include them in her priorities for academic clinical trials in cancer that will be submitted to the Clinical Trial Facilitation Group.

There was discussion about future aims for all the groups present. What model are we aiming at? Do we want a single European cancer centre for paediatric haemato-oncology? Why not a European clinical trials consortium? What about using the expertise of EORTC? – Kathleen Vandendael commented EORTC were forced to concentrate their efforts in a smaller number of large centres where it is easy and relatively cheap to recruit patients. However, paediatric haemato-oncology could be faced with the same forced rationalisation in a resource limited environment with increasing regulatory requirements. She also highlighted the MICE programme for providing an evidence base for use of drugs in children. It now appears as if funding for out of patent drug trials may be available from the EU, through DG enterprise.

Mike Stevens commented that we should consider putting a formal proposal to EORTC to ask how they could facilitate clinical research in paediatric haemato-oncology across Europe. First, we would need to have an agreed vision of what was required. He suggested that this should be a major item for discussion at the next meeting of this group, organised by SIOP Europe, and that this should be held during the ECCO 13 meeting in Paris later in 2005.

Various members of the SIOP Europe Board commented on the need to create a real network of existing trial groups and to build a common source of information, expertise and training. This should facilitate expanded membership of existing groups and provide a resource to allow new institutions/countries less familiar with clinical research, to join studies and be compliant with the EU CTD. This should also provide a common structure to apply for EU funding for the resources we all now require to meet the standards defined by the EU CTD.

As a first step, we need to find a way to have a database of existing paediatric clinical trials in Europe and to provide an information source of key contacts by trial, by disease type and by country. A model for such a resource is the EORTC website. For newly opening trials, there is also now the European registry of clinical trials, EUDRACT. It would require considerable resources to set up a database for all open paediatric trials and a commitment on the part of the various groups to maintain their information up to date. Also, we must

not introduce duplication and need to find a way to exploit to the benefit of all in our speciality, the existing information sources. Such resources are beyond the current resources of SIOP Europe but might be feasible if EORTC were also involved.

Action points:

1. All participants to feed back comments on the list of concerns/questions to be submitted via FECS to the Clinical Trial Facilitation Group. Please circulate the list to all relevant contacts in your country or clinical trial group.
Deadline for return of comments: as soon as possible but no later than **July 15th 2005**.
(return comments by email to kathy.pritchard-jones@icr.ac.uk, copy to secretariat@siop.nl).
2. All participants to consider proposals for discussion at the next meeting, as outlined in these minutes. Please send items for the agenda and any written material to be circulated prior to the meeting to Rosalinde Kennis, SIOP Secretariat, preferably by email: secretariat@siop.nl, copy to kathy.pritchard-jones@icr.ac.uk
3. Date and format of next meeting: exact date to be confirmed. Further information will be announced at the SIOP Europe AGM to be held during the ECCO 13 meeting, 30th October – 3rd November 2005, Paris.

List of questions/issues to be presented to the Clinical Trial Facilitation Group

Common problems/questions	Potential solutions
Inconsistencies in national interpretation of EU CTD	Clarification in guidelines being drafted by Clinical Trial Facilitation Group
<p>Definition of a clinical trial – Should countries be allowed to apply the EU CTD to trials of non-IMPs? Does the EU CTD apply to ‘diagnostic’ trials where the ‘consensus’ treatment recommendations are in the introduction and the scientific question may be a biological one about factors associated with response and outcome.</p>	<p>Clarification in guidelines being drafted by Clinical Trial Facilitation Group</p> <p>Question to Clinical Trial Facilitation Group</p>
<p>Is there scope for ‘best practice guidelines’ or ‘optimisation studies’, especially for rare tumours or scenarios (eg relapse in an already rare tumour type) with simple data collection to avoid the full requirements of the EU CTD eg need for sponsor, insurance, SAE reporting <i>It is assumed they would still undergo ethical approval and written consent would be obtained from patients for data collection. There is an urgent clinical need for such studies in rare clinical situations where current treatments are inadequate.</i></p>	Question to Clinical Trial Facilitation Group
<p>Sponsorship – Definition of responsibilities – how far do they extend? What is legally binding, especially responsibility across national boundaries and outside of the EU? Clarification for multinational trials of need for a single European sponsor as compared to a coordinating sponsor with national sponsors, which is a structure already used in some trials.</p>	Clarification in guidelines being drafted by Clinical Trial Facilitation Group
<p>Insurance/indemnity – Does academic research really need ‘no fault’ compensation to be provided? Need guidance on calculation of risk and consistent approach to costs Is insurance not required for ‘best practice’ guidelines with associated data collection?</p>	Clarification in guidelines being drafted by Clinical Trial Facilitation Group
Requirement for sponsor to provide free drug if it is standard treatment	Clarification in guidelines being drafted by Clinical Trial Facilitation Group
How to reduce the time taken to open studies?	Each national group has to define their own method to get through their national approval processes

The implementation of the EU CTD must allow international participation in clinical trials from centres outside of the EU.	Question to Clinical Trial Facilitation Group
Need to secure funding to provide core support to clinical trial groups in paed haem onc in Europe	Agreement to form a network of clinical trial groups and national children's cancer groups in Europe with a view to applying for European funding. To be further discussed at next meeting organised by SIOP Europe
Standards of statistical support to paediatric clinical trials	Clinical trials group/SIOP Europe to facilitate regular forum for established and new statisticians
Standards for monitoring data quality	Guidance on what is required for trials involving licensed drugs
Inconsistencies in trial templates, data forms, remote data entry etc	Trial groups to consider working towards common standards
Pharmaco-vigilance and SAE reporting – time involved in setting up safe and compliant systems and lack of resources to do so	How far does this apply to clinical trials using licensed/out of patent drugs where the side effects are well documented? Question to Clinical Trial Facilitation Group
Definition of SAEs	Adverse reactions/events that do and do not require expedited reporting should be clearly defined in the trial protocol at time of writing.
Time to get through all the ethical approval processes	Utilise the maximum time lines allowed in the EU directive to query any delays at national level.

Final Agenda for SIOPEurope Clinical Trials Group meeting

Sheraton Hotel
Schipol Airport
Amsterdam

11:00-16:00
Thursday May 26th

Chairmen: Guenter Henze & Kathy Pritchard-Jones

- 11:00 **Welcome, introductions, overview of aims of the day**
Guenter Henze, President SIOPEurope
Kathy Pritchard-Jones, Chair SIOPEurope Clinical Trials Group
- 11:15 **Impact of the EU Clinical Trials Directive on academic
clinical trials in Europe: Results of FECS survey and update
on recent meeting with EU commissioners**
Kathleen Vandendael, FECS Executive Officer
- 11:45 **The EU Clinical Trials Directive: impact on academic trials
in the UK and possible solutions**
Julie Hearn, Cancer Research UK
- 12:15 **The EURAMOS study: an international collaborative clinical
trial with the Children's Oncology Group, North America,
opening after May 1st 2004. Obstacles and solutions**
Jeremy Whelan on behalf of the EURAMOS clinical trial group
- 12:45-13:30 Lunch break
- 13:30 **Round table discussion:**
Summary of key issues for each clinical trial group/other
representatives, with examples of solutions where possible
5 minute oral summary per group
**(Please bring along handouts if you wish. No Powerpoint
presentations allowed due to time constraints).**
- 15:00 **Comments from SIOPEurope Board members and
speakers from the morning session.**
- 15:30 **Final discussion and future plans**
- 16:00 **Close**

**List of Attendees, SIOPE Clinical Trials Group Meeting
26th May 2005**

Amsterdam

Representatives of National Groups/Organisations and/or Specialities	Name	Country
FECS	Kathleen Vandendael	Belgium
Cancer Research UK	Julie Hearn	UK
EURAMOS	Jeremy Whelan	UK
International Trial Statistician	Maria Grazia Valsecchi	Italy
UKCCSG, international trial data centre for SIOPEL	Sue Ablett	UK
Secretary General NOPHO Group	Finn Wesenberg	Norway
President of Baltic Society for Paediatric Oncology and Haematology (BSPOH)	Lina Rageliene (Goda Vaitkeviciene)	Lithuania

Clinical Trial Group Representatives	Name	Country
I-BFM	Andrea Biondi Martin Schrappe	Italy Germany
EORTC ALL	Yves Benoit	Belgium
European Intergroup of Childhood NHL	Catherine Patte Alfred Reiter Angelo Rosolen	France Germany Italy
EWOG-MDS	Charlotte Niemeyer	Germany
Euro-Ewing	Uta Dirksen	Germany
CWS-Group	(Ewa Koscielniak)	Germany
EpSSG	Gianni Bisogno Michela Casanova	Italy
E-SIOP Neuroblastoma	Ruth Ladenstein	Austria
SIOP Wilms Tumour Group	Jan de Kraker	Netherlands
SIOPEL	Dr. J. Zsiros Bruce Morland	Netherlands UK
SIOP Brain tumour trials	David Walker	UK
LCH Study Group	Andreas Zoubek	Austria
European New Agents in Leukaemia Group	Michel Zwaan	Netherlands
ITCC	Gilles Vassal	France

Representatives of the SIOPEurope Board in Attendance	Name	Country
President	Guenter Henze	Germany
President Elect	Andrea Biondi	Italy
Past President	Michael Stevens	UK
Member	Jan Stary	Czech Republic
Member	Kjeld Schmiegelow	Denmark
Member	Willem Kamps	Holland
Chair, SIOPEurope Clinical Trials	Kathy Pritchard-Jones	UK