

Minutes of the SIOP Europe Clinical Trials Meeting
7th March 2006
Hilton Hotel, Schipol Airport, Amsterdam

Chairs: Prof Andrea Biondi & Prof Kathy Pritchard-Jones

The meeting was opened by Professor Andrea Biondi, President SIOP Europe, who welcomed everyone to the meeting. He explained that the purpose of the meeting was an update on progress made by National Groups and Clinical Trial Groups in continuing to open trials in childhood cancer in compliance with the EU Clinical Trials Directive. The aims were to share solutions as well as problems and to work together to facilitate clarification of outstanding issues. Although it was still early days in the planning of the EU Framework Programme 7, this was also our first opportunity to discuss strategies to secure both national and EU funding to support childhood cancer clinical research. An important aim was to discuss if a single, co-ordinated European resource was needed to facilitate clinical research in childhood cancer and what form this might take.

1. Response to document submitted to the EU Clinical Trials Facilitation Group

General

Kathy Pritchard-Jones reported back from a meeting she had the previous week with Dr Martyn Ward, Chair of the EU Clinical Trials Facilitation Group (CTFG). Dr Ward had explained that the CTFG consists of representatives from all national regulatory agencies. It is currently chaired by himself as lead for the MHRA clinical trials unit, UK and there are no immediate plans for rotation of the chair. The Group meets quarterly but has no secretariat to support its activities. It has four subgroups working in the following areas:

- Safety reporting including use of EUDRA vigilance;
- Application process to open a trial (this group has links with a commission group working on definition of an IMP in relation to the supporting documentation required);
- GMP issues;
- Sponsorship issues.

He emphasised that while it is the duty of the national regulatory authorities to implement the EU regulations, the CTFG wishes to hear about clear examples of impediments to research that may be occurring at a national or European level so that a more harmonised approach can be discussed among their group. The paediatric oncology community should therefore be providing clear examples of individual clinical trials that have been prevented from or experienced delays in opening because of national interpretation of the EU clinical trials directive (EUCTD). Any group who feel their trial falls into this category should provide a succinct summary of the issues and submit it both to their own national regulatory authority but also copy it to Kathy Pritchard-Jones at SIOP Europe and to Dr Martyn Ward at the MHRA in his capacity as Chair of CTFG.

Action: All

Dr Ward emphasised that the CTFG has to work through others to provide guidance on how to comply with the regulations as they are not resourced to do this. In the UK the

Medical Research Council has produced a website aimed at academic researchers working in the National Health Service system of the UK (www.ct-toolkit.ac.uk). This is known to be accessed by academic researchers in other countries and found to be helpful. It should soon have a pharmacovigilance section added. None of the other countries represented at the meeting today appear to have any plans to provide a similar resource to assist academic researchers.

New member states, who have not yet introduced the EU CTD into national legislation, still have an opportunity to lobby for on how it is implemented in their country.

Definition of an interventional clinical trial

For trials using licensed drugs, they are only exempt if the drug is licensed and used according to its marketed indications and the decision to prescribe is not related to the trial protocol. In other words this excludes all randomised trials or detailed therapeutic/best practice guidelines. If a drug is used outside its licensed indication or schedule, then it will be considered an IMP and require submission of either a summary of product characteristics (SmPC); investigator brochure or 'reference document'. In the UK at least, the regulatory authorities have accepted reference documents describing historical experience of use of the drug in children, where this has been long established in normal clinical practice. This is particularly important in relation to defining what is 'expected' in terms of side effects, which has an impact on pharmacovigilance requirements for urgent reporting.

Sponsorship

The CTFG have twice made a submission to the European Commission regarding inconsistencies in acceptance of multiple sponsor arrangements for international trials. The Commission have twice stated their position on the requirement for a single European sponsor. However, the reply emphasised that while the sponsor must be a single legal entity, it does not have to be a single individual. This is still a blocking point for clinical researchers in Belgium, whose national regulatory authority does not recognise the existence in law of a national co-sponsor. This needs to be submitted to the CTFG as a specific example of an impediment to national research.

Action: KPJ, Belgian representatives

See attached Powerpoint presentation "CTFG feedback" for further details.

2. Outcome of meeting (January 2006) with representatives from EORTC regarding clinical trials in childhood cancer

Liliana Baila, EORTC & Kathy Pritchard-Jones, SIOP Europe

Andrea Biondi and Kathy Pritchard-Jones had met with Patrick Therasse and Liliana Baila of the EORTC in January 2006. A summary of the main points of this meeting have been previously circulated and are available from the SIOP secretariat (secretariat@siop.nl). In brief, EORTC were sympathetic to supporting more paediatric cancer clinical trials. Their main requirements related to protocol approval and a single database with a single source of generating data queries. This meant that national representatives acted as mailboxes for trial data. While they could assist national investigators with basic tasks such as highlighting missing or confusing data, they were not allowed to raise or interpret data queries in order to ensure consistency in this parameter. While there were

no absolute minimum requirements for centre size or maximum number of centres, both of these were factors taken into account in judging the feasibility and resource requirement of a trial.

Concerns were raised by several clinical trial group representatives that the EORTC system undervalued the contribution made to clinical research management by national lead investigators in co-operative group trials. In particular, the national representatives had considerable expertise both in the tumour type and of the participating institutions and investigators in their own country. Such knowledge was often essential in ensuring a trial ran smoothly in a particular country. The EORTC response was that this was, to some extent, a matter of differences in perception of how rules were implemented rather than any true undervaluing of national expertise.

Note added after meeting:

Subsequent to the EORTC Board Meeting on March 9th, they have agreed in principle to support the new Interfant study. This trial, which treats a very rare disease, will prove an interesting test case as to how the EORTC approaches implementing such a study. This is an important step in the right direction.

3. Presentation of summary document of current status of clinical research in paediatric cancer by trial group and country and impact of EU CTD.

Kathy Pritchard-Jones, SIOP Europe

Responses to a brief questionnaire about implementation of the EU CTD and its impact on newly opening paediatric trials had been received from the majority of countries and some international clinical trial groups. The findings are summarised in the attached Powerpoint presentation (Questionnaire responses 6 Mar.ppt),

Sponsorship remains a major issue for the majority of countries where there is still no national solution to sponsorship requirements for academic clinical trials. Sponsorship tends to be provided by the academic institution of the lead investigator. The issue of the need for a pan-European sponsor is particularly problematic for Belgium, where the regulatory authorities do not recognise the existence in law of a "national sponsor" who can assume delegated sponsor responsibilities. In the Scandinavian countries, sponsor responsibilities can be delegated to a national representative, but the latter has to have written permission from the sponsor in order for them to communicate trial issues to their national regulatory authorities. Encouragingly several countries have found a "workable" solution in this area, even though there is still lack of clarity about the need for and definition of a 'single European sponsor'.

Regarding the definition of a clinical trial, most countries have not succeeded in having any other than epidemiological studies escape the EU CTD. France has found a novel solution to reduce the administrative workload of opening the new European rhabdomyosarcoma protocol, EpSSG RMS 2005. They have split this into two protocols, one of which describes the use of IVA chemotherapy for rhabdomyosarcoma, which is accepted standard practice. As such, any patients following these arms would not be considered to be in a clinical trial and therefore would not require reporting of adverse events etc.

Indemnity Insurance Issues

There continue to be large variations in the requirement for 'no fault' insurance and unaffordable variations in premiums. Several countries have made progress in this area. The German Cancer Society has been involved in definition of ten risk levels with a simplified and much more affordable insurance level. The Italian Parliament has legislated in December 2005 that academic trials do not require 'no fault' insurance or indeed any form of insurance over and above that which is supplied by normal hospital indemnity.

See attached PowerPoint presentation, "Questionnaire", for further details.

Ethical Approval

Although the EU CTD requires a single ethical approval for clinical trials with defined timelines, there continues to be some variation in how this is interpreted. In many countries, although there is notionally a single national ethical approval process, the requirement for local ethical committees to decide whether or not a trial can be run in a particular institution, is still causing additional bureaucracy and delays. Most regulatory authorities are complying with the timelines of a 60-day turnaround for approval. The majority of delays are appearing due to the overall burden of bureaucracy. Time to open new studies since May 2004 has ranged from 3 months for a new drug trial that could be fast-tracked in France to several months to years for the majority and an answer of "indefinite" from the Belgians due to their current sponsorship difficulties.

Professor Maria Grazia Valsecchi, Monza, Italy then gave an invited lecture entitled "Challenges in clinical trial design for limited patient populations".

A copy of her presentation is attached.

4. The Teddy network (Task Force in Europe for Drug Development for the Young) and the assessment of paediatric oncology needs. A FP6 network of excellence.

Prof. Paolo Paolucci, TEDDY Network of Excellence & leader, Oncology Therapeutic Experts Group, Italy

Professor Paolo Paolucci, Italy, presented the Taskforce in Europe for Drug Development for Young (TEDDY) which is a network of excellence funded by the European Community Framework Programme 6. This is a network which aims to facilitate and coordinate an integrated strategy with existing EU research groups, networks and trial groups to drive forward drug evaluation and development for children. This will include links with the paediatric expert group of the EMEA in establishing the paediatric needs. Professor Paolucci is the lead of the TEDDY network for paediatric oncology. Oncology has been highlighted as one of the highest priority disciplines, second only to cardiology, where there is a critical need for paediatric drug evaluation. TEDDY needs to establish an expert group in oncology and SIOP Europe, on behalf of all the groups represented at today's meeting, have formally offered to be involved in identifying suitable people for this group. We were also pleased to hear at this meeting that Dr Janez Jazbec, Paediatric Oncologist, Slovenia is a member of the EMEA Paediatric Expert group. A full copy of Professor Paolucci's presentation is attached.

5. Opportunities for Funding

- **Ideas to engage Pharma to support networking of paediatric oncology clinical trials.**

Gilles Vassal, IGR, France

Professor Gilles Vassal discussed the obstacles and opportunities to work with Pharma to support paediatric drug development. He emphasised that Pharma were not interested in supporting paediatric oncology drug development based on a "marketing approach", as the size of the commercial market would always be too small to be financially interesting. We therefore needed to switch tactics and aim to engage Pharma based on their "Research and Development" approach. However, this requires guaranteed delivery of results within specified timescales and a high degree of organisation and commitment by the paediatric oncology networks working in this way with Pharma. He emphasised that neither Pharma nor EU financial sources would fund infrastructure to undertake clinical trials. It is clear that the EU funders see this as a national responsibility. Although most Pharma have Foundations that can be approached for financial support, these will not support either trials or infrastructure due to the risk of a perceived conflict of interest. However, they may well support other areas such as communication or working with developing countries, as has been the case for Sanofi Aventis who are supporting work in Africa. He emphasised that one of the main problems at present is that the paediatric oncology networks are not 'visible' for pharmaceutical companies. The ITCC (Innovative Therapy for Children with Cancer) Consortium is tackling this issue for trialling new adult cancer drugs in paediatric oncology and has made some progress in the last year or two. As yet, the large Phase III clinical trial group networks have had little success in obtaining industry support. Clearly this is an area where we need to focus. With the forthcoming EU legislation that will oblige Pharma to formally assess the need for paediatric development of their drugs, it is critical that we make ourselves more visible to the commercial world.

Noted after meeting:- there is a forthcoming conference in Barcelona (Optimising Paediatric Drug Development conference to be held on the 22/23 June 2006) where Pharma will be strongly represented. SIOP Europe has committed to providing experts from the oncology community to speak at this meeting. There should also be an opportunity for clinical trial groups to engage with industry. For further details see <http://www.iir-lifesciences.com/>

- **Discussion of potential opportunities for funding in the EU Framework 7 and MICE programmes.**

Kathy Pritchard-Jones & Andrea Biondi, SIOP Europe

The European 7th Framework Programme will be organised in four specific programmes corresponding to four major objectives of European research policy.

- Co-operation, which includes 9 themes (among them Health)
- Ideas, which include the European Research Council
- Marie Curie Actions: People
- Capacities; Infrastructure

As the overall EU Budget was not accepted on time, the whole process of budget allocation has been delayed until late June-early July. It is therefore likely that the first call for proposals will be in early 2007. It is not foreseen that there will be any

opportunities for supporting clinical trial networks under the 'Health' theme of Co-operation. However, it is likely that there will be the opportunity in the Capacities: infrastructure theme. FECS has tabled an amendment requesting that specific research infrastructure support should be provided for paediatric diseases.

- **Mobilising coordinated funding from the major national charities to support cross-country initiatives discussion.**

Julie Hearn, Cancer Research UK

Dr Julie Hearn from Cancer Research UK gave a presentation on sources of cancer research funding across other countries of the EU. There is a wide variation in both total research spending and the proportion that comes from charity versus government agency (see attached presentation). Overall across Europe, approximately 50% of direct cancer research is funded from charitable sources. In the last two years, Cancer Research UK had spent an extra £0.75 million per annum in the UK to ensure that the clinical trials it supports can meet the new regulations of the EU CTD.

She discussed the politics of developing relationships with other funders across the European Union. It was important to ensure that research initiatives were highlighted as project focussed, in order to increase the success of obtaining funding. She drew the Group's attention to the existence of the European Cancer Research Managers Forum website, which contains a lot of useful information about charitable funding. The website address is: www.ecrmforum.org.

A copy of her presentation is attached (Cancer Research UK SIOP Europe.ppt).

6. Co-ordination of response to Drug lists for oncology:

- Assessment of Paediatric needs, Chemotherapy products (part I (attached) & input into part II – to be discussed March 24th 2006, EMEA Paediatric Expert Group).

The EMEA paediatric expert group has already published its paediatric oncology drugs list, part 1. This was developed from work undertaken by the French Regulatory Authority (AFSSAPS). This list should contain all the 'old' drugs in paediatric oncology for which there is a need for paediatric data to support dose, schedule and efficacy. Drugs do not appear on this list if adequate data is already available. Drugs are also not included on this list if they are deemed to only be suitable for adult cancer. Although this list is open to public consultation by the EMEA until May, it will be discussed at the next meeting of the EMEA PEG on the 24th March 2006. Kathy Pritchard-Jones has been invited to that meeting as a representative of SIOP Europe. Dr Janez Jazbec from Slovenia is a member of the PEG. If possible, it would be useful to have early comments on this list fed back to either of us (kathy.pritchard-jones@icr.ac.uk; janez.jazbec@mf.uni-lj.si) in time for discussion at that meeting. Otherwise please feedback the comments from your national group or clinical trial group direct to the EMEA contact with a copy to SIOP Europe (secretariat@siop.nl).

The EMEA PEG is working on part 2 of the paediatric oncology needs drug list. It is currently under debate whether this list should include supportive care drugs which are mainly used in paediatric oncology rather than any other paediatric diseases. This part 2 list will be looking at new drugs available in oncology with the potential for paediatric

use. The ultimate aim of this work is to prioritise drugs for evaluation according to the needs to evaluate them in paediatrics. Clearly SIOP Europe and its partners such as ITCC should have a strong input into this process.

Action: All

- WHO list (attached)

Comments are also invited from SIOP Europe and its partner clinical trial and national groups on the WHO Essential Drug List for Oncology. This has been circulated previously and comments should be fed back directly to Professor Ian Magrath, INCTR (imagrath@inctr.be) who is co-ordinating this piece of work.

Action: All

Final comments:

The meeting concluded with a final discussion about how it was very useful to share information in this forum. It was agreed that the groups represented were interested in coordinating applications to the FP7 programme and in continuing to work on together on issues related to implementing and funding academic clinical research in childhood cancer. The meeting will continue to be organised at least annually and the current mailing list will be used to disseminate relevant information and requests for input from all national groups and clinical trial groups in Europe. *Please do send in contact details for any country/trial group that is currently not represented.* SIOP Europe will organise a further meeting/co-ordinate email discussion of the FP7 opportunities once they are published in their final form.

Action: SIOP Europe Board (KPJ and AB)

It was agreed that a dedicated website for the European childhood cancer research community would be very useful. The SIOP Europe Board are actively pursuing ways of achieving this.

A further question was raised about whether the vision should be to work towards a pan-European children's oncology group and how this might be structured. There was general consensus that the existing trial groups are very successful and that this strength should be built on. There would be benefits from working more closely together, and to share ideas and experiences in areas such as trial statistics, protocol design, adopting a more standardised approach to data collection etc. Maria Valsecchi is keen to organise further meetings of trial statisticians and there will be a relevant symposium on this topic during the next SIOP annual congress on September 21st in Geneva.

K Pritchard-Jones, on behalf of the SIOP Europe Board

List of Attendees, SIOPE Clinical Trials Group Meeting
7th March 2006
Amsterdam

Baila, Lilianna	EORTC and Belgium
Banikova, Karin	Slovakia
Bielack, Stefan	European and American Osteosarcoma Study Group (EURAMOS)
Biondi, Andrea	I-BFM and President, SIOPE Board, Italy
Bisogno, Gianni	European pediatric Soft-tissue Sarcoma Study Group (EpSSG)
Breatnach, Fin	Republic of Ireland
Creutzig, Ursula	German Paediatric Oncology and Haematology Group (GPOH)
Czauderna, Piotr	Childhood Liver Tumours Strategy Group (SIOPEL) and Poland
de Ridder, JG	Stichting Kinderoncologie Nederland (SKION), The Netherlands
Doz, Francois	French National Cancer Institute and France
Ferrari, Andrea	European pediatric Soft-tissue Sarcoma Study Group (EpSSG)
Garami, Miklos	Hungary
Grazia Valsecchi, Maria	I-BFM and International Trial Statistics, Italy
Hearn, Julie	Cancer Research UK, UK
Jazbec, Janez	Slovenia
Kebudi, Rejin	Turkish Paediatric Oncology Group (TPOG)
Kerrigan, Hilary	Republic of Ireland
Kortmann, Rolf Dieter	SIOP Brain Tumour Trials
Ladenstein, Ruth	E-SIOP Neuroblastoma and LCH
Morland, Bruce	United Kingdom Children's Cancer Study Group (UKCCSG)
Moschovi, Maria	Greece
Mueller, Judit	Hungary
Naafs, Marianne C	Parents Representative
Oberlin, Odile	European pediatric Soft-tissue Sarcoma Study Group (EpSSG)
Paolucci, Paolo	Task Force in Europe for Drug Development for the Young (TEDDY)
Pritchard-Jones, Kathy	Chair, SIOPE Clinical Trials Group and SIOP Wilms Tumour Trials
Rageliene, Lina	Baltic Society for Paediatric Oncology and Haematology (BSPOH)
Riccardi, Riccardo	Italian New Agents Group (I-NAG)
Schmiegelow, Kjeld	Member of the SIOPE Board
Schrappe, Martin	I-BFM
Stary, Jan	SIOPE Board; Czech Pediatric Hematology Working Group and the Czech Republic
Taskinen, Mervi	Finland
Tasso, Maria	Spanish New Drug Group and Spain
Uyttebroeck, Anne	Belgium
Vassal, Gilles	Innovative Therapies for Childhood Cancer (ITCC)
Verymylen, Christine	Belgium
Wesenberg, Finn	Secretary General, the Nordic Society of Paediatric Haematology and Oncology (NOPHO) and Norway

Apologies were received from:

Dr Sue Ablett
Dr Peter Arlett
Prof Y Benoit
Dr O Bjork
Prof. Joachim Boos
Ms Gabriele Braun-Munzinger
Dr Julia Dunne
Prof. Dr. RM Egeler
Prof Norbert Graf
Dr Guenter Henze
Prof Jan Inge Henter

Prof. Dr. A. Hirt
Prof.Dr. Med H. Jurgens
Prof WA Kamps
Prof. P. Kajtar
Dr J de Kraker
Dr B Lannering
Prof Sverre Lie
Dr. A. Navajas
Prof. Sebastian Nicolau
Dr Catherine Patte
Prof. A Pearson

Dr A. Saint-Raymond
Dr Alfred Reiter
Prof. Angelo Rosolen
Dr. Richard Sullivan
Dr M Serban
Dr. B.P. Sodre-Borges
Prof Mike Stevens
Prof David Walker
Dr Nicolas von der Weid
Dr Jeremy Whelan
Dr C Zwaan