



***"CLINICAL TRIALS DIRECTIVE"
IMPACT ASSESSMENT***

Response to the European Commission's
**"ASSESSMENT OF THE FUNCTIONING OF THE
"CLINICAL TRIALS DIRECTIVE" 2001/20/EC:
PUBLIC CONSULTATION PAPER"**
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1 General assessment of the CTD from cancer patients' perspective

Clinical trials have been a **key factor in improving cancer survival and advancement in treatment**. In 2005, the Karolinska Report concluded that the more cancer drugs there are on the market in a country, and the more quickly they are licensed for the market, the higher is that country's cancer survival rate. It has been estimated that fewer than 3% to 5% of patients with cancer participate in a clinical trial¹. It is well recognised that the effect on the ground has been to greatly slow the opening of trials, without a justifying large improvement in patient safety, which already had a good track record in trials in oncology, or an acceleration of pan-European cancer research.

Clinical trials are the principal means by which **new treatment approaches** are evaluated in medicine. It has been argued that randomised clinical trials provide the highest standard of care and at the same time help to contribute to scientific knowledge.

CTD has not led to harmonisation, making multinational trials now even more difficult

In looking at the feedback that we received from our member organisations (cancer patient organisations that extend over the EU27), we can say that the transposition of the Clinical Trial Directive has resulted in a multitude of opinions at the level of both national legislations and Ethics committees. **Too many procedures and safeguards applied without discernment to all kinds of research have contradicted in part the original purpose of the regulation, which was to protect patients and to ensure that clinical trials take place in Europe.** Differences in the legal traditions between the common law and civil law system allows for increased divergence between how the legal measure is *interpreted*. As a result, an assessment shows that e.g. UK clinical trials units were unable or unwilling to start in non-UK centres due to different interpretations in different European countries. Major reasons stated related to lack of central guidance, lack of clarity regarding local interpretation of guidance notes, and increased burden of documentation². Harmonization is need in the form of definition in the Directive. For example, protection of clinical trial subjects as set out in Article 3 allows for significant differences of "Informed Consents" across Europe both in term of quality and quantity of the information provided. **So what was really needed by patients – accelerating cancer research and making it more effective across country borders – has not been achieved.**

The CTD has severely impacted progress in optimizing cancer therapies

Most objections to this Directive were based on the conception that the Directive was conceived as a way of facilitating commercial drug development, and that therapy optimization trials and non-commercial trials were forced to fulfil the same requirements as their commercial counterparts³. Out of concern for the **future of academic research** after the implementation of the new Directive, the "**Save European Research**" campaign was started, calling on the European Commission to repeal its Directive. They argued that the new requirements would impose a much greater administrative burden to independent and academic clinical research. Several articles highlighted the essential role of independent research, and expressed concerns about the increasing influence of industrial funding⁴. Their concerns were not taken into account. Very few member states have put in place legislation that recognises the potential benefits of non-commercial clinical trials to patients and public health. Other member states claim that such exceptions are difficult to reconcile with the universally protective character of the legislation on medical research in humans, in view of the repeated mentions of universal patient protection in the GCP-Directive 2005/28/EC, issued as an addendum to the CTD 2001/20. In addition, no common definition exists in the EU to explain what a non-commercial trial is. Such trials may be very wide-ranging, including experimental research into new, unapproved chemical or biological entities, and therapeutic use research into established, approved drugs. For example, research that examines the therapeutic effects of varying dosage or application schedules has played a crucial role in improving overall cancer survival and spread of best day-to-day medical practice.

Due to the burden of the Directive, many groundbreaking therapy approaches are not scientifically evaluated anymore. Thus beneficial advancements in treatment of fatal diseases like cancer have been

¹ Sateren WB, Trimble EL, Abrams J, et al: How sociodemographics, presence of oncology specialists, and hospital cancer programs affect accrual to cancer treatment trials. *J Clin Oncol* 20:2109-2117, 2002

² J. Hearn, R. Sullivan, The impact of the 'Clinical Trials' directive on the cost and conduct of non-commercial cancer trials in the UK; *European Journal of Cancer*, Volume 43, Issue 1, Pages 8-13

³ Anonymous (2003)? Who's afraid of the European clinical trials Directive? *Lancet* 361(9376):2167

⁴ Bodenheimer T (2000) Uneasy alliance—clinical investigators and the pharmaceutical industry. *N Engl J Med* 342(20):1539– 1544

prevented. **European investigators – and patients – call for an adaptation of the Directive in order to promote research in critically ill patients and other patients who are not able to consent.**

The breakdown of numbers of clinical trials registered in EudraCT (1 May 2004 to 1 August 2007) show that there is not a high number of non-commercial sponsors. Clinical trial applications: 22.697 - Type of sponsors: a) Commercial sponsor: 18.319 (80,7%) and b) Non-commercial sponsor: 4.470 (19,7%).

CTD has created a shift from academic to oligocentric, industry-led cancer research

The Clinical Trials Directive has strengthened oligocentric, industry-driven cancer research and has severely affected non-commercial networks, collaborative and translational research. It has increased costs and delay from approval to first **patient in**, it has reduced the number of **trial sites** offering participation to patients, and it has led to a **further commercialisation of cancer research**. This is not in the interest of cancer patients, which benefit from competition between research entities for the best treatment and care, and access to best in class cancer care in all regions.

Since the Directive's application, key problems have been reported by academic researchers in published letters and conference presentations: 1) a requirement for single sponsorship for multicentre and, more demandingly, pan-European multicentre studies; 2) definition of the investigational medicinal product (IMP). The key question here is what portion of a patient's comprehensive medication scheme constitutes background and/or supportive medication and what portion is exerting the pharmacological effect under investigation; 3) *free-of-charge supply principle* of the investigated medicine, which requires that trial sponsors provide the IMP for free; 4) increased cost of insurance coverage; 5) increased cost of *quality assurance systems* for supervision of ongoing trials.

Cancer patients need effective research and a research-friendly framework in Europe. Not only drug development in optimized conditions, but also population-based follow-up and therapy optimization are essential to improve therapies and survival. Trials are often the last resort, especially for relapsed/refractory patients with no treatment options. The development of new innovative therapies for cancer depends on a combined (and competing) effort by commercial and non-commercial cancer research. This includes: (i) the discovery of new targets within cancer cells, and in cells interacting with tumours, against which new innovative cancer therapies can be developed, (ii) the clinical proof of concept of these new cancer drugs, essentially proving the theory that these drugs are effective and do provide benefit and (iii) the clinical development and clinical trials process to prove efficacy and effectiveness in comparison with established treatments.

However in Europe, the **median duration of regulatory procedures was longer** in countries where the CTD applies, compared with countries following local legislation (75 vs. 59 days; $P < 0.001$). Five EUCTD countries had a time to approval of >60 days (maximum within EUCTD rules). The long duration of regulatory procedures was the consequence of (i) sequential instead of simultaneous submission of trial application to regulatory authorities, and (ii) involvement of local ethics committees in procedures that should be followed only by central ethics committees. The duration of regulatory procedures was similar in Australia (67 vs. 68 days, $P = 0.388$), but significantly shorter in the USA (67 vs. 15 days, $P < 0.001$).⁵

Directive 2001/20/EC has a particularly wide scope and applies to every clinical trial on medicinal products, whether sponsored by industry, government, research organizations, charity or a university. It does not address the specific concerns of non-commercial clinical trials and their particular situation that they exist within. Innovative clinical and translational research, instigated and conducted by motivated physician-scientists, has had an important part in the development of modern oncology. For example, **adjuvant treatments for breast and colorectal cancer, shown in randomised trials to be effective in preventing recurrence, have been developed and tested through research performed largely by academic clinicians**⁶.

Through his research, Hannings highlighted this by stating that 'by the end of 2005 one group in Cardiff noted that they had "almost stopped doing drug studies", and it was estimated that the number of European trials submitted for grants or ethical review had fallen by 30% to 50%, and that the proportion

⁵ Hiddo J Lambers Heerspink, Daniela Dobre, Hans L Hillege, Diederick E Grobbee, and Dick de Zeeuw.; Does the European Clinical Trials Directive really improve clinical trial approval time? Br J Clin Pharmacol. 2008 October; 66(4): 546–550

⁶ Akseli Hemminki Harmful impact of EU clinical trials directive, BMJ 2006;332:501-502 (4 March)

of non-commercial trials was reduced from **40% to 14%**⁷. The largest independent cancer research network in Europe, **EORTC**, has reported that the number of new trials dropped from 38 in 2001, to 19 in 2004, to seven in 2005; trial costs have increased by 85% and trial initiation was five months slower⁸. Senior oncologists have concluded that cancer patients in the future “should be worried”⁹.

The CTD achieved that cancer studies are now predominantly carried out by the pharmaceutical industry – or are not done at all. Clinical research that was carried out in the past by non-commercial institutions like university hospitals decreased, while industry dependent studies with commercial interest increased. Furthermore, even we observe that **investigator-initiated trials are now trying to include investigational compounds just to secure sufficient trial funding from the industry.** So what has previously been done independent of commercial interests is now dependent on the industry.

CTD has severely impacted conduct of paediatric cancer trials

The Directive had also led to the abandonment of e.g. a trial to address fibromyalgia, and of a trial of melatonin, and it was eroding the normally very high rates of recruitment into pediatric cancer trials (an area of very little interest to the pharmaceutical industry)¹⁰.

Regarding paediatric clinical trials, McMahon highlights that there were around 10-20 studies in paediatric oncology starting per annum before implementation of the Directive, and this has afterwards dropped significantly. The future of non-commercial pediatric trials in general is in difficulty, as the number of studies “decrease dramatically in the future”.¹¹ The results of this study confirm a decline in the number of European and UK research studies involving human subjects in the 3 years following the introduction of the ECTD, and a disproportionate decline in the number of CTIMP studies. Expressed as a percentage of research studies involving human subjects, the decline in reported CTIMPs has fallen significantly (Europe 9.2%; UK 5.2%)¹².

Examples from Oncology where CTD had a major impact

ECPC would like to provide some anecdotal examples about the Directive's impact on cancer research, as received from clinicians our members have been in touch with:

- **Acute Lymphoid Leukaemia:** More than 80% of all adult ALL patients and more than 90% of all childhood leukaemia patients were treated within trials prior to the CTD. Rates have significantly gone down with the CTD, despite a great unmet need not addressed by single drugs: Adult ALL still has a survival of approx. 8%.
- **Low grade lymphoma (2007, OSHO 70 study).** Protocol approval process took four times longer (2 years) to complete under the CTD. Costs for CTD approval rose by tenfold to 50.000 EUR. Many investigators backed out during the prolonged process, and finally of 150 centres that agreed to participate, only 56 enrolled patients in 18 months. Recruitment rate of earlier trials dropped from 150 patients/year before CTD to 70/year in newly setup trials.
- **Acute Myeloid Leukaemia (AML).** From 5 study groups that performed multicenter trials for many years, 4 decided to participate in industry studies instead of performing own non-industry studies.
- **Acute Lymphoid Leukaemia (ALL) in elderly patients.** The same post-CTD study recruiting just 25 patients recruited the first patient in Germany more than 1 year after France, due to Ethics review procedures, increased fees and heavy safety reporting despite using only approved medicines.
- Phase III studies in **Multiple Myeloma and Chronic Lymphocytic leukaemia (CLL)** in Ireland: The IMB did not agree with the Risk Management Plan in Multiple Myeloma phase III protocol, although it

⁷ Hall JE, Diaz-Navarro C (2005), Living with the European Clinical Trials Directive: one year on. *Anaesthesia* 60: 949–951; Bosch X (2005) Europe's restrictive rules strangling clinical research. *Nat Med* 11: 1260.

⁸ Hemminki A, Kellokumpu-Lehtinen PL (2006), Harmful impact of EU clinical trials directive - Academic clinical research in cancer seems to have no future in Europe. *BMJ* 332: 501–502. . Rice M (2006) New data on clinical trials directive in Europe show few favourable outcomes. *J Nat Can Inst* 98: 159–160.

⁹ Sinha G (2006) European move affects academic trials research. *J Nat Can Inst* 98: 1100–1101.

¹⁰ Hanning CD, Rentowl P (2006), Harmful impact of EU clinical trials directive - Trial of alerting drug in fibromyalgia has had to be abandoned. *BMJ* 332: 666.; Watson M (2006), Harmful impact of EU clinical trials directive ... and so has trial of melatonin in cancer related weight loss. *BMJ* 332: 666.

¹¹ Cannell E (2007) Clinical Trials Directive slows registration of paediatric studies. *Lancet Onc* 8: 10.; Welzing L, Harnischmacher U, Weyersberg A, Roth B (2007) Consequences of Directive 2001/20/EC for investigator-initiated trials in the paediatric population - a field report. *Eur J Ped*; 166: 1169–1176.

¹² AD McMahon, DI Conway, TM MacDonald, GT, The Unintended Consequences of Clinical Trials Regulations, *PLoS medicine*, 2009

is identical to the Risk Management Plan for the same commercial product. Study could not be initiated for over 1 year. Clinical trial applications for same product for two other phase III studies in CLL could not be submitted due to unresolved issues with Risk Management Plan. **All three studies were approved at least 12-18 months earlier in all other 11 participating EU countries.**

- The **German Hodgkin Study group** was required to provide 100.000 copied pages of documents to Ethics reviews and authorities for a single study with 280 participating clinics and 65 ethics committees. Furthermore, the **GMALL study group** had to provide 35 folders and 12.000 pages for a study conducted in 13 centres.
- **T-Cell Prolymphocytic Leukemia (T-PLL)**. Approximately 50-100 cases per year occur Europe-wide, leading to death within 2 years. For more than 3 years, the Germany CLL Study group has tried to initiate a pan-EU Study (T-PLL2) but failed on bureaucratic hurdles: The costs for the trial for 14 patients would have been 400.000 EUR (29.000/patient), for 30 patients 523.000 EUR (17.000/patient). Since the first T-PLL study that was initiated before the CTD, no progress in that disease has been made. **Rare cancers and rare molecular subtypes** are no longer covered, because these studies are only feasible internationally due to low number of cases, which has become impossible under the “sponsor” definition of the CTD, and as long as not more than 3-5 cases per trial site can be expected.
- **Cancer patients with co-morbidities** (e.g. secondary cancers due to earlier chemotherapy) **or older patients** are no longer treated within clinical trials, as industry-led studies strive to assess drugs in ideal conditions – very different to follow-up/therapy optimization trials which aimed to cover large parts of a population.

Summary

ECPC welcomes that the Clinical Trials Directive introduced Good Clinical Practice (GCP) principles to ensure that trials are conducted in accordance with high standards of ethics and science. Although the practice of GCP were standard in all Member States, only a minority of Member States had previously codified the obligations of the different parties and the involvement of the competent authorities as now imposed by the Directive.

However, ECPC believes that even if the CTD provided some benefits like central trial registration, CTA principles, and some reduction in complexity in Ethics reviews and standards in informed consent, it has severely hampered cancer research in Europe, and threatens to further destruct existing multi-national research networks which have been established prior to the CTD.

The Directive and implementing guidelines imposed many administrative requirements that did not exist, or were not similarly developed in the Member States. Especially exhaustive reporting on adverse reactions and on the qualification of doctors seem to have led to problems causing a reduction of participating centres and hence local availability of cancer trials to patients.

The CTD has created many additional burdens for the conduction of trials, while it did not meet the primary objective of harmonizing and simplifying the legislation in the Member States. Whilst the CTD was based on the requirements for studies aiming to approve distinct drugs or modalities (commercial studies), it did not take into account studies to improve treatment or diagnostic procedures on the basis of already approved drugs or modalities (investigator-driven trials, therapy optimization trials) irrespective of potential commercial consequences.

Suggestions

ECPC thinks a future revision of the Directive or Regulation on Clinical Trials should reflect the following points:

- **Risk-adapted approaches should be considered.** *Therapy-optimization and follow-up studies* with drugs or modalities for which the efficacy and side effects are known through approval and daily practice should follow a less strict framework than studies that aim at approval of a *new compound or modality*. New drugs require complete documentation of safety parameters. Approved drugs are known well, so differences in side effects and/or efficacy between different regimens or modalities are relevant. This might result that only clinically relevant SAEs need to be filtered and distributed to every single investigator. In oncology, SAEs are very frequent given very aggressive diseases and treatments which, following the CTD, have created a flood of SAE reports which have in practice decreased patient safety.

- **Applicability to non-drug trials should be re-considered.** For example, stem cell transplant does not use "Investigational Medicinal Product".
- **Assessment of cost/benefit of new insurance requirements.** The increased requirements of the CTD on insurance has created expectations amongst patients, however in cancer it is unclear whether this has really been a necessary step. It is unclear to patients what risk is now insured in comparison to pre-CTD, and where patient protection has been increased with this. Adequateness of insurance requirements should also be reconsidered also *in long-term observational* studies in oncology, e.g. when following up for 10-15 years.
- **Patient involvement in Ethics Committees** should be considered, to make sure ethics review is patient-centric and does not overestimate risk over potential benefit. Divergence and lack of coordination in their conclusions of patient involvement on Ethics Committees across different Member States should be assessed.
- **Increase transparency of public information about trials**, e.g. registry, minimum data set for all trials, easy to read and available in key languages. (EudraCT made public - lack of availability of information on ongoing/concluded clinical trials to the patients and general public, Article 11) – Presently, legislation in several countries mandated the registration of clinical trials as an effective means of promoting information access and full transparency in medical research. However, comprehensive registers have not been adequately supported by law, particularly in Europe, where legislation has ironically contributed to fragmentation rather than harmonisation.
- **Therapy continuation when trials end.** Need to offer extent of (experimental) treatment at the end of the trial free of charge for patients, to make sure those that benefited from the trial medication can continue to do so.

2 Comments to the Consultation Items of the Impact Assessment

2.1 Consultation Item N°1: Multiple and divergent assessments of clinical trials

Member State	Drug trials	Multi-modal therapy trials	Radiotherapy trials	Surgery trials	Behavioral / Cosmetic product trials
Belgium	Loi du 7 May 2004				
France	Loi n° 2004-806 du 9 Août 2004				
Germany	12. Arzneimittelgesetz-Novelle		Strahlenschutzverordnung		
Italy	Decreto N°211	Decreto 17 Dec 04	A definition for 'Therapeutic strategy trials' is provided in the decree		
Netherlands	Wet medisch-wetenschappelijk onderzoek met mensen (WMO)				
Spain	Real Decreto 223/2004				
Sweden	Läkemedelsverkets författningssamling (LVFS 2003 :6)				
UK	Med. Human Use Regulations 2004				

Although the EU Member States were required to have implemented the Directive by May 2004, not all Member States were able to transpose the Directive in their national legislation by this date. There does not seem to be much harmonisation of laws across the European Union, one of the main goals of the

Directive¹³. This requirement is needed as because proportionally the majority of clinical trials are carried out in multiple sites – single site clinical trials represent only 6.412 (28,2%) while multiple sites trials represent 15.017 (66,2%). This is also shown by the fact that before the CTD came into effect, majority of clinical trials were carried out in multiple Member States which represented 60.1% of clinical trials carried out in Europe. However there are indications multi-nationality of trials has reduced largely through the CTD.

- **Article 9 (2)** of the Directive states that, before commencing any clinical trial, the sponsor will be required to submit a valid request for authorisation to the competent authority of the Member State where the trial takes place. **Article 9 (8)** confers power on the Commission to draw up and publish detailed guidance on the application format and contents of the request.
- However, a comparison of revised legislative texts in eight EU member states shows that differences remain for many types of clinical trials. France appears to have the most comprehensive legal definition on biomedical research, with public authorities rigorously supervising all kind of trials, including those on cosmetics. The Directive was set up with the intention of governing clinical research into medicinal products (medicines, drugs). Therefore, problems may arise in applying the Directive to trials that investigate complex modes of treatment¹⁴.
- As a consequence, researcher were obliged to fulfil the new guidelines of the Directive for some of participating centres, while for other centres their original national requirements were still applicable. Due to this dichotomy in requirements, the responsibilities and obligations of our hospital, as the initiator and coordinator of the study, were not completely clear, not even to the Ethic Committees or Competent Authorities involved. **Most member countries implemented the Directive with only the deep pockets of industry in mind, the scientists argue.**
- The **linguistic problems** in the communication with the local authorities of some of the countries, demanding correspondence in their own local language, hampered communication considerably. Surprisingly, in most cases an English translation was not accepted, since in certain countries official documents will only be issued in their local language. Obviously, official documents need to be in a mutually understandable language and the sponsor cannot sign a contract in a language he does not understand. Next to these linguistic problems, most official documents still refer to several national laws of which we did not know the exact content.
- The lack of central guidance, lack of clarity regarding the interpretation of the guidance notes, and increase in essential documentation and paperwork were causes of major concern for experienced staff who were anxious about whether they were interpreting the Directive correctly. Moreover, the CTUs were unable or unwilling to open trials in non-UK centres because of the different interpretation of the EUCTD by member states.
- Art. 6(1) sets out the rules for Ethics committees. They state that they should adopt relevant rules of procedures (functions and operations) to implement the requirements set out in **Directive 2001/20/EC Art. 6 and 7**. However, the principles and guidelines for these rules and procedures are not detailed and there is no full set of provisions in or referred to in the Directives that ensure that **Ethics Committees work in accordance with (ICH) GCP**.
- **Liability factor:** Problems caused by the CTD 2001/20 arise from the multitude of liabilities affected by each clinical trial. Many of the open questions have to be solved by each individual EU member state. Each state is responsible for tort and liability issues, for public health care provisions including reimbursement, and for science and research. Therefore, rules for non-commercial trials in the EU continue to be divergent: on the one hand, clinical trials are subject to the harmonization obligations of the EU, and, on the other hand, they are subject to the legal codes of each individual member state where the trial is conducted. This discrepancy inevitably leads to a significant rise in administrative workload for large, multinational clinical trials because such trials must obey a host of different administrative requirements in each country in which they are conducted.

¹³ Hartmann M, Hartmann-Vareilles F (2006) The clinical trials directive: how is it affecting Europe's noncommercial research? PLoS Clin Trials 1: e13. doi:10.1371/journal.pctr.0010013.

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

In short, there is no evidence that the intense bureaucracy of centralized politically driven procedures has improved the care of trial participants to a significant extent. As administrative burden increases, the efficiency of the trial process decreases. There is a phrase for over interpretation of regulatory advice that is sometime used when discussing EU competition and tendering rules called “regulatory creep.” Hearn and Sullivan have pointed out that “regulatory creep” is being caused by over interpretation of trial “guidance”. Instead of regulatory creep in clinical trials, ECPC would like to see some “regulatory retreat” where academics try to ensure that the interpretation of any rules and procedures that are not mandated by law are the most favorable for research whilst ensuring patient safety.

2.2.1 Administrative costs for clinical trials, and thus clinical research, increase without added value

Under the new Directive, application forms have grown to the size of books, carrying a message of general distrust of physicians, and information requested should bear relation with its purpose. Administrative concerns remain in a number of areas, including:

- **lack** of infrastructural support available
- **burden** of safety-reporting requirements on all parties, with limited benefit
- **need** to address specific situations such as consent in emergency-care settings
- **differences** between Member States in application forms and dossier requirements for **submission** to ethics committees
- **complex interactions** between local and regional/national administrators in arriving at a single opinion
- **access** to information for committees, in particular the EudraCT and EudraVigilance databases
- **need** for clarity on the applicability for different sponsors

2.2.2 “Patchwork” of separate assessment procedures of clinical trials by the various national competent authorities of the Member States concerned

- Despite the new Directive, **separate approval** from each national authority is still required before a clinical trial can start (e.g. in the UK, the MHRA).. This, in combination with a lack of uniformity in the procedures and communication in a mutually understandable language, make conduction of clinical trials a needlessly difficult experience.
- In terms of ‘**informed consent**’, In the UK - although the Medicines for Human Use (Clinical Trials) Regulations 2004 governs the design and conduct of clinical trials, research in general is governed by, inter alia, the common law principles of battery, consent and negligence. As far as consent is concerned, by law a person cannot consent to the infliction on himself of grievous bodily harm or his or her own death. The level of risk involved in any research project must be ascertained prior to commencement. Guidance on this matter has been provided by interested parties. The Royal College of Physicians has delineated different categories of risk for research and suggests that participants should only be enrolled where the benefit outweighs any potential detriment. Consent based upon adequate information with understanding is an essential prerequisite, whatever the level of risk involved. In the event of litigation, it would be a matter of evidence as to how much information had been provided to the participant. Furthermore, recent case law has indicated that failure to warn about a risk (even one that is inherent and may materialise without fault or negligence) can lead to liability in law. Whether these principles of clinical negligence might apply to injury or damage occurring as a result of participation in a research project remains to be tested in court.
- This should not only be a central **Ethics Committee** that approves the trial for all European countries, but a central organ that also provides the authorization for all Competent Authorities involved. This would have significantly contributed in simplifying and harmonizing the legislation regarding clinical trials.
- The Directive made no direct exception for **emergency and critical care situations**, and therefore threatened to prevent all emergency trials causing loss of decision-making capacity and facing (very) short therapeutic time windows. However progress in therapy development for emergency situations might be essential especially in life-threatening diseases like cancer.

2.2.3 Inconsistent approach to the Clinical Trials Directive leads to longer delays for starting the clinical trial (“first patient in”), thus depriving patients of the results of clinical research.

The EU Directive is still not entirely enforced by all national countries such as the requirement that explicitly requests a single IEC approval within each national country. In Germany, a local IEC approval is needed for every investigational centre, plus a national IEC opinion, meaning that if you plan a multicenter trial, involving, e.g., 20 German centres, 20 local IEC positive approvals are required

2.3 Consultation item n°3: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

2.3.1 Reliance on voluntary cooperation of NCAs

Cost/complexity factor of "single sponsorship": The directive specifies that a single “sponsor” – be that a person, a company, or an organisation – must take overall responsibility for the initiation, management, and financing of a trial. In practical terms, sponsors would deal with submission of trial applications (for both drug manufacturing and ethics approval), trial registration, and pharma-covigilance. For the pharmaceutical industry, this is not a new concept, but for publicly funded trials the practicalities are unworkable. How can a principal investigator take on the responsibility of pharma-covigilance across multiple trial sites in one country, let alone in a multicentre international trial.

Different NCAs can ultimately reach different conclusions about the award of the CTA, and different NCAs can make different requests for amendments to the research proposed. Voluntary Harmonised Procedure (VHP) provides an option to tackle this but it is accepted that it would not be possible to assess multinational trials through VHP. Furthermore, VHP still involves long delays in starting clinical trials.

2.3.2 Community-wide streamlining of NCA-authorisation process for clinical trials

2.3.3 Streamlining the procedures

- The Directive's definition of a sponsor leaves room for doubt over whether **international co-sponsorship could also mean co-liability**. The obligation of the sponsor to provide insurance or indemnity to cover the liability of the sponsor and the investigator is perfectly reasonable, however, if the sponsor has to accept liability for areas beyond its control, as would be the case in an intergroup trial involving international cooperation and different national laws, many academic organisations will not be prepared to take the risk. Clarification in terms of key question here is what portion of a patient's comprehensive medication scheme constitutes background and/or supportive medication and what portion is exerting the pharmacological effect under investigation.
- To conduct clinical research in compliance with existing guidelines and national regulatory requirements is a challenge not only for an academic research center, but even more for local oncologists treating patients within long-term observational trials. The implementation of the current binding rules in the daily practice of a study center **requires administrative staff dedicated to the conduct of clinical trials**. The organization and structure of the research staff have to be adjusted to the growing needs of the regulation. Local oncologists, even if strictly following the guidelines of a therapy optimization trial, cannot afford to establish a research director or administrative staff just for the different domains of clinical trials. The regulatory burden is now obstructing high quality science and has become the biggest single threat to research carried out in academia.
- Drug trials initiated in academia have similarities with conventional pharmaceutical company trials but often also important differences. The primary aims of academic trials are to **improve patient care using existing treatments rather than to develop new pharmacological**

entities. Among the Directive's requirements are the obligations that one sponsor take total legal and financial responsibility for a trial - be it national or pan-European, industry or academic. Many charities and academic groups have found that they cannot afford the financial burden that this stipulation imposes or the increased administrative burden that has resulted from compliance with other directive requirements.

- Since the Directive's application, **key problems have been reported by academic researchers** in published letters and conference presentations: 1) a requirement for single sponsorship for multicentre and, more demandingly, pan-European multicentre studies; 2) definition of the investigational medicinal product (IMP). The key question here is what portion of a patient's comprehensive medication scheme constitutes background and/or supportive medication and what portion is exerting the pharmacological effect under investigation; 3) free-of-charge supply principle of the investigated medicine, which requires that trial sponsors provide the IMP for free; 4) increased cost of insurance coverage; 5) increased cost of quality assurance systems for supervision of ongoing trials; and 6) increased cost of submissions to ethics committees, national authorities, and fees for GCP inspections, carried out by national authorities or the European Medicines Agency (EMA). These are a particular burdensome on commercial trials, and for investigators who want to start their own, independent research.
- A comparative analysis of Member States' provisions illustrates that the promises of the Directive have not been fulfilled. To resolve liability issues, in each country **cascades of agreements** have been required between investigators and hospitals, hospitals and their public or private shareholders, and between hospitals' owners and the state authorities. It appears that member states with tax-financed public health systems, such as in the UK or Sweden, have found it easier to solve the liability problem of public sponsors. For example, in the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA), Universities UK, and the Department of Health have carried out a regulatory impact assessment¹⁵. This assessment has enabled charities and associations in the UK to act as a sponsor in multinational studies taking place across the EU.
- The European Commission has recently provided a new definition for **non-IMPs** (NIMP), clarifying the current situation considerably. The new definition states that "support or escape medication for preventive, diagnostic or therapeutic reasons" or medications "used in accordance with the protocol to induce a physiological response" should be distinguished from an IMP. However, many other aspects of the Directive still remain to be commonly understood or adopted. **For example, the issue of reimbursement or supply chain of commercially available drug supplies by public health insurance systems is still problematic.** For trials in oncology that test the best therapeutic use of innovative medicines in combination with existing therapy schemes, the free-of-charge supply implicates cost takeover of investigated medicines as well as of established co-medications. In Italy, Belgium, Sweden, and the Netherlands, specific mechanisms have been set up for non-commercial trials, which allow for public cost takeover for tested drugs and co-medications (support or background treatments).
- Although the processes differ between countries, these provisions nevertheless show the willingness of some national policymakers to encourage patient oriented research and access to new therapies. In the fields of paediatrics and research into rare cancers, clinical trials provide a key role in giving patients access to innovative treatments. The requirements of The Directive have dissuaded Universities from taking on this role. Accumulating evidence suggests that many research units and individual researchers have withdrawn from non-commercial randomised clinical trials altogether because of The Directive. Patient care is confronted with an increasing degree of bureaucracy topped by the need to keep an eye on the study's internal procedures. In many cases, the latter is the real problem, namely the room for interpretation of GCP. The fact that the SOPs are usually constructed in extreme detail, can lead to conflict situations, which impair the practicability of clinical trials in research centers. Examples for GCP and protocol violations occur for instance, with the patient information and informed consent.
- **Informed consent prospectuses created by the sponsor often contain an enormous amount of information, and are too extensive and incomprehensible for the layman.** The goal of informed consent is to provide sufficient information to patients about the treatment, its

¹⁵ Universities UK and Department of Health (2004) Responsibilities, liabilities and risk management in clinical trials of medicines. Available: <http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con009387.pdf>. Accessed 30 May 2006

benefits and side effects and the alternative treatments in order for the patient to make an autonomous decision. There are a number of essential elements of informed consent sought for participation in clinical trials, and additional elements of informed consent including the need to explain the nature and purpose of the study, any additional tests, procedures or risks involved in the study compared with standard treatment, the voluntary nature of the research and the provision of written information.

- **There is evidence that the goals of informed consent for clinical trials are not always achieved.** Several studies demonstrate that patients receiving either standard treatment or treatment as part of a clinical trial recall only a small proportion of information provided to them. Olver surveyed oncology patients about to receive chemotherapy in the context of a clinical trial. Williams and Zwitter surveyed investigators from multicentre randomised clinical trials published in the European Journal of Cancer over a two-year period. Only 62% of respondents routinely told all of their patients that treatment would be selected at random and only 58% gave patients information about all of the treatment options.
- Cancer patients considering entry onto clinical trials are generally provided with written information. However, the complexity of material presented in consent forms may impede patient understanding and recall of information. Grossman et al. examined the readability of consent forms from oncology protocols at Johns Hopkins Oncology Centre over a two-year period. The reading age or readability reflects the average number of years of education required to read and comprehend the material. The mean reading age of consent forms was 14.1 years suggesting that consent forms for clinical trials were too complex for many patients to read and understand. Davis et al. Randomised subjects to receive a standard Southwest Oncology Group (SWOG) consent form (readability 12th grade, equivalent to 12 years of schooling) or a simplified form using headings text and diagrams (readability 7th grade, equivalent to 7 years of schooling) [66]. Subjects preferred the simplified form (62% vs. 38%) and more subjects would be discouraged to participate by the more complex form (12% vs. 2%). There would appear to be a paradox between the need to provide greater amounts of information about clinical trials when seeking informed consent and the apparent preference of patients to receive more simplified information. **These studies would suggest that strategies to improve informed consent procedures for clinical trials need to look at ways to improve patient recall of information, as well as ways to increase both the amount of information provided to patients and patients' comprehension of that information.**
- As stated before, one central European authority should give approval for all Member States involved. This should not only be a central Ethics Committee that approves the trial for all European countries, but a central organ that also provides the authorization for all Competent Authorities involved. This would have significantly contributed in simplifying and harmonizing the legislation regarding clinical trials.

2.3.4 Scope for Streamlining

- **The bureaucratic burden for investigators has tremendously increased without representing any contribution to patients' safety or to the scientific value of research.** The Directive has undoubtedly reduced the enthusiasm and commitment of the middle-ground investigators, who make up approximately 60% of the research community. Because they are essential to the future of clinical investigation in Europe, the difficulties of the directive need to be addressed as a matter of urgency before this disenchanted group walks away entirely. " In the end, the effects of the Directive on the patients who may not be able to enrol in clinical trials because of red tape which leads to a decrease in patients' access to innovative medicines, which will be the final result of the legislation. This surely is exactly the opposite of what the European Commission had in mind when introducing the measure, and they should tackle this situation as soon as they possibly can. Furthermore some large European academic trials cannot be conducted anymore due to the new regulations. This result in a reduction in the number of trials and additionally in a reduction in the number of patients enrolled in a study. European research and thus European patients will suffer from the loss of potential benefits of research.

2.4 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?

2.4.1 Options to address the issue as regards the assessment by Ethics Committees

The evaluation of the ethical foundation of the design and implementation of clinical trials needs to assess not only the degree of uncertainty surrounding the trial question, but also the anticipated benefits from the trial, the assumed risks by the participants and the alternative treatment options available for the patient.

From a patients' perspective, it is questionable whether local ethics review has any added value for patients in oncology, given variations in procedures, composition of committees, opinion building criteria and language might cause further delay without largely contributing to more patient safety or ethical viability of cancer research.

Only one country, France, has a centralized ethics committee system; in other countries, there is often confusion between the roles of central and local ethics committees, which led to large variations in assessments. Given that one of the objectives of the directive was to make European medical research more competitive and to give it a level playing field with the United States, where regulations are more harmonized, the outcome is disappointing. Since the release of the 2001 European Union Clinical Trials Directive (EU CTD) (2001/20/EC), an approval from an IEC is mandatory before starting an interventional clinical trial. Moreover, the composition of the IECs has been widened to other categories of the civil society among which of the users' and patients' representatives.

This **legislation** should **guarantee the rights, safety and well-being** of trial subjects, and insure that the results of the clinical trials are credible and reliable. It is obvious that the ethical and scientific quality should be verifiable to judging authorities and that this demands provision of sufficient information to these authorities. The information being requested, however, should bear relation with its purpose. Under the new Directive, application forms have grown to the size of books, carrying a message of general distrust of physicians, and it overlooks the fact that it is also in the best interests of the physicians to comply with demanded quality standards. The currently increased administrative requirements are inversely correlated to the physicians' ability to conduct independent clinical trials.

In terms of Ethics reviews, the Directive is still not entirely enforced by all national countries such as the requirement that explicitly requests a single IEC approval within each national country. For example, in Germany, a local IEC approval is needed for every investigational centre, plus a national IEC opinion, meaning that if you plan a multicenter trial, involving, e.g., 20 German centres, 20 local IEC positive approvals are required

The paper of **Peboeck et al.** raises the crucial question whether IECs are competent for giving ethical and scientific opinions. Indeed, the role of IECs is not to refine continuously the major ethical principles that rule the clinical research. This is devoted to international organizations (such as Helsinki). For example, it is not the role of IECs to decide, and to have opposite position between IECs, whether in general a placebo arm in clinical research is ethical or not (obviously a placebo arm is unethical when an efficient treatment is available for a fatal or severe pathology). The right inquiry of an IEC for a given clinical trial is to ensure that all actions to reduce the potential risks of being under placebo have been implemented in the protocol (e.g. strict eligibility criteria, frequent visits, add-on therapy, early stopping rules, rescue treatment, unbalanced randomisation scheme...)

2.4.2 One-stop shop for submission of assessment dossier

In many member states, policies for graduated application review or risk assessment strategies for clinical trials do not exist. The Directive requires a stand-alone dossier submission for each trial protocol, and in each member state is too time consuming. A single initial investigational new drug (IND) dossier has to be established for a non-marketed drug before clinical tests can start and subsequent trial protocols are submitted as amendments to the IND would be more efficient as in the US. This offers clinicians more choice in patient-focused research. Establishing such a risk-assessment approach along with a single European trial evaluation and approval process for multinational clinical studies would be patient focused and competitive.

2.4.3 Strengthening networks of national Ethics Committees involved in multinational clinical trials

- Individual clinician research that involves the study of **rare conditions** falls uneasily between clinical investigation (which may not require ethical approval) and a research project that would need evaluation by an ethics committee. Ethical standards are an essential requirement for all clinical research, but the idea that 'one size of ethics review fits all types of evaluation' is not tenable. The level of detail and stringency required by an ethics committee should be proportionate to the type and nature of research for which approval is being sought.
- Furthermore, it is possible that modifications to study design required by ethics committees could distort methodology to the extent that conclusions may be flawed. There is also a tension between the need to comply with the protection of individuals' confidentiality while allowing sufficient access to medical information for epidemiological research.
- An option would be to have a central and cautious regulation so as to facilitate the committees in terms of their relevance, their accountability, and structured ethical deliberation. Under conditions not adversarial to ethical, reflection, a stricter form of regulation may temporarily become justified. Careful implementation of central and weak forms of regulation, however, will remain the main aim. A temporary tightening of regulation, which may at times be a means of choice, should therefore be revoked as soon as space for harmonization is recognised.
- To successfully accomplish the task of reviewing all research projects necessitates a working and well funded committee. Especially in some eastern European countries a lack of funding for those committees may endanger the functionality of the committees and make compliance with the 60 day limit (Directive 2001/20/EC, Art. 6, (5)) a difficult task to say the least.

2.5 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?

- For academic trials, new regulation should a) recognise the importance of academic trials for the current evaluation of medicinal products; b) harmonization of provisions in favour of independent trials for example waiver of fees, insurance and costs of drugs; c) classification of the requirements for GCP in relations to the risk of the product for patients.

3 KEY ISSUE N°2 TO BE ADDRESSED: INCONSISTENT IMPLEMENTATION OF THE CLINICAL TRIALS DIRECTIVE

3.1 Consultation item n°6: Is this an accurate description of the situation? Can you give other examples?

3.1.1 Insufficient patient protection

- For many years, a key element of **patient protection** has been the **assessment of risk**. Risk can be defined in many ways, but perhaps the most obvious would be an evaluation of the extent of patient exposure to an investigational drug whose **toxicological profile** is not fully known and whose manufacture is not done to the same controlled standards of commercially available drugs.
- But, it is important to remember that many clinical trials do not investigate new drugs. Indeed, many trials **are actually driven by investigators and academic organisations aiming to improve therapeutic strategies and establish new state-of-the-art treatments**; for example, **organ preservation in patients with cancer is now a real possibility by use of a combination of commercially available chemotherapeutic agents and surgery or radiation therapy**. But importantly, these types of trials are often done without the involvement of the pharmaceutical sector. The toxicological profiles of marketed drugs have already been assessed in great detail to obtain marketing authorisation, and extensive documented follow-up data from clinical practice is known thus negating the need for repetition of safety profiling as dictated by the new Directive.

- Information about **side-effects, symptoms and treatment options** are important to cancer patients as they enable them to make informed treatment decisions. Cancer patients require information not only related to survival estimates, but also regarding HRQOL issues. Providing patients with such information, from a methodologically sound research basis, is therefore of paramount importance.
- **Increased Transparency:** The Directive has created a number of hurdles that prevents patients having increased transparency. There is a lack of availability of information on ongoing/concluded clinical trials to the patients and general public (Article 11). Non-interventional clinical trials are not covered by the current legal text. This is evidenced in the following:
 1. The **archiving of the documentation** by the RECS for the minimum period of 3 years, according to the Directive 2005/28, is problematic at times due to a lack of resources and professional support.
 2. The **definition of substantial amendment** at article 10 of the Directive 2001/20 is not clear and gives too much room for various individual interpretation, resulting sometimes in either unnecessary or conversely inadequate information being provided to the RECs from the sponsors or competent authorities.
 3. Concerning **safety information**, RECs are frequently overloaded with information that is not relevant and does not add to their role of subject protection. Conversely it may sometimes limit their capacity to fulfil that role.
- **Reimbursement Factor:** Within the issue of reimbursement of commercially available drug supplies by public health insurance systems is still problematic. For trials in oncology that test the best therapeutic use of innovative medicines in combination with existing therapy schemes, the free-of-charge supply implicates a cost takeover of investigated medicines as well as of established co-medications. In Italy, Belgium, Sweden, and the Netherlands, specific mechanisms have been set up for non-commercial trials, which allow for public cost takeover for tested drugs and co-medications (support or background treatments). Although the processes differ between countries, these provisions nevertheless show the willingness of some national policymakers to encourage patient-oriented research and access to new therapies. In the fields of paediatrics and research into rare diseases, clinical trials provide a key role in giving patients access to innovative treatments.

3.1.2 Increase of administrative cost:

- The heart of the problem lies in the increased obligations that the directive imposes on the sponsor of a trial—an individual or organization who must now take total legal and financial responsibility for the clinical trial. This responsibility will include paying for all drug and device costs (even the cost of routine non-investigational aspects of the treatment) while patients are on study. For example, an academic sponsor, rather than the health service, would have to pay for all the drugs that a patient receives, including fully licensed drugs, if even one component of the treatment is experimental. The Directive has created many additional burdens for the conduction of academic trials independent of medical industry, while it did not meet the primary objective of harmonizing and simplifying the legislation in the Member States. Directive will force sponsors to introduce databases for efficient collection and analysis of safety information to provide detailed annual reports to various authorities. In addition, the ability to do expedited electronic reporting of Serious Unexpected Suspected Adverse Events could be a problem for some academic organisations. Indeed, the value of increasing the amount of reporting of such events, together with the perceived duplication of information submitted to various authorities and ethics committees, is questionable.
- High among the concerns was that the directive would greatly increase the cost of clinical trials. And indeed, costs have risen by about 85%¹⁶. This is partly due to the increased cost of insurance and fees to regulatory authorities or ethics committees, but largely because of the massive increase in staffing that has been necessary to deal with managing the complicated procedures that the directive has installed,” he said. “For example, every minor change in a protocol — even something as small as changing the name of the data manager — has to be submitted.

¹⁶ Patrick Therasse, M.D., European Organization for Research and Treatment of Cancer in Brussels, Belgium, at the European Cancer Conference in Paris, September, 2005

- Under the Directive, there can be only one sponsor of a study, so collaborative academic researchers are therefore required to take out a multicenter sponsor insurance policy. Such insurance is expensive and sometimes difficult to obtain. A survey of eight cancer clinical trial centres in the UK also found that the cost of non-commercial trials had doubled, trials have been delayed, and staff were demoralised in many trial centres. Many charities and academic groups have found that they cannot afford the financial burden that this stipulation imposes or the increased administrative burden that has resulted from compliance with other directive requirements.
- In terms of SUSAR reporting to National Competent Authorities (NCA), there has a large variations between countries which leads to increased administrative costs for example in high duplication rate of case safety reports. Safety information, collection, reporting and review of safety information is unbelievably & unnecessarily complex for multinational trials. For multiple national submissions, there are diverse formats and procedures. Article 17 should be revised to define notification of SUSAR and other important safety information in a way that the RECs can properly evaluate the ratio benefits/risks without creating an administrative burden

3.2 Consultation item n°7: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

3.2.1 Options to address this issue

- Reviewing the Clinical Trials Directive with a view to clarifying provisions, where necessary
- It is necessary to modify the language in the provisions of the Directive which are open to misinterpretation and misapplication of the law by Member States.
- If there is revision, this should not be limited to the Directive 2001/20/EC but also cover other EU regulation of CTs, including CTs on medical devices and other types of research. More attention should be given in this process to other existing sets of European regulation such as the Council of Europe Convention on Human Rights and Biomedicine and its additional protocol. A stronger coordination and consistency with those texts would be a great improvement for all stakeholders.
- The European Commission could utilize Article 9 (8) which confers power on the Commission to draw up and publish detailed guidance on the application format and contents of the request.
- Amend the Directive and/or provide adequate exemptions to protect independent research. There are clear opportunities to improve the situation for non-commercial trials, without discrimination between sponsors, with some amendments to the current legal text.
- In terms of informed consent, Article 3 should give guidance on means of waiver to informed consent in emergency situations where many member states have currently instituted individual rules.
- Training and education: case-studies database
- Criteria for validation of training programmes and training curricula
- Development of harmonised documents
- Communication between ethics committees
- An amendment to the legal measure should make information on trials entered in EudraCT accessible to public Results must be made available within defined timeline
- A revision of the legal measure should provide for a minimum delay in time from Ethics Committees when they give an opinion, in order to ensure that a proper evaluation is performed
- In terms of increased transparency through accessible documents - Article 6 should make it an obligation on Member States to provide the necessary resources to the RECs in terms of finance, training, administrative support.
- In terms of reporting,
 - Clear content and reporting rules of SUSARs and ASR
 - Clear reporting rules to Ethics Committees and
 - Better use of EudraVigilance database - Common repository for SUSARs and SSARs to assist overall safety assessment of IMPs
 - Work sharing for the SUSARs and ASRs assessment

4 Key issue N°4: Adaptation to peculiarities in trial participants and trial design

- **INFORMED CONSENT:**
- Cancer patients considering entry on to clinical trials are generally provided with written information. However, the complexity of material presented in consent forms may impede patient understanding and recall of information. Grossman et al. examined the readability of consent forms from oncology protocols at Johns Hopkins Oncology Centre over a two-year period. The reading age or readability reflects the average number of years of education required to read and comprehend the material. The mean reading age of consent forms was 14.1 years suggesting that consent forms for clinical trials were too complex for many patients to read and understand. Davis et al. Randomised subjects to receive a standard Southwest Oncology Group (SWOG) consent form (readability 12th grade, equivalent to 12 years of schooling) or a simplified form using headings text and diagrams (readability 7th grade, equivalent to 7 years of schooling). Subjects preferred the simplified form (62% vs. 38%) and more subjects would be discouraged to participate by the more complex form (12% vs. 2%)¹⁷. There would appear to be a paradox between the need to provide greater amounts of information about clinical trials when seeking informed consent and the apparent preference of patients to receive more simplified information. These studies would suggest that strategies to improve informed consent procedures for clinical trials need to look at ways improve patient recall of information, as well as ways to increase both the amount of information provided to patients and patients' comprehension of that information.
- Several studies demonstrate that patients receiving either standard treatment or treatment as part of a clinical trial recall only a small proportion of information provided to them. Olver surveyed oncology patients about to receive chemotherapy in the context of a clinical trial. Nearly half the patients could not name any of the drugs which they were about to receive and less than half could remember at least half of the side effects described on the consent form. Poor recall and understanding of information may also arise as a consequence of doctors' views about informed consent for clinical trials¹⁸. Taylor surveyed 170 physicians involved in clinical research. The majority of doctors felt that informed consent requirements for clinical trials were an intrusion into the doctor patient relationship and many doctors remain unconvinced that full disclosure is in the patients' best interests, even when patients express a desire to know all the facts.
- Williams and Zwitter surveyed investigators from multicentre randomised clinical trials published in the European Journal of Cancer over a two-year period. Only 62% of respondents routinely told all of their patients **that treatment would be selected at random and only 58% gave patients information about all of the treatment options**¹⁹.

4.1 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?

- There is an ethical need to study medicines as data obtained in adults cannot be extrapolated to children
- Many of the drugs used for the treatment of children with cancer, despite being well established in clinical practice, are not appropriately authorized for use in children and adolescents. For example, in one recent study of children treated for Acute Lymphoblastic Leukaemia, unlicensed preparations were used in 40 % of prescriptions for chemotherapy, due to a lack of approved formulations suitable for the paediatric patients.
- In terms of new drug development, pharmaceutical companies are reluctant to support studies to evaluate new cancer chemotherapy drugs for use in children. This stance is taking due to

¹⁷ Davis TC, Holcombe RF, Berkel HJ et al. Informed consent for clinical trials: a comparative study of standard versus simplified forms. *J Natl Cancer Inst* 1998; 90: 668-74.

¹⁸ Olver IN, Buchanan L, Laidlaw C, Poulton G. The adequacy of consent forms for informing patients entering oncological clinical trials. *Ann Oncol* 1995; 6: 867-70.

¹⁹ Williams CJ, Zwitter M. Informed consent in European multicentre randomised clinical trials - are patients really informed? *Eur J Cancer* 1994; 30A: 907-10.

economic grounds, legal, administrative and ethical challenges of conducting clinical trials in children.

- Currently, limits for paediatric research without direct benefit are defined in two European documents. According to the Council of Europe's European Convention on Human Rights and Biomedicine such research may only be approved if it entails 'minimal risk and minimal burden'. In contrast, in a document aimed to provide guidance on the application of the Clinical Trials Directive with regard to trials with minors, the EU recommends to allow 'a minor increase over minimal risk' in case of benefit for the group of children with the same disease. **This inconsistency between these two documents may either prohibit important research or expose participants to unjustified risks of harm.**
- Registration of new non-commercial paediatric trials in Europe essential for optimising paediatric treatments—has fallen since the Clinical Trials Directive 2001/20/EC was implemented, according to sarcoma experts meeting in Stuttgart, Germany (Nov 30—Dec 2, 2006). "Before implementation, 10—20 studies were opened per year in the UK, but this has now fallen to just a handful", says Kathy Pritchard-Jones (Royal Marsden Hospital, London, UK)²⁰.
- The Directive requires that surrogate consent from a nominated legal representative is provided before critically ill patients without relatives can be enrolled in a clinical trial. This requirement has been tackled in different ways by each member state, and has an obvious impact on emergency care research.
- These challenges include: ensuring that effective infrastructures are in place to safely and efficiently conduct early phase clinical trials in children while meeting all ethical and regulatory requirements associated with such trials; obtaining timely access to new agents from pharmaceutical sponsors for both preclinical testing and for phase I and phase II testing; and effectively prioritizing new agents for evaluation in children so that those agents most likely to benefit children with specific cancers are brought forward for clinical testing.

4.2 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?

- Article 5 outlines the conditions for research in incapacitated patients unable to give informed consent. The article, however, is framed to address the needs of individuals who are incapacitated for long periods, many even permanently. A clinical trial can only be done if "informed consent of the legal representative has been obtained." This will be difficult in many emergencies—when a patient is suddenly and perhaps temporarily incapacitated. In some countries, such as the United Kingdom, there appears to be no provision for a legal representative for incapacitated patients. This means the doctor in charge takes responsibility for entering the patient into the trial. The situation appears to be similar in Spain and in Norway. In the Netherlands consent may be given by the life partner, at least in acute emergencies. In Germany patients may be enrolled if it can be assumed that the effectiveness of a treatment appears to be unclear. In other countries such as Ireland and Austria the situation may be more difficult. Legal representatives cannot be produced quickly and usually do not even exist, since a healthy adult person does not need a legal representative. Therefore, many studies previously performed in emergency medicine were no longer possible after the CTD came into effect..
- Increased harmonisation on the issue of 'informed consent' across the EU, in terms of both the quality and quantity of the information provided.
- Directive as a tool for respecting the rights and interests of patients and provide the adequate protection of what duties physicians and others have towards patients such as following a controlled protocol that details what researchers will do in the study and right to informed consent.

Ethics committees bear directly on patients' rights, enable and guide life-and-death decision-making, and provide ethical input into hospital policies and guidelines.

²⁰ Mitchell C (2007) Clinical trials in paediatric haematology-oncology: are future successes threatened by the EU directive on the conduct of clinical trials? *Arc Dis Child* 92: 1024–1027