ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC
PUBLIC CONSULTATION PAPER

Response of the Society of Pediatric Oncology and Hematology (GPOH) representing Germany and Austria

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Preamble:

This paper includes already a lot of background information and good ideas.It is not easy to answer some of the question, but we tried to do.
Our main problem is that our pediatric studies include all patients nationwide and represent the standard of care for these patients. These studies include at some extent new treatment options which can or should also include new drugs in general already tested in phase I/II studies in children and adolescents. On the one hand, these studies cannot be done by the pharma-industry, because of the study treatment algorithms which are not of particular interest for the industry. On the other hand, we need the assessment of new drugs because otherwise children will have no approach to them.
One solution could be the foundation of a European Institute for pediatric drug investigation with independent review, which can distribute the pharma-funding (which should be collected in a common cash desk for all trials), but does not depend on the interests of the industry.

Questions:

Consultation item n°1: Can you give examples for an improved protection? Are you aware of studies/data showing the benefits of Clinical Trials Directive?
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Since at this point, experiences with running clinical trials according to the clinical trials directive (CTD) are limited; it still has to be elucidated whether the CTD has indeed contributed to improved patient care/treatment/outcome. For example, the improved results achieved by the trials for treatment of childhood Hodgkin's disease and of relapses of malignant central nervous system tumors (HIT REZ) are more certainly the result of a modified study design than of structural changes. However, treatment modalities might be improved also for small cohort studies, such as by the transient myeloproliferative disease (TMD) study. That is why small cohort studies are so important; analysing these patient data may lead to optimized treatment and thus to higher safety of the patients.

In general, better pharmacovigilance as well as optimized concepts of quality control of both data and study centers might contribute to an improvement of the current situation. However, the logistics of SAE-reporting remain to be optimized. These, regarding conventional combination treatment, currently don't provide new information at all (especially not reporting to all investigators, since the quantity of reports is rather overwhelming than helpful).
The current reports are mostly not filtered. In case of frequent SUSARs concerning fatal or nearly fatal events the interpretation and judgment is most important as well as conclusions

concerning recommendations for therapy or monitoring for future therapies or studies. Only reporting will not improve the security for the patients.

SUGGESTION: Limiting SUSAR-information for principal investigators to quarterly reports as lists rather than as single reports, as suggested by the CTD on SAE-reporting. In addition, forwarding IIT-reports should be limited to events reported within the corresponding study and exclude those from others, such as the manufacturer.

Consultation item n°2: Is this an accurate description of the situation? What is your appraisal of the situation?
Page 12
Yes

Consultation item n°3: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?
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This situation is well-described - the Euro-LB study can certainly be considered as an appropriate example, since patient recruitment was lagging and finally had to be finished ahead of time due to serious difficulties with local national agencies. Also, the start of the study INTERFANT was delayed in Germany due to bureaucratic hurdles including patient insurance and ethics. These examples suggest that patient recruitment for small studies is challenged and patients cannot be treated according to currently best standard care regimens.

Only few GPOH trials opened after May 2004:

- new trials: 2002 - Apr. 2004: n=14
  May 2004 - 12/2009: n=7 (see Table page 6)

Some studies in rare diseases will even not be performed because the patient population is too small and the costs and the administration effort for national and especially for international studies are too high.

Concerning No 3.2 dot 1: the increased charge/staff needed by the pharma-industry is mentioned, but not what this means for academical trials.
A note is necessary for
No 3.2 dot 4 (last phrase): in pediatric oncology this even means NO ACCESS to standard of care WITHIN study protocols! These trials have not the aim of marketing authorisation, but partly only the aim of data collection!

Consultation item n°4: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?
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In our group preferable option 1: the assessment should be done by one Member State, hereinafter referred to as reference Member State.

Consultation item n°5: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?
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Options are currently incomplete. 3.4.1 deals with ethic approval and NCA. 3.4.2 excludes NCAs. Independent of this, 3.4.3 is most certainly relevant.

In Germany the main problem are the numerous and different drop-in centers for appraisal. A one-stop center for the NCA und EC would not only simplify and harmonize the procedure but also increase the quality of the appraisal. However, independently of this option the different options cannot be separated easily, because as well in the national as in the international area networking has to be improved. Clear objectives and duties of the NCA and EC have to be defined, taking in mind that implementation rules in the separate countries or institutions will lead again to very different contents and different times of appraisals.

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Consultation item n°6: Is this an accurate description of the situation? Can you give other examples?
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Yes, it is. In addition it has to be mentioned that "interventional trials" often include normal clinical practice with "off label" drugs, because these drugs are regularly used in pediatrics (especially in pediatric oncology).

One problem is the issue of interpretation of SUSARs – which is different in different studies and cannot be handled objectively.

Consultation item n°7: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?
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Yes for both points
There is a significant increase in costs when compared to the time prior to the CTD. Especially concerning the staff and in addition costs for monitoring (personal, traveling etc.); who should pay this for international studies?

The increase in cost was at least 40-100% per study. The smaller the studies the higher were the relative increase of costs per patient.

Example: ALL-Interfant protocol: Submission of the protocol to the ethics committees (EC) (15.01.08):
EC in charge 35 EC involved - Charges by the involved EC: 0 to 1,300 € ~ 6,000 €

Submitted documents and financial efforts
INTERFANT 99 vs. INTERFANT 06

		INTERFANT 99	INTERFANT 06
Study protocol		150 pages	317 pages
Patient information (documents to be read by the parents)		4 pages	18 pages
Application to the EC		1 copy of the protocol + covering letter	79 copies of the protocol + 25,000 pages additional documents
Costs	**Submission**	~ 7,- €	~ 3000,- €
	Insurance	0,- €	27.887,00 €
	Charges by the EC	0,- €	~ 6000,- €

(A. Mörike, DIRECT Symposiums, 15.-17. Mai 2008, Wien)

Example TMD study: Patients from about 1200 centers can be recruited (ie. ca. 30 patients per year). Hence, given the resulting high workload and low patient numbers, initiation of centers and investigators would rather be inappropriate than efficient. For example, the study for the treatment of acute promyelocytic leukemia (APL) recruits an average of 7 patients per year in Germany, however, participating in this study requires an initiation of about 50 treatment centers - efforts and expenses are too high, even for larger cohort-based studies. Patient insurance costs have increased (previous CoALL study: 17,000€ versus current offer: 100,000€). Also, the monitoring now required even for patients without change of treatment course has led to an immensely higher bureaucratic effort for approval and realisation of studies. For example, the form of the BfArm for the new CoALL consists of more than 200 pages to be filled.
Realization of an IIT is not possible without funding by the German Childhood Cancer Foundation or the German Cancer Society.

Consultation item n°8: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail? In particular, are the divergent applications really a consequence of transposing national laws, or rather their concrete application on a case-by-case basis?
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4.3.1
This question is difficult to answer, since the CTD is still lacking harmonization throughout the different member states. However, also the **concrete application** *is different in different countries due to different structures in the different countries.*

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

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Special patient groups such as children as well as the use of "off-label" drugs should not automatically be categorized as highest risk level. Accordingly, pediatric oncological therapy optimizing studies could be considered within lower categories, such as B and C for the insurances (B, standard treatment/care; C, medium risk such as most phase-III-studies).

The awareness of studies examining more than only an IMP must be increased; that is the normal situation in our trials. So far, these don't fit into the system, thereby causing difficulties already during the application process.
Example: What is the IMP in case of comparing the intensity of therapy courses or the order of these courses? The same concerns the definition of SAE's: severe haematological or infectious toxicities occur in most patients with leukemia not only in trials, but also with standard treatment.

Consultation item n°10: Do you agree with this description? Can you give other examples?

Yes, we agree

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Consultation item n°11: Can a revision of guidelines address this problem in a satisfactory way? *Probably yes* **-Which guidelines would need revision, and in what sense, in order to address this problem?**
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See preamble, our therapy studies are different from pharma studie. The aim is the optimization of therapy concepts, mostly with drugs, which were already used since many years. Therefore the rules are not adequate for our studies.)

Consultation item n°12: In what areas would an amendment of the Clinical Trials Directive be required in order to address the issue? If this was addressed, can the impacts be described and quantified?
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See **Consultation item n°11:** *our therapy studies are different from pharma studies – comparison of concepts – not of single drugs (see also preamble).*

Especially in pediatric oncology alleviated requirements for academic trials are necessary. Otherwise the standard treatment and their development / optimizing are endangered.

Consultation item n°13: Would you agree to this option and if so what would be the impact?
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We would prefer to say "yes" at this point. However, the question is what the different agencies in Germany will do as a consequence. The agencies treat all clinical studies the same way, but do not consider that clinical studies in pediatric oncology do not fit into the general scheme.
According to our opinion the directive should be tapered for academic trials. *However, to take our studies out of the directive may have consequences for future studies or for*

publications or it might be difficult to use such data in revised professional information. This is not assessable now especially concerning the needs of children.

For us the main point and the only way for international studies is ONE EUROPEAN APPROACH without national differences: ONE application, ONE ethical vote, etc. which are ADAPTED for pure academical studies, which are NOT focused of the market authorisation of a single drug, but will ensure the care of children with cancer.

Consultation item n°14: In terms of clinical trials regulation, what options could be considered in order to promote clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants?
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The listed "measures" like „enhance of transparency" and „avoid study duplications" are only of marginal importance: academic trials are of high importance in pediatric oncology. These studies have to be performed mostly in an international context. ***Therefore it is essential to find solutions for funding these trials on an INTERNATIONAL platform*** *(for one cooperative study), in case of study monitoring and logistic of SAE reporting (professional offers are extremely costly). To find the solution of the financial problems, which occurred with the EU Directive is the most important measure for the „promotion of clinical research for paediatric medicines" and even more for the STANDARD of care innovation.*

e.g. "off lable" drugs which are used since many years should not be regarded like new experimental drugs and not require the same safety rules

Consultation item n°15: Should this issue be addressed? What ways have been found in order to reconcile patient's rights and the peculiarities of emergency clinical trials? Which approach is favourable in view of past experiences?
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We have no experience

Consultation item n°16: Please comment? Do you have additional information, including quantitative information and data?
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Our experience are that these countries have an advantage to recruit patients, on the other side are the surveillance of the patients and reporting of SUSARs mostly bad, respectively, depending on the institution or clinic.

Consultation item n°17: What other options could be considered, taking into account the legal and practical limitations?
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The 2nd option seems to be good
The specialities of clinical trials in countries outside the EU are only touched here. The need of financing is important, in addition the already existing or not existing regularities in these country and taking over the responsibilities., Monitoring, auditing and inspections are other points, as well as the reproducibility of data and the education of study doctors and Study

nurses, etc.. It will be necessary to lay the foundations for this, in order to include these countries and their patients in the medical progress, but also to develop the possibilities for faster data recruiting, which will become in favour also fort the patients within the EU.

Consultation item n°18: What other aspect would you like to highlight in view of ensuring the better regulation principles? Do you have additional comments? Are SME aspects already fully taken into account?
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Our main points are:

1. ***The directive should be tapered for academic trials.***
2. ***The only way for international studies is ONE EUROPEAN APPROACH without national differences: ONE application, ONE ethical vote, etc. which are ADAPTED for pure academical studies, which are NOT focused of the market authorization of a single drug, but will ensure the care of children with cancer.***
3. ***It is essential to find solutions for funding these trials on an INTERNATIONAL platform*** *(for one cooperative study).*

TABLE: Active therapy optimising studies (TOS) in paediatric oncology according to the new EU regulations in centres of the GPOH[#]

DISEASE	STUDY SHORT CUT (Study Center)	TYPE/DESIGN OF STUDY - COLLABORATIVE SITES/GROUPS	RUNNING PERIOD	PATIENTS (n)
Leukaemias				
Acute lymphoblastic leukaemia (ALL)	**AIEOP-BFM ALL 2009** (Kiel, Germany/Monza, Italy)	*International (I-BFM), multicentric. interventional, randomised, controlled, prospective* - > 140 centres in Austria, Germany, Italy, Switzerland	01/2010/ -2014	4750 expected
ALL (infants < 1 year at diagnosis)	**INTERFANT-06** Rotterdam, The Netherlands	*International (I-BFM), intercontinental, multicentric, interventional, randomised, controlled, prospective* –	01/06-n/a ****	expected total enrollment **112** (total
Lymphomas				
Hodgkin-Lymphoma (HL), HL-relapse	**EURO-Net-PHL-C1**; Halle, Germany	*International, interventional, multicentric, randomised, controlled, prospective* – European network of paediatric Hodgkin's lymphoma (13 European countries)	01/07-01/13	expected total enrollment: **2150***
Central Nervous System (CNS) tumours				
Relapsed ependymoma, medulloblastoma, supratentorial Primitive Neuroectodermal Tumour (stPNET)	**HIT-REZ 2005** (intraventricular therapy with etoposide in neoplastic meningitis with subarachnoid tumor manifestation) Bonn, Germany	*International, interventional, multicentric, phase-II, safety- and efficacy-, window-, non-randomised, controlled, prospective* – Austria, Germany	02/06-01/12	expected total enrollment: 231 [> 3 months-30 years]
Other solid tumours				
Ewing sarcoma	**EURO EWING 2008** Münster, Germany Newcastle, UK	*International, interventional, multicentric, randomised, controlled, prospective* EUROpean Ewing tumour Working Initiative of National Groups: GPOH, UKCCSG, EORTC, SFOP, SIAK, COG	07/2009-2015	Total enrollment expected: **1371** [<50 years]
Soft tissue sarcoma (high risk)	**CWS-2007HR**; Stuttgart, Germany	*International, interventional, multicentric, randomised, controlled, prospective*	07/09-07/15	expected total enrollment: **320** [6 months-21 years]

[#] including international studies coordinated from other European centers
* 0-18 years at diagnosis;

** infants < 1 year are enrolled and treated according to protocol INTERFANT 99;
*** 0-21 years at diagnosis;
n/a: information currently not applicable
****study opened in Germany two years later
Abbreviations (see also list of abbreviations): BFM-Berlin/Frankfurt/Muenster-Study Group, COG-Children's Oncology Group (USA, Canada), COSS- Cooperative Osteosarkom Studiengruppe, EOI-European Osteosarcoma Intergroup, EORTC-European Organisation for Research and Treatment of Cancer, SFOP-French Society of Pediatric Oncology, SIAK-Swiss Pediatric Oncology Group, UKCCSG-The United Kingdom Children's Sarcoma Group, SSG-Scandinavian Sarcoma Group