Appendix C-4

Questions/comments received after the conference

In closing the meeting the European Commission gave the participants the opportunity to send some additional comments within 10 days of the conference.

The comments submitted are listed in this appendix.

Title and name	Organisation	Sector	Comment
Shayesteh Fuerst-Ladani	Kuros Biosurgery AG/EuropaBio	Commercial sponsors	• Companies more and more ask for scientific advice / protocol assistance before starting clinical trials and incorporate CHMP feedback into the trial design as at the end it is the CHMP that would review and accept/reject the study data for registration purposes. • Companies that do so submit clinical trial application to the respective competent authorities where the study should be performed. Some competent authorities question the study design that was agreed with CHMP and request changes although the minutes of scientific advice meeting was included in the CTA. • Would it be possible to have a link between results of CHMP scientific advice meeting and the competent authorities' assessment? Would it be possible that competent authorities mutually recognize the feedback from scientific advice? This is especially important for orphan medicinal products and paediatric studies.

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Dr David Baldwin	European College of Neuropsychopharmacology	Non-commercial sponsors	• The boundaries of experimental medicine are important and need to be clarified (and kept as broad as possible). If studies are unlikely directly to change clinical practice, they should not be classified as clinical trials, and the onus should not be that studies are clinical trials until proved otherwise, but rather the other way round. • The perhaps more major problem is that the directive makes it impossible to do small investigator-led trials of innovative treatments that we used to undertake under the old CTX system. These studies clearly have the potential to generate very important advances in understanding. Indeed, arguably all the major advances in clinical psychopharmacology were originally made by 'trials' of this kind. However, the administration and expense involved for conducting what are often simple and non-hazardous studies are prohibitive given current regulations. • We suggest that what is needed is a new class of study - 'a small clinical trial' with maybe under 100 participants, which could be dealt with as an experimental medicine protocol. In a literal sense that is what it would be. Without this change, the Directive will strangle research innovation in Europe, to the great advantage of our competitors in other continents.

Title and name	Organisation	Sector	Comment
Dr. Karin Heidenreich Dr Beatrice Oberle-Rolle Dr Detlef Niese	Novartis European Public Affairs/EFGCP Novartis Pharma AG/TOPRA Novartis International AG/Europabio	Commercial sponsors	Since we are of the opinion that the main difficulties of dealing with the Clinical Trials Directive lays with its implementation on Member State level rather than issues with the text of the directive, we propose: **As short term/mid term measures** • that the Commission, Heads of Medicinal Agencies as well as other relevant European authorities more actively endorse and support the harmonisation aspect of the directive • this can be done by giving the Clinical Trials Facilitation Group a legal status with the official mandate to harmonise the requirements for clinical trial application and safety reporting. We however consider that the meeting frequency of the CTFG group should be increased and reporting back to HMA should be a standard agenda topic at the HMA meetings. Furthermore the status of implementation of harmonisisation related to specific topics should be made publicly available. • electronic SUSAR reporting should be consistently used by all Member States' competent authorities • to avoid the bureaucratic paper overload of Ethics Committees we consider it necessary to adjust the directive to allow for quarterly adverse events (safety) listings. • EU definition of non-commercial sponsors currently excludes any agreement with third parties for later use of data for regulatory or marketing purpose or part of development program, we would ask for reconsideration of this and suggest that within defined limits this exclusion should be reversed. **As long term measures - change the legal framework** • to use the EudraCT database as a single point of entry for CTA for all multinational trials (The current process asks for submissions for a clinical trial application by each participating country. The proposal is that a single submission to EUDRACT should be sufficient and then shared electronically with all participating countries. This will also support a centralized CTA assessment.) • to have two parallel approval systems for CTA, a central (by regulation) for multinational trials and those products which require a centralised registration procedure and a national procedure (with the adjustment to the directive as requested during the workshop)

Title and name	Organisation	Sector	Comment
Annagrazia Altavilla	Task Force in Europe for Drug Development for the Young	Non-commercial sponsors	1. Comment: To implement the Directive 2001/20/EC in the different European Countries a stronger coordination seems to be needed. 1.1 Question: How are you planning to guarantee this coordination? 2. Comment: As underlined in our written submission as well as during the conference, some relevant international ethical/legal provisions related to the protection of subjects involved in clinical trials exist (see e.g. the Oviedo Convention and its additional protocol on biomedical research etc.). They could be a reference not only to reinforce human being protection but also to guarantee the equality of treatment among European citizens. 2.1 Question: Will these provisions be included in the Directive and Guidelines revision process? 3. Comment: Children only partially can be covered by the current European ethical/legal framework (for an in-deep analysis see TEDDY written submission and in particular provisions related, for example, to authorisation-assent/information process, risk minimisation, long-term adverse events occurrence, etc). 3.1 Question: Will specific ethical guidelines for clinical trials in paediatrics be considered in the next revision process? Will the art. 4 of the Directive 2001/20 be emended in order to meet specific paediatric issues?

Title and name	Organisation	Sector	Comment
Ms Ólöf Ýrr Atladóttir	National Bioethics Committee, Iceland	National Competent Authority	In Iceland we are experiencing an ambiguous and problematic situation concerning insurance for participants in clinical drug trials. We would like to ask whether there has been any inclination towards coordinating insurance requirements within the member states and whether it might be possible to start a discussion about these requirements with the .e.g. of establishing some base line.
Prof Alan Tyndall	European League Against Rheumatism	Non-commercial sponsors	1. The need to more tightly define a "commercial" trial in order to allow flexibility in unrestricted industry and third party funding of purely academic studies. 2. A desire for an ongoing dialogue with experts from EULAR and EMEA, rather than ad hoc problem solving meetings. Such a proposal was contained in the European Science Foundation bulletin 26, June 2006.

Title and name	Organisation	Sector	Comment
Prof Adam Cohen	Central Committee on Research Involving Human Subjects (CCMO)	National Competent Authority	**Comments** • Overload of SUSAR's reported to EC and CA. • Overload of substantial amendment for EC and CA. • Validity of data in Eudravigilance: some SUSARs are not reported, there are a lot of expected reactions in Eudravigilance, there are a lot of duplicates, it's difficult to create an informative output of data from Eudravigilance, difficult identification of IMPs in Eudravigilance: different names used for the same IMP. • Simplify the import of SUSAR's into the database for investigators in non-commercial trials • Quality of EU ECs is not clear. Review is not harmonised • The difficulties in filling out the current EudraCT application form imply a database with incorrect, incomplete data. The inconsistencies, generated by the system, are not clear to applicants. • Too much regulation that is too complicated. **Suggestions** • Less substantial amendments by a better definition. • Optimize Eudravigilance for analysis to create informative overviews. • Report all SUSARs to Eudravigilance. • Make Eudravigilance available for accredited EC to perform safety assessment. • Make a simple and informative electronic SUSAR report form with all the E2B mandatory data fields. • Establish an accreditations system for ECs in the EU • Evaluation, and then simplification and reduction of EudraCT application form to create an informative database is required. Make EudraCT available for EC. • Simplify the EU-directive, do not add extra guidelines and additional directives

Title and name	Organisation	Sector	Comment
Dr Umberto Filibeck Ms Angela Del Vecchio	Italian Medicines Agency	National Competent Authority	During Clinical Trial (CT) Conference, many reports, both by commercial and non commercial sponsors, asked for a modification of EU legislation aimed to a simplification of Clinical Trial Authorization (CTA) procedures to avoid multiple authorizations by National Competent Authority (NCA) of each Member State (MS) involved in multinational CTs as, for example: 1) an European Union Central CTA (EU CTA); 2) CTAs mutually recognised by Member States (MSs) 3) Measures aimed to avoid a double evaluation by Research Ethics Committee (REC) and CA in each MS. On this topics, AIFA (Italian Medicines Agency) GCP Inspectorate's opinion is: 1) an EU central CTAs could be possible only in a very limited cases, under the following conditions: a) a request by the sponsor on a voluntary basis; b) EU CTA allowed only for phase I CTs with Advanced Therapy Medicinal Products (ATMP) This approach is feasible because the number of these CTs is at the moment limited (only 10-15 per year, according to EUDRACT) and the predictable number by next 3 or 4 years will be not too high (may be 50-60 per year) to be evaluated , while all phase I CTs or all First Human Administration are too many (more than 1000 and more than 300 per year, respectively) to be evaluated by an EU Central Committee. 2) In order to avoid multiple evaluations by NCAs of different MSs, a CTAs mutually recognised by MSs could be acceptable for all CTs, except phase I CTs and CTs with ATMP phase I-II-III .

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			3) Alternatively to provision of point 2) and to avoid in each MS a double evaluation by REC and NCA we propose the following measures: a) only REC opinion and not a CTA as currently released (except a local, administrative and not scientific authorization, where required) for all CTs except CTs whose evaluation requires a specific expertise (as phase I and CTs with ATMP); b) RECs necessarily will evaluate also IMP quality and safety without any inconsistency with CT Directive, which provides that RECs have to release their opinion taking into consideration Investigator's Brochure, whose contents have to describe all data for the IMP quality and safety evaluation (ICH GCP). (Moreover CT IMPs exempted from a NCA evaluation are related to phases II and up and therefore, they have already been evaluated by CA in phase I); c) If RECs have doubts about IMP quality and safety, a NCA authorization will be required according to Directive 2001/20 provisions.

Title and name	Organisation	Sector	Comment
Prof Francois Lemaire	European Society of Intensive Care Medicine	Non-commercial sponsors	Research in emergency situations like cardiac arrests, strokes, acute respiratory distress, shocks etc. is a public health priority. But lawmakers have always had a hard time drafting relevant and pertinent legislation, as consent can never be granted from the patient himself or from any surrogate, rarely present on the scene. In such situations The US regulation allowed it in 1996 (21 CFR 50-24 (2 10 96). The additional protocol to the Oviedo convention specifically mentioned research in emergency situations (chapter VI, article 19). But directive 2001/20 forgot it (hopefully, unintentionally?) as it specified that consent always had to be obtained before research can be started, without any exception whatsoever. This was partially and not very clearly corrected in directive 2005/28, in recital 10 *("… The detailed rules adopted by Member States pursuant to Article 3(1) of Directive 2001/20/EC, to protect from abuse individuals who are incapable of giving their informed consent should also cover individuals temporarily incapable of giving their informed consent, as* in emergency situations.") But, as a consequence, the current situation within the EU is now totally chaotic, with a huge discrepancy of state members legislation: - some legislations, like in Belgium, the Netherlands, France and more recently in the UK, have a special provision concerning emergency research, allowing deferred consent under specific conditions (no added risk, research impossible to do with another population) - others have not, like Poland, Portugal, or Italy - others, like Austria and Germany, allow this waiver of consent only if there is a direct benefit to patients (forbidding de facto any type of non therapeutic research, even mere blood sampling) - deferred consent: has to be obtained in France from the patient, if he/she regains consciousness or from the legal representative, if it shows up later - use by researchers of data obtained under the conditions of emergency is rarely specified, giving the possibility to ethics committees to forbid it if the patient does not survive (as in the Netherlands, see E Kompanje in Intensive Care Medicine, 2007) The current situation is totally unacceptable, making multi-national studies extremely difficult to design and conduct, which was probably not the goal of the directive A clarification is necessary. Simple and pragmatic procedures for emergency research should be implemented in a revised directive.

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Prof Francois Lemaire	French Coalition of Academic Sponsors	Non-commercial sponsors	Directive 2001/20 has been implemented in all State members legislation since 2004. It became immediately clear for all academic sponsors that its provisions, designed for early phases of drugs trials (phases 1,2 and 3) sponsored by the pharmaceutical industry, were totally inadequate for post authorisation studies sponsored by Academia and other non commercial sponsors. A key distinction between interventional and non interventional research has been embedded in the directive. An *intervention* linked to research is indirectly defined in Article 2-c: - If a drug is not used according to usual care guidelines ("…*the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation…").* - and/or if research modifies the usual care of study patients ("…*No additional diagnostic or monitoring procedures shall be applied to the patients…")* **1. Current situation** Depending on the existence and range of the "intervention" added by the study protocol, all different types of (drug) research can be grouped in 3 broad categories: 1.1: Interventional studies This research is covered by the present scope of the directive. All procedures – for authorisation, monitoring, reporting of adverse events - have been designed in the perspective of early and inherently "risky" trials. All sponsors – including those from the industry- agree now that the implementation of these rules has considerably increased the (bureaucratic) hurdles imposed and at least doubled the cost of these trials. Non commercial sponsors and investigators have been vocal in claiming that it now made it very difficult for them to run such research. It is not within the scope of this note to argue whether or not this is legitimate, yet of even more concern to them is that the current regulation also concerns post authorisation studies, a domain of great importance for public health and in which non commercial sponsors play a major role. For this research, the current legislation is largely irrelevant and greatly dissuasive (see 1.3)

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			1.2 Non Interventional research The corresponding studies –observational, cohort studies…- have been left in a total legal vacuum. This lack of regulation was probably based on the absence of risks for patients, but it missed the point of the necessary control of the quality of data. It is why a recent European guideline (Vol. 9A) proposed a welcomed frame for such studies. But it has no binding value, and the present complete dys synchrony between State members will certainly pertain. 1.3 "minimally" interventional studies This is certainly a key issue for academic sponsors. Many if not most of the studies they fund and promote imply what could be called "minimal" interventions, like use of **questionnaires, blood samples, non invasive monitoring, and randomisation**. These interventions have no added risks to patients, but their quality needs to be adequately monitored and controlled, because of the importance for public health they usually have. For the "minimally" interventional trials, the current regulatory frame is largely irrelevant and should be revised. A "risk-adjusted regulation" could be introduced, as was repeatedly asked for by the recent EMEA/EC meeting attendees. **2. proposal** A pragmatic solution would be to introduce a third category of research, along with interventional and non interventional. The provisions for this third arm would be close to those proposed in Vol. 9A, with in addition a declaration to the Competent Authority, in order to guarantee traceability of trials and to make inspections by the CA possible. Such a possibility, identified as "*recherche portant sur les soins courants*" has been introduced in the French legislation in 2004 (law 2004-806). But, of course, it did not concern research on drugs, as it was not foreseen by directive 2001/20.

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Prof Janet Darbyshire	Medical Research Council, Clinical Trials Unit	Non-commercial sponsors	The UK Medical Research Council Clinical Trials Unit and UK Clinical Research Network are most grateful to the Commission and EMEA for holding the meeting on 3 October 2007 and allowing interested parties to contribute their views. There was substantial consensus from both commercial and non-commercial sponsors about the priorities to improve the implementation of the Directive. We would like to highlight a few issues that are of particular importance to us: 1. Sponsorship Large-scale non-commercial trials are commonly the result of international collaborations between several organizations, often with more than one funding body. International collaboration is a key element in answering questions of importance to patients and the public in a timely fashion, particularly in rarer diseases. For a non-commercial sponsor in one member state to take on all the responsibilities, liability and administrative burden of sponsorship in several other member states is a real barrier to undertaking such trials. The definition of a sponsor given in the Directive, "an individual, company, institution or organization which takes responsibility for the initiation, management AND/OR financing of a clinical trial", would seem to allow for the possibility of division of sponsorship responsibilities. And indeed, the regulations that transposed the Directive into UK law allow two or more bodies to take either joint responsibility for sponsorship, or to allocate responsibility for carrying out the functions of the sponsor between them. We were therefore very disappointed in the answer to Question 3 in the Questions and Answers published on the Commission Website with Volume 10, making it clear that a single sponsor was required. We fully recognize the importance of absolute clarity and for formal agreements that specify how the responsibilities are being divided between sponsors to be in place, but we believe that it would be of benefit to patients and the public to allow such arrangements to be made. The suggestion in the Q&A document that several parties agree to form a new organization to sponsor a trial and distribute the various duties between them is not a practical solution as considerable work, time and costs would be required to create a new legal entity, and it would inhibit new collaborations.

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			2. Insurance and indemnity Putting in place suitable arrangements for insurance and indemnity in other European member states is both complex and costly and requirements vary. Permitting separate sponsors in individual member states would help, but if the Commission were able to support the development of a harmonized approach that provided adequate protection to patients without undue financial burdens for sponsors, this would greatly facilitate multi-national non-commercial clinical trials in Europe. 3. Harmonization of processes though the Clinical Trials Facilitation Group (CTFG) We are appreciative of the work of the CTFG on streamlining and harmonization of processes across the member states. We would like to see this work taken further so that mutual recognition of authorizations for a clinical trial and substantial amendments becomes possible. This would greatly reduce the administrative burden in conducting multi-national clinical trials in Europe. It would also speed up clinical trials, which must be to the good of all. 4. Supply of drugs in the control regimen The requirement that medicines used in the control regimen must be provided free of charge is a financial burden for non-commercial trials, and is not always appropriate where the control regimen is the normal standard of care for that patient. In our view the normal arrangements for payment for drugs in each member state should apply.

Title and name	Organisation	Sector	Comment
			5. Eudravigilance We fully support the aims of Eudravigilance and would like to see it realize its full potential as a comprehensive source of data on serious adverse reactions in the European Community. The efficient sharing of information through submission of single electronic reports into one database that can be accessed by all those who need to receive the information should be an achievable goal. However the problems highlighted at the meeting arising from the variation in requirements of the member state competent authorities and leading to unnecessary administrative burden, duplication and omissions, should be addressed as a matter of urgency. Until uniform reporting requirements have been agreed and implemented at a European level, with a single data entry point, reports on paper should continue to be accepted by member state competent authorities. 6. Real acceptance of risk-based processes The implementation of the Clinical Trials Directive has raised awareness of the standards that the public should expect of clinical research. However, the risks to participants and the public associated with clinical trials of medicines vary greatly according to such factors as the level of knowledge, or lack of it, about a medicine, its known or anticipated toxicity, clinical familiarity with the product, the indication for which it is being tested, the characteristics of the population in which it is being studied, and the robustness of the trial design, etc. To expect identical processes in all circumstances is inappropriate, inefficient and costly. However, whether a trial is sponsored by a commercial or a non-commercial organization should not be relevant. We would like to see the same high standards applied to all clinical research, together with a real appreciation of the varying levels of risk reflected in the approach of the competent authorities to trial documentation, medicinal product labeling, and the expectations of inspectors in relation to pharmacovigilance procedures and trial monitoring.

Title and name	Organisation	Sector	Comment
Mr Francis P. Crawley	Good Clinical Practice Alliance – Europe	Non-commercial sponsors	**Appreciation** The Good Clinical Practice Alliance – Europe (GCPA) wishes to express its appreciation to the European Commission and European Medicines Agency for the 3 October 2007 Conference on the 'Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future'. The GCPA appreciated the excellent organisation of the conference as well as the open and generous spirit of dialogue demonstrated by the Commission and EMEA leadership. Following on the opportunity provided by Mme. Lalis in her closing remarks, we are pleased to provide here questions and comments in appreciation of the need for ongoing interaction and arriving at realisable actions and concrete solutions. Submitted here are 2 questions and 6 comments. The comments are provided in the form of suggestions for what the GCPA considers as short-term to medium term actionable items. **Questions** 1. Following the 3 October 2007 conference, do the European Commission and EMEA believe that Directive 2001/20/EC is a major contributor or detractor to public health in Europe. 2. Following the 3 October 2007 conference, do the European Commission and the European Medicines Agency (EMEA) believe that Directive 2001/20/EC is a key contributor or detractor in making Europe competitive in the global market place of clinical trials?

Title and name	Organisation	Sector	Comment
			Comments 1. A permanent and ongoing clinical trial legal, scientific, and ethics observatory should be established at the European-level for the ongoing review of the implementation of Directive 2001/20/EC into Member State laws, regulations, and administrative provisions to identify variances and provide guidance on corrective measures, as appropriate, and to maintain an ongoing evidence-based system for impact assessment. The review should be mandated to consider all law, regulation, administrative procedures, standards, and guidance related to clinical trials in Europe. The EU Clinical Trial Observatory should include a small scientific group, administration, and advisory panel consisting of representatives of patients, researchers, sponsors, and competent authorities. The observatory should operate according to published standard operating procedures. The information gathered and prepared reports should be regularly updated and published on an open-access public electronic web-based portal. 2. The European Commission should propose to the European Parliament and Council a limited number of amendments to Directive 2001/20/EC. The following amendments should be submitted for review: a. The EUDRACT database should be made publicly accessible for all clinical trials in its totality. EUDRACT should also be brought in conformity with the WHO 20 required items; it should be listed as a WHO Primary Registry; and consultations should be undertaken between EUDRACT and other key clinical trial registries: India, China, South Africa, US.* b. A publicly accessible clinical trials results database should be added to EUDRACT or opened parallel to EUDRACT. c. A clear definition of 'investigational medicinal product' should be added to the Directive. d. The term 'sponsor' should be redefined as follows: 'The legal entity responsible for the organisation of a clinical trial.'

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			e. The term 'investigator' and its definition should be deleted. (There is no further mention of the investigator in the Directive and the Directive assigns no responsibilities to the investigator. The definition provided in the Directive is, further, inaccurate (following on an error in ICH GCP). The primary responsibility of an investigator is the care of the research participants.) f. Sponsors should be made fully responsible for SUSAR reporting and SUSAR analysis. SUSARs should continue to be reported in a timely manner to the Eudravigilance Database. Reports to Ethics Committees of SUSARs should done periodically (e.g., every 3 months, every six months, every year, depending upon the nature of the clinical trial). SUSARs should only be reported to ethics committees in the form of 'notifications' (no actions required). g. All distinctions between commercial and non-commercial/academic clinical trials should be eliminated from the Directive. Sources and nature of funding are not GCP considerations. Similarly, distinguishing clinical trials on the basis of risk assessment is inappropriate.* 3. The European Commission Clinical Trials Facilitation Group (CTFG) should draw up a list of areas in which the 27 member states are in agreement and a list of areas in which the 27 member states have differences regarding the implementation of Directive 2001/20/EC. The CTFG should identify which areas of disagreement it will address and provide timelines for addressing these areas of disagreements. These lists and timelines should be made available for public discussion prior to finalisation. 4. Two representatives of European patient organisations should be invited to participate as observers in the meetings of the European Commission Clinical Trials Facilitation Group (CTFG).

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			5. The EMEA should develop a strategic plan for cooperation with Third Countries in clinical trials. This strategic plan should be made a subject of public debate during its development. 6. The European Commission should engage a global discussion on a revised GCP standard that corrects the inaccuracies and incompleteness of the ICH GCP (1996) as well as updates the guideline based on developments in clinical trials over the past 12 years. This revision process should not be limited to industry and regulatory authorities from the European Union, United States, and Japan. In particular, all regions of the world should be included and patients provided a leading role. *FP Crawley is a member of the World Health Organization's Scientific Advisory Group for the International Clinical Trial Registry Platform (WHO ICTRP) **FP Crawley is co-founder of the Vienna Initiative to Save European Academic Research (VISEAR)

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Prof Kathy Pritchard-Jones	SIOP Europe	Non-commercial sponsors	Thank you for giving us the opportunity to attend the joint meeting between Regulators, clinical trialists and the European Commission held on October 3rd, 2007 at the EMEA, to represent the point of view of academic clinical researchers in the field of childhood cancer working in Europe. We found the presentations and discussion stimulating but were concerned at the apparent divide between the views of the Regulators and those of the clinical trial groups. Clearly, there is a very marked difference in the perception of where the block to clinical research lies. We were very concerned to see that the presentations from the representatives of the Clinical Trials Facilitation Group thought that the EU Clinical Trials Directive was basically sound and that only some "fine-tuning" was necessary. This is very far away from the view held by the academic clinical trials community, who have struggled to find the resources (man-hours and money) to meet the exacting standards now required by the Regulators. These were designed to meet the needs of early phase clinical trials and our experience is that they have not improved patient safety in phase III trials. Indeed, the diversion of scarce resources to comply with the EU CTD has, in our view, compromised access to clinical trials, which are viewed as best standard of care for children with cancer. This has been a particular problem in paediatrics, where many drugs are used "off-label" since their manufacturers have never been required to address paediatric needs in their marketing authorisations. We appreciate that this situation is set to improve for the better for children with the Paediatric Regulation. However, the majority of clinical trials in childhood cancer, and indeed in paediatrics in general, will continue to test optimisation of therapy using existing products, many of which are out of patent. These are mainly used outside of their licensed indication, due almost exclusively to lack of testing in the paediatric age group. Most of the issues we raised in our written submission on behalf of professionals treating children with cancer in Europe were addressed during the meeting on October 3rd. However, we would like to re-emphasise two areas that cause us particular concern across several European countries and which we hope can be resolved by this fresh look at the European Clinical Trials Directive. One issue that was not discussed at the meeting on October 3rd and which is having a major and disproportionately negative impact on clinical trials in children is the definition of IMPs. The majority of phase III trials in childhood cancer compare two long established therapies, each of which would be considered "standard of care" by different national groups or introduce a new risk stratification.

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			Alternative designs are to intensify a standard backbone or sometimes to test the removal of a drug with known long-term side effects in the growing child (e.g. doxorubicin). If one takes the strictest definition of IMP, when applied to a product with a marketing authorisation, namely "when used for an unauthorised indication", then the majority of paediatric use of the current armamentarium of anticancer products falls into the "off-label" category. Since the majority of these drugs are already out of patent, there is no commercial interest in developing these products to include a paediatric indication in their marketing authorisation. Therefore, clinical trials in children which use these drugs have a disproportionate bureaucratic burden imposed upon them by the need to treat these drugs as IMPs. We did submit detailed comments on this point to the European Commission's Consultation on IMPs in Non-commercial Trials, in September 2006. We were therefore disappointed to see that the recent guidance on IMPs, issued May 2007, made no mention of any special consideration for offlabel use of drugs in children, when they have a long established safety and efficacy profile. We urge the Commissioners to readdress this important question in order to exempt the routine definition of any off-label use of a drug in children as an IMP within a clinical trial. Even with the reduced labelling requirements for marketed products described in Annexe 13 of the European Commission Guidelines on Good Manufacturing Practice, this places an unworkable administrative burden on already overstretched pharmacy staff. In some circumstances, these labelling requirements can negatively impact on recruitment to clinical trials, since it is likely that children would have to return to their main treatment centre for dispensing of all of the drugs they receive in the trial, whereas if they were a non-trial patient, they could easily receive the same medication via their local hospital, with considerable benefits for the quality of life of the entire family, such as increased school attendance, less loss of parental work time and earnings etc. We appreciate that the definition of IMPs and how strictly the guidance on labelling requirements etc is followed shows different national variations. Some countries are accepting that drugs with a long established safety and efficacy profile in children may not be defined as IMPs even though they are being used outside of their marketing authorisation. Clearly, it would be a benefit to children if there could be a harmonised approach to defining what should and should not be considered an IMP in relation to its use in childhood cancer, or indeed any paediatric disease. We would urge the Commission to facilitate a means whereby each of the currently used anticancer drugs without a licensed paediatric indication can be evaluated for their safety and efficacy profile to produce a common dossier that all clinical

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			trialists using these agents could refer to, in order to exclude their medicine being defined as an IMP. However, although the academic paediatric community has the expertise, it does not have the resources and administrative support to produce the required documentation in isolation. The final point which we wish to reemphasise but which was well discussed in the meeting, is the issue of trial sponsorship. We were disappointed to see that the representatives of the Regulators did not appreciate how great an obstacle this is to launching clinical trials. Indeed, as exemplified in our written submission, several important clinical trials in rare childhood cancers are failing to be activated in several centres or countries, due to the disproportionate bureaucratic workload to recruit just a few patients. In the meantime, the standard arms of these trials are being used as best practice (which indeed they are) but valuable clinical patient data is being lost to the trial. In our view, it is unreasonable to expect universities to accept the role of pan-European sponsor with all of the responsibilities as currently defined, as they have no aegis or understanding over healthcare systems in countries other than their own. This is a very important issue which must be solved in order to facilitate multinational non-commercial trials in Europe. In our written submission, we did make a suggestion that the roles and responsibilities of the pan-European sponsor could be limited to those of communication and coordination. However, this requires well-written contracts between the national co-sponsor and the overall sponsor. Currently, each trial group is drawing up these contracts from scratch with all of the expense of involving international lawyers etc. Again, it would seem sensible to have a harmonised approach and a single source of the necessary information and template contracts for academic trials to use.

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Ms Zoë Doran	European Group for Blood and Marow Transplantation	Non-commercial sponsors	Much reference was made to the need for definitions, in particular Investigational Medicinal Product (IMP) and Non-Commercial Studies. There was no discussion on how they should be defined. Many problems could be alleviated with clear and sensible definitions of these terms. Our suggestion for IMP would be "A novel agent being studied in a trial conducted by the prospective Marketing Authorisation Holder (MAH) as part of the process of registering a new product, be it Phase I, II or III." Our suggestion for a Non-commercial trial would be "Any study not being conducted by a MAH or prospective MAH as part of a registration programme or extension of a previously awarded marketing license". In the draft directive on non-commercial study the current 3.1.1. point 3 would preclude any funding of academic studies by industry, these may have already been amended but again we would like to point out the following: If use for marketing purposes or to strengthen the evidence for registration efforts is not permitted then there will be no benefit for Pharma to give grants, this would effectively kill academic studies. It is not clear how stakeholders are included in the consultation process. If the expertise represented in this meeting has been involved early in this process, then it is likely that many, if not most of the problems would have been averted. It was a great step forward to hold this meeting but it would be a step further if there had been a workshop type mechanism to debate solutions to some of the problems or perhaps this could be held in the future. The presentations were repetitive, but at least that reinforced the message that changes and clarifications are needed. In addition one would think that most of the delegates would wish to actively participate in future consultations without having to reply on keeping an eye on the website. The Commission should actively search out consultation partners rather than a passive reliance on interested parties seeing a draft in time. It appears that the Pharmacovigilance (PhV) issues are being actively and well addressed by the committee appointed to do so, but just in case we would like the following considered:

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			SUSAR reports should be analysed through the Eudravigilance database and a report generated evaluating the updated risk/benefit ratio. This should be submitted, not a meaningless line listing. The same mechanism should be imposed on MAHs in respect of SAEs. Current reporting requirements are suffocating the system and are detrimental to the safety of patients. I would doubt if any study has been suspended in response to SUSAR line listings. There should be one reporter of SUSARs, probably the Sponsor to prevent duplications. All safety reporting should be driven by the risk/benefit ratio, including frequency reports. Careful consideration should be given to who needs to know what, when. The issue of insurance must be addressed. It appears that in Germany there is active discrimination towards academic studies, we are informed by industry colleagues that they pay considerably less. The might of the Commission needs to investigate and ensure that reasonable insurance policies are available for academic studies. If the need for one overall sponsor was removed then we could almost go back to the old model of each institution sponsoring themselves. If the Commission wants a point person/institution then a lead investigator/institution for administrative purposes only could fulfil this role. Currently even if you delegate all responsibilities for sponsorship to each institution by contract, you would still be liable in law for any litigation.

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Prof Gunnar Alvan	Medical Products Agency, Sweden	National Competent Authority	**The Clinical Trial Directive (2001/20/EC)** had the highly relevant goal to improve "…good clinical practice in the conduct of clinical trials on medicinal products for human use…." Over time, the methods applied in Clinical Trials (CT) have developed considerably and now constitute an area of specialised competence and complexity. Among critical items to consider in relation to performing CT are the following: • design of protocol • often small and changing effects of drug • suitable biomarkers • difficult to treat severe diseases and special patient groups • finding suitable controls • placebo and active controls • ethics according to Hippocrates, Helsinki, EU and National • ethical (EC) and competent authority (CA) reviews and approvals • GMP of trial drugs and GCP all through • adequate analysis of results • results publically available, also negative • high demand on resources, human, health care, economical The directive was created and introduced with some effort, emphasizing eg general scope and consistency quality and reliability of observations, dual approval by EC and CA (fig) and time lines. It implied considerably changes in many countries.

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			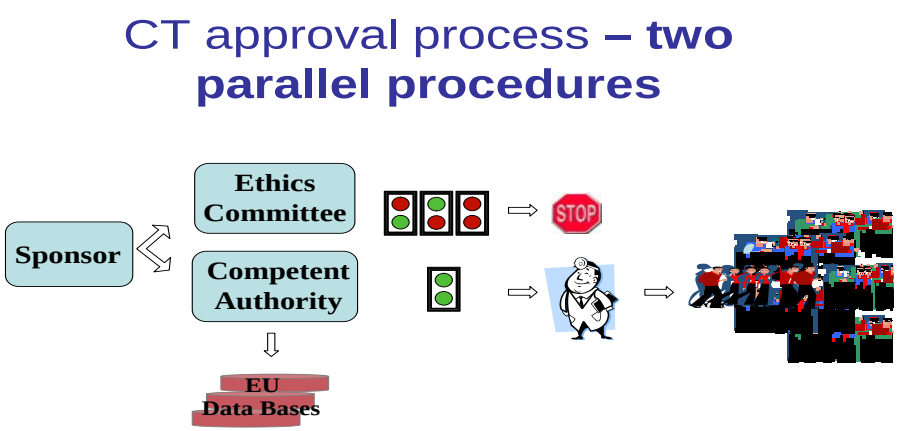 The Directive gives detailed instructions to the EC, for its judgement of CT applications as exemplified below. No guidance for the contribution of the CAs is given. 3a) the relevance of the clinical trial and the trial design 3b) …evaluation of anticipated benefits and risks… 3c) the protocol 3d) the suitability of the investigator and supporting staff 3e) the investigator's brochure 3f) the quality of the facilities 3g) adequacy and completeness of the written information, informed consent, persons Incapable of giving informed consent 3h) …compensation in the event of injury… 3i) …insurance 3j) …compensating investigators and trial subjects…agreement between the sponsor and the site 3k) …recruitment of subjects 5) …60 days…

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			A number of authorisations are given to CA and EC. Article 12 Suspension 1) …the CA shall inform other CAs, the EC concerned, the Agency and the Commission of its decision to suspend or prohibit the trial… Article 17 Notification of serious adverse reactions 1b) …suspected serious unexpected adverse reactions shall be reported to the CAs concerned and to the Ethics Committee concerned… 1c) Each MS shall ensure that all … serious adverse reactions … brought to its attention are recorded [CA] 2) Once a year … the sponsor shall provide the MS and the Ethics Committee with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects´ safety. 3a) Each MS…adverse reactions are immediately entered into a European database to which … only the CA of the MS, the Agency and the Commission shall have access. [CA, EMEA, Eudravigilance] 3b) The Agency shall make the information available to the CAs of the MS **Suggestion** It is time to clarify the procedure for CT approvals for transparency and cutting redundancies by defining what are the responsibilities of the EC and CA. **Responsibilities of Ethics Committee** General ethical aspects on the trial, its design, adequacy, use of human resources in relation to anticipated value of results, reference treatment e.g. placebo, statistical evaluation, informed consent, competence of investigator and resources available and information to participants. **Responsibilities of Competent Authority** Preclinical and clinical safety concerns about the investigational substance. Considerations on doses and dose- effect relationship. Possibility of drug interactions and pharmacogenetics. Possibility of duplicate or “marketing” study. Check whether safety cautions have been issued on the investigational drug. Labelling, GMP and GCP issues including inspections. All handling of adverse reactions, annual safety report if needed at all, power to suspend a trial.