Appendix C-2

Written submissions

Organisations who were invited to take part in the conference, were invited to prepare 5-10 page written submissions prior to the meeting to be submitted to the EMEA by 2 October 2007. The template for the written submissions containing the four questions below was provided by the organisers.

Each written submission was asked to answer the following four questions:

- What aspects of the Directive 2001/20/EC and its implementing rules work well?
- What does not work well?
- What can be remedied within the present legal framework?
- What should a new legal framework look like?

Some additional organisations submitted written submissions spontaneously and these are included under the heading “Spontaneous written submissions”.

List of organisations and National Competent Authorities

Nominating organisations

Spontaneous written submissions

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Please note that the written submissions and the presentation slides from the meeting will be included in appendix to the report of the meeting and be published at the same time as the report.

Name of Organisation	Country
ACRO (Association of Clinical Research Organizations)	ACRO member companies are located throughout the European Economic Area (EEA), Eastern Europe, the Americas, and Asia-Pacific regions.

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1) **Acceptance of a common IMP Dossier by the majority of competent authorities**	1) For multi-national clinical trials, there should be a single competent authority review for the EEA so that a common IMPD is maintained throughout and the current situation where a minority of competent authorities require more detail in certain sections of the IMPD is avoided.
2) **Acceptance of a common (EudraCT) application form by the majority of competent authorities**	2) The EudraCT form should be revised to be more "user friendly" – some fields are not adequate to allow entry of data.
3) **Adherence to predictable timelines in the majority of member states for the review of applications and substantial amendments by the competent authority and ethics committee**	3)
4) **A legal basis for good clinical practice (GCP) and adherence to GCP standards in all member states**	4)
5) **Sharing of information between competent authorities via the confidential EudraCT database so that member states are aware of decisions and activities in other member states, thus promoting the safety of research participants**	5)

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) Inconsistency in documentation requirements for competent authority and ethics committee submissions Attachment 1 of the *Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (Revision 2, October 2005)* lists 43 items of administrative information/ documentation that may be required in the submission in addition to the common application form and the IMP Dossier, depending upon the member state. Only 8 of these items are required by all member states. In addition, there are further local administrative requirements in some member states that are not listed in Attachment 1. A similar list in Attachment 1 of the *Detailed guidance on the application format and documentation to be submitted in an application for an ethics committee opinion on the clinical trial on medicinal products for human use (Revision 1, February 2006)* also lists 40 items that may be required in specific member states, of which only 11 are required by all member states. Again, there are further local administrative requirements in some member states that are not listed in Attachment 1, and individual ethics committees in almost all member states may impose additional administrative requirements. While the majority of competent authorities accept the EudraCT application form, a minority still require that a local application form is used. The application forms needed for the ethics committee application vary considerably, both between member states and (in some member states) between ethics committees. ACRO members and the sponsors of our trials question the value that these varied administrative documentation requirements bring to the local process for the regulation of clinical trials. It is our view that these additional national requirements lead to delays and confusion in the preparation and submission of	1) ACRO recommends that a unified standard for the contents of the clinical trial application is implemented in all member states for applications to competent authorities and ethics committees. This should include a standardised application form for the application to the competent authority, a standardised form for the application to the ethics committee, uniform requirements for the IMP Dossier, standardisation of the number of copies of the application required, and a unified standard for electronic submissions.

clinical trial applications, and create a perception by sponsors that the EEA is a complex and "difficult" region in which to initiate clinical trials.	
2) Inconsistency in national procedures for the review of applications to the competent authority and ethics committee It is disappointing that several member states that were members of the European Union on the date at which the directive was to be implemented (1 May 2004) have still not completed the passage of all of the national legislation required to implement the directive's provisions fully. However, the processes that have been put in place further the confusion caused by a lack of harmonisation. For example, the national laws of several member states allow for a formal validation period (of varying duration) before the review period laid down in the directive starts, and in some member states, but not all, national law allows for a "clock stop" (also of varying duration, but up to 3 months) within the formal review period. Furthermore, the competent authorities and ethics committees in some member states fail to comply routinely with the timelines stated in their national laws and there is a need for much stricter enforcement of timelines. In addition, for certain categories of IMP, some member states have implemented a mandatory (pre-submission) process to enable the competent authority to receive expert advice before the clinical trial application is submitted formally. While ACRO supports the aim of ensuring the safety of trial subjects, such processes can be perceived negatively as a means of circumventing the review timelines laid down in the directive. The original intent of the directive was that sponsors would notify the competent authorities and ethics committees of their intent to conduct a clinical trial, but the processes that have been established are those of a formal authorisation of a clinical trial application. In this context, the fact that some member states have retained a tacit approval system (ie, if no objection has been raised by the end of the designated review period the application is approved) adds to the confusion, particularly in cases where issues are subsequently raised after the formal review period has ended. In several member states, a truly central ethics committee does not exist and there is a coordinating ethics committee instead, which will issue the single opinion for the member state, but this is based on feedback from the individual ethics committees responsible for the trial sites. In practice, this means that applications to multiple ethics committees within the member state are still required. There remains considerable variation in the way that applications are handled and assessed by individual ethics committees, both within and between member states, and many ethics committees/member states have been reluctant	2) Ideally, ACRO would like to see a situation where approval of an application for a multi-national trial by a single competent authority and a single ethics committee (plus the involvement of local ethics committees to assess the suitability of the site for the study) would permit initiation of the trial across the whole of the EEA. We believe that this would reduce the perception of difficulty in conducting trials in the region and would significantly increase the desirability of the EEA as a region for conducting clinical research when the compared with the USA (the major competitor for the location of clinical research). However, ACRO recognises that this may be difficult to achieve politically in the short term and therefore the following suggestions are offered as a "second best" approach to improve the current situation: Several member states are able to validate and review the clinical trial application, including the responses to any questions raised, within the review period (60 days for most products) laid down in the directive and without the use of pre-submission and "clock stop" mechanisms. ACRO recommends that this should be a harmonised standard for all member states, that timelines for review by the competent authority and ethics committee in each member state should be strictly enforced, and that all competent authorities and ethics committees should be required to issue a formal letter of approval or refusal within the designated timeframe. A truly central system of ethics committee review should be established in all member states and, at least within a member state and preferably across member states, the requirements and procedures for ethics committee approval and continuing review should be unified and clearly described in written guidance. Further, ACRO has identified a need for improved training of ethics committees in clinical trial law and recommends that this is implemented.

to produce local guidance documents in writing. There is also considerable variation in the requirements of different ethics committees, following approval, for other information necessary to fulfil the requirement for continuing review of the trial. In addition, ACRO members have reported several examples of situations where ethics committees appear not to understand their own national laws relative to clinical trials.	
3) Confusion concerning the legal representative Volume 10 of The Rules Governing Medicinal Products in the European Union (*Questions and Answers: Clinical Trial Documents, April 2006)* states under Question 3a that the legal representative should be responsible for the civil and criminal liability of the sponsor in respect of the clinical trial. However, a Frequently Asked Questions page on the website of a national competent authority (http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=995) states that the legal representative "does not assume any of the legal liabilities of the sponsor(s) for the trial by virtue of the role of legal representative and does not therefore require insurance or indemnity to meet such liabilities, but may in some cases enter into specific contractual arrangements to undertake some or all of the statutory duties of the sponsor in relation to the trial, in which case the legal representative would also be regarded as a co-sponsor and would then require insurance or indemnity cover." The first part of this statement appears to contradict the statement in Volume 10. It is not clear from the directive if the delegation of responsibilities is restricted to a single legal representative or if it is feasible to use several. Although the situation is clarified in the European Commission's *Questions & Answers* document (April 2006), the experience of our members is that there are inconsistent opinions on this at the competent authority level. Transferring the responsibility for the civil and criminal liability of the sponsor to a legal representative has many legal and practical consequences for both the sponsor and the legal representative. Legal advice received by many ACRO member companies has been that they should not take on the role of legal representative for a non-EEA sponsor. This has resulted in sponsors establishing "shell" companies with limited liability within the EEA, but with the owner of the company (and its staff) located outside the EEA, which we do not believe was the intention of the directive and which may not provide adequate	3) ACRO recommends that the directive is revised to require the submission of applications to competent authorities and ethics committees by an authorized representative of the sponsor, while ensuring that the sponsor retains overall civil and criminal liability in respect of the trial, as is the situation in other major territories (such as the USA) that compete with the EEA for the conduct of clinical trials. The respective roles and responsibilities of the sponsor and of the authorized representative should be unambiguously defined.

compensation in the event that legal action is pursued.	
4) Confusion concerning the sponsor of a clinical trial It is understood from the directive that a specific trial may have only one sponsor. However, national legislation is unclear as to whether this means one sponsor per member state or one covering the entire trial. It is understood from the EMEA that the Commission's position is that the former applies, due to liability issues. However, nothing is available in writing to confirm this. Furthermore, the EMEA has been unable to advise on the acceptability of different affiliates of the same parent company, each with separate legal entity status, acting as a sponsor in different member states. In practice, this appears to relate to whether or not the parent company would ultimately be considered liable for the entire trial or whether limited liability to each legal entity would apply.	4) The concept of multiple sponsors within a parent organisation is not inconsistent with the concept of one sponsor per trial, so long as there are clear agreements between the various parties regarding responsibilities for trial duties, in particular for tasks such as pharmacovigilance of the trial as a whole. ACRO recommends that the European Commission publishes a written position on this issue.
5) Confusion about amendments There is confusion around the classification of amendments as substantial or non-substantial. The definition of a substantial amendment provided by the directive and the *Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (Revision 2, October 2005)* is open to wide interpretation by sponsors, competent authorities and ethics committees (at least one competent authority has published some national guidance). In addition, some competent authorities and ethics committees continue to take the view that all amendments should be submitted, irrespective of any change in the benefit-risk assessment. In the case of ethics committees, there appears to be a conflict between the requirements of the above European guideline and the ICH *Guideline for Good Clinical Practice (E6(R1), June 1996)*, which states that (other than for urgent safety measures or logistical/administrative changes) there should be no change to a protocol without prior ethics committee approval. Directive 2001/20/EC establishes a maximum time of 35 days for the review of substantial amendments by the ethics committee. However, the directive sets no maximum time for the review of substantial amendments by the competent authority. While some member states have incorporated a similar timeline for competent authority review in their national laws, others have not, leading to delays in approval. There is also a suspicion that some competent authorities	5) ACRO recommends that more detailed, harmonised guidance is published on the changes that will be considered a substantial or non-substantial amendment, and that the European Commission ensures that a unified standard is applied by all competent authorities and ethics committees as to what constitutes a substantial amendment and therefore requires submission. ACRO also recommends that a maximum time for review of substantial amendments by the competent authority is established in EU law, just as for the review by the ethics committee, that such timelines are strictly enforced, and that an expedited process for the approval of efficacy amendments by both the competent authority and ethics committee is established.

may backdate their approvals to within the national legal timeframe when, in practice, the total time taken was significantly longer. While urgent safety amendments can be implemented without prior approval, no such provision exists for urgent efficacy amendments (for example, if data show that one treatment arm in a study provides insufficient efficacy) so that such changes incur delay while approval is awaited. It would be in the best interests of patients participating in clinical trials to have an expedited process for such efficacy amendments.	
6) Inconsistency in requirements for SUSAR reporting The directive requires that all SUSARs, no matter where they occur, are subject to expedited reporting to the competent authority. While several member states comply, several others have implemented a variety of different requirements for reporting of SUSARs arising outside the member state concerned. Also, there are differences between competent authorities as to whether reports should be blinded or unblinded. "Mandatory" electronic reporting of SUSARs to the competent authorities of all member states was to have been introduced from November 2005, but several competent authorities are still unable to receive electronic reports and require the submission of paper copies. ACRO members submit SUSAR reports on behalf of the sponsors of our clinical trials and must therefore register with the EMEA in order to access and report to the EudraVigilance database. However, this registration is sponsor-specific and therefore an individual CRO is required to register its details on multiple occasions for each sponsor for whom it takes on this role. This is administratively inefficient and does not acknowledge that the CRO's pharmacovigilance system has been tested previously. The *Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (April 2006)* allows for sponsors to submit to ethics committees periodic line listings of SUSARs rather than case-by-case expedited reporting. However, the submission of periodic line listings is not accepted by the ethics committees in several member states and case-by-case reporting is necessary. The guideline is not clear about the requirements for reporting to investigators and some competent authorities permit sponsors to provide periodic line listings whereas others insist investigators must be notified on a case-by-case basis. In addition, where the directive indicates that an annual safety report is required for each clinical trial, the above guideline allows for an annual safety report to cover	6) ACRO recommends that a uniform SUSAR reporting standard is implemented in all member states. In ACRO's view, this standard should include a common requirement for either blinded or unblinded reporting, and require electronic expedited reporting to the competent authorities and submission of periodic line listings to ethics committees and investigators. ACRO also recommends that a single standard is established for the format and content of the annual safety report to competent authorities, based on a single annual safety report for all trials within a clinical development programme. ACRO further recommends that a system is put in place such that a CRO need register with EudraVigilance on one occasion only.

all trials within a clinical development programme. However, some competent authorities will not accept such a report. Also, the guideline is not clear if line listings and summary tables should provide data on a periodic or cumulative basis, and again the competent authorities take different views on this.	
7) Inconsistency and/or lack of transparency in good clinical practice (GCP) standards ACRO welcomes the legal basis that the directive provides to ensure GCP compliance. However, the experience of our members during inspections by national competent authorities reveals differences in thinking in terms of what is acceptable under GCP. For instance, some national competent authorities have identified that the use of protocol waivers to include patients who do not meet strict protocol entry criteria is considered a breach of GCP whereas others find this practice acceptable provided the waiver process is clearly described in the trial protocol. We understand that this example has been discussed, with the aim of harmonisation, within the GCP Inspectors Working Group. However, we have recent evidence that different interpretations are still being applied and there has been no formal statement from the Working Group to clarify the situation.	7) ACRO recommends that there is improved communication of information on harmonised GCP standards and that a mechanism is put in place for stakeholders outside the GCP Inspectors Working Group to request the Group to agree and publish a harmonised position on issues where it becomes apparent that divergent standards are being applied.
8) Coordination of GCP inspections ACRO welcomes the obligation that the directive places on competent authorities to conduct GCP inspections of clinical trials and recently our members have seen a significant increase in the number of inspections being performed. While a competent authority may select one representative study from a specific sponsor for routine inspection, ACRO members, who work with many sponsors, are finding that their studies are selected frequently – during the last year, some members have experienced more than one inspection per month across the EEA. Preparation for and managing such a high number of routine inspections is disruptive to our members' workload and results in higher costs for sponsors performing clinical trials in the EEA.	8) ACRO recommends that there is greater coordination of routine GCP inspections to take into account the added burden to all parties involved in the clinical trial. Across the EEA as a whole, ACRO considers that there should be no need for more than one routine inspection of a clinical trial (as in other major territories).
9) Inconsistency in the definition of an Investigational Medicinal Product (IMP) ACRO members have experienced considerable difficulties and delays in initiating trials as a result of different interpretations by national competent authorities of the definition of an IMP included in the directive. This not only adds to confusion around the clinical trial process in the EEA but can also have a significant impact for sponsors on the cost of performing the trial, as the	9) ACRO recommends that the implementation of the 2007 guideline is monitored and, in the event that competent authorities are inconsistent in their implementation, it should be revised and simplified. As there is no distinction made in the directive for documentation requirements for different types of IMP, ACRO recommends that, in order to facilitate clinical trials, harmonised standards are agreed and published for the scientific information required for different classes of product: (1) the product under study, (2) active and placebo

directive requires that all products classified as an IMP are made available free of charge. The *Guidance on Investigational Medicinal Products (IMPs) and other products used in clinical trials (May 2007)* was designed to address these issues but still allows significant opportunity for different interpretations. ACRO considers that a comparator product with an EEA marketing authorisation should be classified as an IMP only if it is used in a modified form and/or it is not used in accordance with the terms of the marketing authorisation.	comparators, and (3) standard treatments, concomitant treatments and established procedures.
10) Inconsistency in importation requirements for IMPs Some member states continue to require an additional application, following approval of a clinical trial application by the competent authority, for the importation of the IMP and other products to be used in a clinical trial, whereas in the majority of member states the competent authority approval serves also as the importation approval.	10) ACRO recommends that a single standard is adopted in all member states such that the competent authority approval of a clinical trial application automatically provides for the importation of the IMP and other products to be used in the trial.
11) Other difficulties with national legislation in the member states In some cases, national law is ambiguous (eg, the need for registration of Phase I trials in the Ministry of Health database in Italy), duplicates EEA-level requirements (eg, the need to register trials in both EudraCT and the Italian database), and/or differs in detail (eg, the definition of extemporaneous preparation differs between member states, inconsistencies within and between member states in the legal framework allowing a representative of a legally-incompetent patient to make decisions on the patient's behalf). Such cases add to the perception of confusion and difficulty in conducting clinical research in the EEA and are detrimental to the interests of patients. In many member states, the national law regulating clinical research is not consolidated into a single piece of legislation, resulting in inconsistencies and delays.	11) Ideally, ACRO would like to see an EU Regulation that establishes a unified, comprehensive and fully integrated standard for clinical trials with medicinal products for human use in the EEA. However, ACRO recognises that this may be difficult to achieve politically in the short term and therefore as a "second best" approach to improve the current situation recommends that a pan-EEA office to monitor the conduct and execution of clinical trials, from an administrative aspect, is established. The office would monitor member state implementing legislation to ensure that it is comprehensive and consistent with EU law, that implementing legislation lists other applicable laws and states clearly which takes preference, and would provide a mechanism for the rapid resolution of issues referred by sponsors and other stakeholders where conflicting or ambiguous requirements are identified or where national legislation, guidance or practice leads to a lack of harmonisation across the EEA.
12) Factors not regulated by Directive 2001/20/EC and its implementing rules In many cases, ACRO members report that significant delays in initiating clinical trials in the EEA are caused by factors that are not currently regulated under the directive. A common reason for significant delay (several months) in trial initiation is the finalisation of agreements with participating investigators and their institutions (which, currently, can delay the submissions to competent authorities and ethics committees in those member states where a copy of the	12) To avoid these considerable delays, ACRO recommends that a standard template for investigator/institution agreements is established in each member state, and that the government and professional bodies in each member state are required to take account of the principle that local processes governing clinical investigators should not delay the initiation of a clinical trial once the competent authority and ethics committee approvals have been issued.

agreement is required in the submission). Other processes that have been set up by governments and professional bodies within member states to ensure that investigators participating in a clinical trial are not subject to a conflict of interest can also delay the initiation of trials.	

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
1) Harmonisation of requirements and procedures for ethics committee review, and improved training of ethics committees in clinical trial law.	1) ACRO recommends that the requirements and procedures for ethics committee review should be unified and clearly described in written guidance, that the European Commission should provide advice to member states to ensure that ethics committees understand fully the law governing clinical trials, and that competent authorities are empowered to correct incorrect interpretations of the law by ethics committees.
2) Harmonisation of standards concerning substantial and non-substantial amendments.	2) ACRO recommends that more detailed, harmonised guidance is published on the changes that will be considered a substantial or non-substantial amendment, and that the European Commission ensures that a unified standard is applied by all competent authorities and ethics committees as to what constitutes a substantial amendment and therefore requires submission.
3) Harmonisation of standards for the format and content of the annual safety report submitted to competent authorities.	3) ACRO recommends that the current guideline is revised to establish a unified standard for the format and content of the annual safety report to competent authorities, based on a single annual safety report for all trials within a clinical development programme.
4) Reduction of the administrative burden placed on CROs by EudraVigilance registration.	4) ACRO recommends that a system is put in place that allows a CRO to register with EudraVigilance on one occasion only.
5) Harmonisation of Good Clinical Practice (GCP) standards.	5) ACRO recommends improved communication of information on harmonised GCP standards and that a mechanism is put in place for stakeholders outside the GCP Inspectors Working Group to request the Group to agree and publish a harmonised position on issues where it is apparent that divergent standards are being applied.
6) Improved coordination of Good Clinical Practice (GCP) inspections.	6) ACRO recommends greater coordination of routine GCP inspections to take into account the added burden to all parties involved in the clinical trial. Across the EEA as a whole, ACRO considers that there should be no need for more than one routine GCP inspection of a clinical trial (as in other major territories).
7) Harmonisation of the documentation requirements for different types of IMP.	7) ACRO recommends that the implementation of the 2007 guideline is monitored and, if competent authorities are inconsistent in their

	implementation, it should be revised and simplified. ACRO recommends that harmonised standards are agreed and published for the scientific information required for different classes of product: (1) the product under study, (2) active and placebo comparators, and (3) standard treatments, concomitant treatments and established procedures.

What should a new legal framework look like?	
Comments	**Suggestions**
1) Ideally, ACRO considers that there should be an EU Regulation that establishes a unified, comprehensive and fully integrated standard for clinical trials with medicinal products for human use, with a process where approval of an application for a multi-national trial by a single competent authority and a single ethics committee (plus the involvement of local ethics committees to assess the suitability of the site for the study) would permit initiation of the trial across the whole of the EEA. Failing this, ACRO considers that the recommendations below should be implemented, together with the establishment of a pan-EEA office to monitor, from an administrative aspect, the conduct and execution of clinical trials in the member states, and which would provide a mechanism for rapid resolution of issues referred by sponsors and other stakeholders where conflicting or ambiguous requirements are identified or where national legislation, guidance or practice leads to a lack of harmonisation.	1)
2) It should ensure there is a single common dossier that is accepted in all member states without additional documentation requirements for clinical trial applications to competent authorities and ethics committees. This should include a standardised application form for the application to the competent authority, a standardised form for the application to the ethics committee, uniform requirements for the IMP Dossier, standardisation of the number of copies of the application required, and a unified standard for electronic submissions.	2)
3) It should ensure that the timelines laid down in EU law for review of clinical trial applications and substantial amendments by competent authorities and ethics committees are respected, and prevent the addition of pre-submission, validation and “clock stop” periods to the standard review timelines. It should also establish a maximum timeline for the review of substantial amendments by competent authorities, in line with that for ethics committees.	3)
4) It should ensure that a truly central system of ethics committee review is established in all member states, and that competent authorities and ethics committees are required to issue a formal letter of authorisation or refusal before the completion of the standard review timeline for clinical trial applications.	4)

5) It should require the submission of applications to competent authorities and ethics committees by an authorized representative of the sponsor, while ensuring that the sponsor retains overall civil and criminal liability in respect of the clinical trial. The respective roles and responsibilities of the sponsor and of the authorized representative should be unambiguously defined and the issue of whether one sponsor is required for the entire trial or per member state clarified (including the liabilities, if any, of legally established affiliates of the sponsor in the various member states).	5)
6) It should incorporate an expedited process for the approval of efficacy amendments by the competent authority and ethics committee.	6)
7) It should ensure that a uniform SUSAR reporting standard is implemented in all member states. ACRO recommends that the unified standard should require electronic expedited reporting of all SUSARs to the competent authorities and submission of periodic line listings to the ethics committees and investigators.	7)
8) It should ensure that the competent authority approval of a clinical trial application automatically provides for the importation of the IMP and other products to be used in the trial without the need to request specific importation approvals.	8)
9) It should require each member state to establish a standard template for sponsor agreements with the investigator and/or institution, and to require that the member state government and professional bodies take account of the principle that local processes governing clinical investigators should not delay the initiation of a clinical trials once the competent authority and ethics committee approvals have been issued.	9)

Agence française de sécurité sanitaire des produits de santé

11th September 2007

THE CLINICAL TRIALS DIRECTIVE = NEEDS FOR IMPROVEMENT
Contribution to the preparation of the October 3d conference

The major objectives of EU Clinical Trials (CT) Directive 2001/20/EC are:

- to implement a set of good practices (manufacture and clinical), in order to ensure protection of all CTs participants and the quality of results;
- to harmonize the technical requirements, the procedures and the timeframes among Member states (MS) for commencement, conduct and follow up of clinical trials;
- and to set up exchange of information on CT between Member States in the field of CTs by establishing European data bases.

Those objectives have been broadly achieved although important issues remain to be resolved, and there is scope for improvement.
Some discrepancies are still remaining leading to a lack of regulatory and scientific cohesion across MS, regarding in particular the CT scientific value, the amendments and Susars notification and assessment.

In this context,

i) The Heads of Medicines Agencies (HMA) have established the Clinical Trials Facilitation Group (CTFG) to contribute, alongside with other concerned bodies at the EMEA or the Commission, harmonisation of the protection of participants and secure the scientific value and the conduct of multinational CTs. They have recently discussed the issue of clinical trials, in particular with a view to improving coordination and possibly harmonisation of the evaluations of mutli-center trials for which applications have to be examined by several national authorities across Europe.

ii) Upon request of the European Commission, the Emea organises a workshop on CTs (3 oct. 2007) aimed at assessing the implementation of the directive, to identify difficulties and to propose solutions.

As a contribution to the collective debate that will take place during the conference with representatives of various categories of authorities and stakeholders, Afssaps wants to highlight some key points.

1. Need for harmonisation in the regulation of CTs.

The Commission's detailed guidances aimed at assisting sponsors, national competent authorities (NCAs) and Ethics Committees (ECs) in interpreting the CT directive. Those guidances have been differently implemented into national regulations, leading to a wide range of national practices and resulting in some administrative burden for sponsors.

It that context, it seems necessary to identify as soon as possible the remaining differences in transposition and divergences of interpretation as discussed at the December 2006 pharmaceutical committee meeting.

The most important points in terms of consistency could be made mandatory.

2. Need for harmonisation in the multinational CTs scientific assessment

Diverging outcomes of national assessments in multinational trials have been pointed out and are not completely justifiable from a point of view of protection of the participants. That is the reason why there is a clear need for harmonisation of CTs review by NCAs.

Meeting that need does not imply a purely centralised system.
It can be handled in a viable and pragmatic way. To that effect, a 2-step plan for CTs assessment sharing could be considered.

a) It could start with a pilot phase of CTs scientific assessment sharing by the CTFG
   - on a voluntary basis
   - provided an assessors network has been implemented
   - with monthly advice meetings via teleconference or mails
   - and written standard operating procedures (draft SOP to be proposed by PEI and France)
   - on a predefined scope of assessment (quality of the product and/or non clinical part and/or clinical part of the CT dossier)
   - on a priorisated limited set of CT involving at least 2 MS:
     - First in human CT potentially at risk
     - Gene or cell therapies CT
     - "difficult" CTs as judged by the NCAs or the sponsor
   - by discussion on difficulties occurring during the scientific assessment phase and on rejections or withdrawals.

This procedure requires a significant improvement of data sharing by NCAs, particularly through Eudract modifications (see attached document) :

- Eudract :
  - Sharing of :
    - MS CT assessment reports
    - Intermediate decisions of NCAs
    - Reasons for withdrawal of a CT application by the sponsor
    - Scientific advices (by EMEA or MS)
    - Warnings on similar products
    - Non clinical and CTs results and warnings
  - Improvement of data population by MS by allowing an automated batch process
- Pre-clinical data sharing on potentially high risk investigational medicinal product. This would be made possible by requiring an electronic transmission of these data by sponsors in an European database (Eudract ?)

b) This should lead at a further stage, after careful evaluation of the implementation of the pilot phase, to a mutual recognition procedure of predefined areas of CTs scientific assessment for such trials, while ethics should remain completely within national remit.

This procedure requires NCAs to have similar quality assessment processes, scope of assessments and time-lines. A modification of the legal framework would be necessary to achieve that goal.
This MR procedure could cover the set of categories mentioned in a), extended with the followings:

- CT on minors,
- Orphan products
- CT on medicinal products of Part 1 of the Annex of Regulation N° 726/2004

- "Commitment" studies requested by the Agency

3. Need for harmonisation on what is a substantial amendment

The CTFG is establishing a list of the most frequent examples of amendments regarded as substantial or not.
This work should be published as soon as possible on the HMA/CTFG web site.

4. Need for harmonisation/simplification in Susars and annual safety report (ASR) reporting and assessment system

For that purpose, we would suggest:

- to emphasize the role of NCAs in CTs safety assessment vis à vis the Ethics Committee
- to simplify Susars reporting to Ethics committees by replacing expedited reporting by semi-annual periodic reports, as it is recommended in the concerned guidance and yet done in several MS.
- to harmonise the obligation to report Susars electronically in Eudravigilance in all MS and by all kinds of sponsors
- to organise free training of academic sponsors to report Susars electronically
- to organise ASRs work sharing by NCAs, as it is done for PSURs.

5. Need for harmonisation of research sites conducting phase 1 CTs in Europe

Further to the TGN 1412 incident and to the first in human EMEA guidelines (July 2007), it is necessary to lay down requirements for investigator sites in charge of such CTs, related to personnel, equipment and procedures aiming at the safety of subjects, or even conditions to authorize research sites to conduct phase I CTS, based on those requirements.

6. GCPs

ICH GCP is the international standard for designing, conducting, recording and reporting clinical trials, recognised by the three ICH regions. This recognised standard is not referred to as a reference guideline in the Directive 2001/20/EC (it only has to be taken into account, according to Recital 8 of Directive 2005/28/EC). A legal way to refer to this consensus paper, agreed upon by CHMP and published by the Agency, should be found.

It would be useful to agree on measures of adaptations or interpretation of this GCP standard according to the type of trial (purpose, characteristics…). In particular, some provisions on labelling, monitoring, study documentation could be adapted for Phase IV clinical trials.

7. Need for supporting European Academic Sponsors

It seems also necessary to make funding and/or resources available for European academic sponsors in order to help them to comply with the duties of sponsors defined in the directive.

The possibility for a sponsor or a EU legal representative of the sponsor to appoint national legal representatives should be opened.

8. Need for transparency and communication on CTs

8.1. An European CTs public registry
Since some of the MS implement national CTs public registries (France), and taking into account that major Medical Journal Editors now require registration of CTs in publicly available databases before publishing their results. In that context, it would be useful to create a public European CT register *via* Eudract.

8.2. Communication with stakeholders.
Regular meetings between the CTFG and stakeholders (commercial and non commercial sponsors) need to be organised in order to allow exchange on possible difficulties and to devise appropriate solutions together.

8.3. Availability on line of data concerning CTs
All recommendations, proposals or other useful data concerning CTs (CTFG, GCP-IWG, ad hoc experts working group…) should be made available on line, whether on a specific CT web site to be created or on another existing one.
In any case, whichever site may be used would have to be flexible and adjusted to operational needs.

9. GCP inspections : need for strengthening exchange of information and transparency

Although exchange of information is planned for inspections in Article 11.1(f), these exchanges currently do not cover planification of inspections in the context of national programs. This type of exchanges should be strengthened, and this topic will be discussed at the next GCP IWG (GCP Workplan 2008).

Where a NCA has objective grounds for considering that a person/facility/institution which is involved in clinical trials (not necessarily a CT conducted in EU) no longer meets the obligations laid down in the legal framework or in the guidelines, it shall inform the other competent authorities and the Commission (example : critical findings on a bioanalytical facility during a GLP inspection, when this facility also carries out assays for CTs). Article 12 should be amended accordingly.

Inspection findings and statistics / trends by categories, could be made available to the public while safeguarding confidential aspects.

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

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Name of Organisation	Country
AESGP (Association of the European Self-Medication Industry)	Belgium

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1. Generating a EudraCT number	1) No improvement necessary
2. Generating the application form on the EudraCT webpage	2) Making the final application form more readable (reader friendly), especially for the Ethical Committees (ECs). This would avoid requests for additional papers (TOCs for the documentation, short summarys, etc)
3. Application procedure to NCA and timelines	3) a- Improve structure of the electronic submission of the documentation. b- Publish a directory structure template for optional use. c- Parallel submission to NCA and Ethical Committee should be possible in all MS d- Establish a kind of MRP for the application procedure in multinational trials e- Stricter timelines to be defined in the Directive f- Validation period should be clearly defined in the Directive
4. Application procedure to ECs and timelines	4) See 3) a-c Increase acceptance of the English version of the application form
5. Filling the EudraCT database	5) To allow public access to non-confidential information on the EudraCT as official European register of clinical trials (following the WHO recommendations). This will already be mandatory for paediatric CT in January 2008.

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1. Availabillity of the concerned ECs must be guaranteed in all involved MS.	1) Allow the submission in all countries on any day of the month. Ethic Committee meetings should be scheduled on a regular basis in all countries - minimum once a month.
2. Lack of harmonisation in the additional documentation (over and above that stipulated in the current guidance) that is required by various Member States	2) Harmonisation of requirements of ECs in order to reduce the number of country's specific requirements and administrative effort. Organise a meeting of EC's representatives to find a European solution.
3. Lack of harmonisation between individual Member State Authorities and also the ECs as to what is classified as a substantial amendment and what is a notification. Article 10 of Directive 2001/20/EC, as amended includes the term "otherwise significant" as a definition of a substantial amendment. This term is unclear and has been variably interpreted by ECs. Many companies have experienced situations where the same amendment in different trials was considered as being 'otherwise significant' by some ECs and as 'not otherwise significant' by other ECs.	3) The wording "otherwise significant" in Article 10 should either be removed or be defined. Similarly to the Serious Risk to Public Health guideline, publish criteria to help define a 'substantial amendment' and examples of what is not.
4. The safety reporting requirements have to be improved. Investigators and ECs are complaining about the amount of reports they receive.	4) Allow listings to be submitted every 3 or 6 month instead of spontaneous reporting (for ECs and investigators). Report to investigators: There should be no expedited reports except in the case of Safety Alert Letters. Only six monthly line listings of all SUSARs that occur with the investigational medicinal product. Reports to the relevant EC: There should be an expedited reporting of all domestic SUSAR that occur in the concerned trial, an additional six month report and the Annual safety report. The EC should not receive expedited reports of SUSARs occurring in that trial from centers outside that country or from other trials of the same IMP ongoing either in that country or outside that country. This would not compromise patient safety since in each case appropriate SUSARs would still be received and reviewed not only by the relevant Competent Authority but also by the relevant EC. Such revised reporting would avoid unnecessary duplication, ensure clarity and define responsibility, thus further ensuring enhancing patient safety.

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
5. The requirements for submission of safety updates differs between countries i.e. there are requirements in addition to the annual safety report with different time points/cut off dates.	5) Ensure that the requirements for safety updates are harmonised between MS and not exceed that stipulated in the Directive.
6. In some countries the labeling requirements exceed those stipulated in annex 13 of the GMP directive	6) Limit the labeling requirements to those pointed out in annex 13.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
1) In the checklist in Section J of "Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use…" there is no tick box for the xml file of the application. This could lead to an omission.	1) Add a check box for the xml file of the application
2) Some countries are still requesting import licences within the EEA	2) Within EEA countries import licences should not be requested
3) Expedited reporting requirements of SUSAR differs from country to country	3) Requirements should be harmonised
4) The possibility to delegate sponsors' obligations to a legal representative inside the EEA is most important for sponsors in third countries wishing to perform CTs in the EEA.	4) Give clarification on the constellation between sponsor and legal representative and the possibility to delegate obligations/responsibilities. Improve the definition.
5) Divergent interpretation by MSs of some of the provisions in the directive. Sometimes only provides a frame to MSs wherein the MS can choose what suits best.	5) Increase harmonisation by avoiding (rewriting) passages where national interpretation leeds to non-harmonised requirements. After 3 years of experience with the legal framework it should be possible to streamline the requirements in between all MS. Make clear that in all cases where the directive gives clear and ultimate requirements, additional requirements are not to be recommended.

What should a new legal framework look like?	
Comments	**Suggestions**
1)	Revision of the Directive including strict timelines (i.e. not subject to national interpretation).

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Name of Organisation	Country
Cancer Research UK	United Kingdom

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1) The inspection process promotes a written quality system – in the form of Standard Operating Procedures which should be continuously reviewed and updated. In addition, inspection helps to ensure that IMPs are manufactured, packaged and handled according to the requirements of GMP.	1) With respect to investigator site GCP inspections – globally we need to move towards a 'standardised' approach so that the investigator either is or is not deemed to be independent of the sponsor (i.e. is the investigator the subject of the inspection, or the sponsor?)
2) The requirement to prepare an IMPD has ensured that New Chemical Entities (NCE) administered to patients are well characterised which allows for the generation of more robust trial data.	2)
3) The requirement to supply a formal non-clinical safety data package has increased patient safety. However, this is unwarranted for Investigational Medicinal Products (IMPs) with a Marketing Authority.	3)
4) The increasing social and regulatory need to carry out paediatric studies is supported by the Directive. This issue is also covered by the new Paediatric Regulations	4)
5) Ethics Committees and Competent Authorities have clear time limits within which they must respond to sponsors' applications	5)
6) Explicit guidance for Ethics Committees has assisted constitution and procedures for the latter – e.g. the need for expertise in the relevant disease or patient group. This is also covered in the UK by 268110/Report of the Ad Hoc Advisory Group on the Operation of NHS Research Ethics Committees published in 2005	6)

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
7) Standards in academic early phase trials have improved significantly as a result of being covered by the Directive. Extra resource implications are real but necessary and all funding parties across Europe have to accommodate these extra costs.	7) We should **not** accept dual standards even in the administration of clinical trials as to do so undermines our commitment to the well-being of the patients. However, there is no evidence that late phase trials of IMPs with an existing marketing authority have improved. In addition, there has been a major detrimental knock-on effect on academic studies not including an IMP.
8) The single favourable ethics committee opinion within a member state has been beneficial in eliminating the different versions of a protocol and simplifying applications	8) Consideration might be given to establishing a single opinion across Competent Authorities for multi-centre trials in more than one Member State – i.e. a 'Rapporteur' system for trial applications

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) Lack of harmonisation with respect to GMP between Europe and the US	1)
2) Difficulties with multi-state multicentre studies given the inconsistent interpretation of this Directive (and others) by member states. The unpublished FECS survey of each country's regulatory body highlighted these discrepancies.	2) EMEA to identify the major differences and assist member states to resolve these
3) Lack of clear definitions such as 'end of trial'.	3)
4) Lack of clarity regarding the interpretation of 'substantial amendments'.	4) Changes to Principal investigator should not be considered as a 'substantial' amendment. As this is time consuming and causes unnecessary paperwork.
5) Difficulties regarding the identification and confirmation of the trial sponsor lead to increased cost and time delays.	5)
6) Lack of standard Clinical Trial Agreements between host institutions and participating centres were being developed on an ad hoc trial-by-trial basis.	6)Multi-centre studies are still being hampered by delays in securing contracts with multiple host institutions, even though there is now a standard template in the UK.
7) In relation to Phase III academic trials there are increased staff costs due to increased paperwork preparing the CTA, IB and MREC submissions. In addition, whilst the UK Research Governance Framework is clear on which studies require a sponsor it takes excessive time to get the same confirmation in accordance with the Directive, and this results in prolonging the time it take to run the trial and increasing staff costs.	

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
1)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

What should a new legal framework look like?	
Comments	**Suggestions**
2)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

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Name of Organisation	Country
CPP Ile-de-France XI	FRANCE

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
2)	2)
3)	3)
4)	4)
5)	5)
…	…

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) Article 2 (k) Ethics committee CPP considers the rules of composition of Ethics Committee shall be more detailed. CPP considers that a rule about pluridisciplinarity shall be adopted by all Members State because Ethics Committee should involve philosophy, law, psychology and patient's association members. Only such a rule could confirm the independence of Ethics Committee.	1) CPP Proposal : (k) "ethics committee" : an independent body in a Member State, consisting of **pluridisciplinary members, notably** healthcare professionals and non medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subject involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators, and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent.
2) Article 9 – Commencement of a clinical trial CPP considers a need for rules concerning the distribution of the files in Ethics Committee. In France, the lack of such rules allows sponsors to choose their Ethics Committees. A new rule will be adopted in 2008 to change this context, notably to guarantee the independance of Ethics Committees. The directive will require all Members State to do the same.	2) CPP Proposal: 1. Members States shall take the measures necessary to ensure that the procedure described in this Article is followed for commencement of a clinical trial. 2. The sponsor may not start a clinical trial until the Ethics Committee **designed by a rule of distribution of files** has issued a favourable opinion and inasmuch as the competent authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance. The procedures to reach these decisions can be run in parallel or not, depending on the sponsor.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
1)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

What should a new legal framework look like?	
Comments	**Suggestions**
2)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

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Name of Organisation	Country
Clinical Trials Facilitation Group	All member states

Session 4
Potential solutions and recommendations for the future including views from patients, health professionals and investigators :

- implementation with current framework
- implementation requiring changes to guidelines
- implementation requiring changes to the legislation

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1) Objective of harmonising the CT subjects' protection	1) Broadly achieved, bearing in mind previous national legislations.
2) Harmonisation of definitions, documents, procedures, time lines.	2) Broadly achieved, taking into account i) the large differences between previous national legislations ii) the identified care data set of CTA dossier ; but to be improved
3) CTA and IMPD	3) • Approval from EC and CA with time-lines • Content of applications defined in guidances • Single opinion
4) Substantial amendments	4) • Requirement proportionate. • Non substantial amendments not to be reported • Simple form.
5) Eudract Database	5) • Simple, useful, efficient system • Allows MS to exchange information and alerts
6) Safety information	6) • Shared definitions. • Only Susars required as expedited reports • Electronic reporting system available. • Eudravigilance allows MS to exchange information
7) Eudravigilance Database	7) • Electronic format efficient • Potential for analysis for signals

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) Different implementation of guidelines in MS.	1) Make the main points of guidelines mandatory in EU. Particularly harmonise what documents needed in a CTAA and in the EC opinion dossier.
2) Different outcomes of national scientific assessments of multinational CTs.	2) Harmonisation of CTs scientific review by NCAs *via* the CTFG.
3) All relevant information on CT review by NCAs is not available to others.	3) Improve data sharing by NCAs via Eudract. Implement links from Eudract to Eudravigilance CTM
4) The same amendments are regarded as substantial in some MS and not in others.	4) Clarify and harmonise substantial amendments through agreed rules and a list of worked examples.
5) Susars and ASRs management by NCAs is not optimised.	5) Clarify the definition of SUSARs and expected assessment before reporting. Create possibility for work sharing of at least ASRs by NCAs. Set up safety data analysis by Eudravigilance.
6) Susars and ASRs management by Ethics Committee seem not to be convenient.	6) Clarify the role of the sponsor/NCA/EC in assessing SUSARs and ASRs. Simplify Susars reporting to Ethics committee, ie : organise the information for ECs via SUSARs periodic reports.
7) Susars reporting in Eudravigilance is not optimised	7) Make mandatory the electronic report of SUSARs by Sponsors. Organise free training for academic sponsors to assess adverse reactions, to use MedDRA and to report in Eudravigilance CTM.
8) Difficulties for academic sponsors to comply with the directive and guidelines requirements	8) Make fundings and/or resources available for European academic sponsors. To simplify, make it possible to have one sponsor per MS in multinational trials.
9) Need to set up transparency on CTs in Europe and not only at national levels.	9) Create an European public registry applicable to autorised CTs.
10) Communication with stakeholders to be improved.	10) Organise a system of exchange of information and regular meetings of CTFG/ad hoc experts group with sponsors.
11) First in Human CTs should be conducted in appropriate research sites and conditions in all Europe.	11) Define conditions to allow accreditation or authorisation of research sites to perform FIH-CTs in Europe.
12) No reference to ICH-GCP in the concerned directive.	12) Refer to ICH-GCP in the directive.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
1) Different implementation of EU Guidelines in MS	1) Harmonisation of the content of CTAA (CTFG)
2) Different outcomes of national scientific assessments of multinational CTs.	2) Harmonisation of CTs scientific review by NCAs via the CTFG (under way).
3) All relevant information on CT review by NCAs is not available to others.	3) Improve data sharing by NCAs via Eudract. Implement links from Eudract to Eudravigilance CTM
4) The same amendments are regarded as substantial in some MS and not in others.	4) Clarify and harmonise substantial amendments through agreed rules and a list of worked examples (under way/CTFG).
5) SUSARs/SARs management by NCAs is not optimised.	5) Set up safety data analysis by Eudravigilance.
6) Difficulties for academic sponsors to comply with the directive and guidelines requirements	6) Make fundings and/or resources available for European academic sponsors ; organise free training to ADRs assessement, to use MedDRA and report in Eudravigilance CTM for Academic sponsors.
7) Communication with stakeholders to be improved.	7) Organise a system of exchange of information and regular meetings of CTFG/ad hoc experts group with sponsors.
8) First in Human CTs should be conducted in appropriate research sites and conditions in all Europe.	8) Define conditions to allow accreditation or authorisation of research sites to perform FIH-CTs in Europe.

What should a new legal framework look like?	
Comments	**Suggestions**
1) Different implementation of guidelines in MS.	1) Make the main points of guidelines mandatory in EU.
2) Susars and ASRs management by NCAs is not optimised.	2) Clarify the definition of SUSARs and expected assessment before reporting. Create possibility for work sharing of at least ASRs by NCAs.
3) Susars and ASRs management by Ethics Committee seem not to be convenient…	3) Clarify the role of the sponsor/NCA/ECs in assessing SUSARs and ASRs and simplify requirements relating to ECs (for instance organise the information for ECs via SUSARs periodic reports).
4) Susars reporting in Eudravigilance is not optimised	4) Make mandatory the electronic report of SUSARs by Sponsors.
5) Reference to ICH-GCP is not clearly mentioned.	5) Refer to ICH-GCP in the directive.
6) Need to set up transparency on CTs in Europe and not only at national levels.	6) Create an European Public registry applicable to authorised CTs.
7) Difficulties for academic sponsors to comply with the directive.	7) Make it possible to have one sponsor per MS in multinational trials.

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Clinical Trials Facilitation Group	All Member States and EEA countries

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
Substantial Amendments Article 10 (a)	1) Regulatory requirement proportionate; 2) Non-substantial amendments don't have to be reported; 3) Sponsor identifies whether substantial or non- substantial; 4) Simple notification form.
Safety information: expedited reports Article 17(1)(a) & (b) Article 17(3) (a) & (b)	1) Regulatory requirement consistent with ICH; 2) Only SUSARs required as expedited reports; 3) System for electronic reporting available.
Safety information: annual safety reports Article 17 (2)	1) Format and content described in Vol 10: PhV guidance; 2) For marketed products international birth date can be used for start of annual period.
Databases: EudraCT Article 11 (1)	1) Obtaining EudraCT number simple; 2) Form can be completed online or offline; 3) Electronic format is efficient; 4) Allows MS to exchange information quickly – automatic alert system;
Databases: Eudravigilance Article 17 (3) (a) & (b)	1) Electronic format is efficient; 2) Allows MS to exchange information; 3) Potential for analysis for safety signals

WRITTEN SUBMISSION FOR SESSION 3

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
Substantial Amendments 1) NCAs, ethics committees and sponsors not harmonised on what is substantial amendment; 2) Sponsors submit non-substantial amendments overloading NCAs and RECs; 3) Sponsors need to keep application form updated without submitting a substantial amendment.	**CTFG applications subgroup** 1. Needs to simplify management and assessment of SA : 1.1. Current guidance not clear enough e.g. concerning: • Changes to the application form • Changes to the Investigator Brochure • How to identify the amendment • Annual Safety report 1.2. NCA and RECs tools to compare the CTA form before and after the amendment(s) in order to simplify assessment of SA; 2. Agree harmonised approach and provide clear guidance on maintaining updated information in EudraCT database
Safety information: expedited reports 1) Need for all SUSARs to be reported electronically to EVCTM; 2) Some MS require reporting to NCA and Eudravigilance; 3) Sponsors reporting all serious events instead of SUSARs; 4) NCAs and Ethics Committees overloaded with unhelpful reports.	**CTFG pharmacovigilance subgroup** 1) Clarify that MS legislation must ensure that all SUSARs are reported electronically to Eudravigilance CTM; 2) Clarify definition of SUSAR and guidance on what should be reported – allow NCAs and RECs to return inappropriate reports 3) Simplify reports of SUSARs to RECs. Harmonise interval for periodic report to RECs and allow NCAs to be responsible for informing RECs of SUSARs when necessary. 4) Design a Eudravigilance report that NCAs could send to RECs. 5) Promote pharmacovigilance training for academic investigators.
Safety information: annual safety reports (ASR) 1) Difficult to assess paper line listings of all serious adverse reactions (SARs); 2) Sponsors have different SOPs for determining “expectedness”	**CTFG pharmacovigilance subgroup** 1) Propose sponsors to submit line listings of serious adverse reactions electronically to EV CTM; 2) Harmonise the definition and procedure for ‘change of expectedness’.

WRITTEN SUBMISSION FOR SESSION 3

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
Databases: EudraCT 1) Entry of data into Eudract 2) Public registries of CTs are being built by several NCAs	**CTFG applications subgroup & EudrCT TIG/JOG** 1) Improve data entry by MS. Need to provide an automated batch process. 2) Promote creation of an European public CTs registry
Databases: Eudravigilance 1) Need for all SUSAR reports to be entered electronically; 2) Link EudraCT application to Eudravigilance reports by identification of IMP using codes; 3) Provide standardised reports that help identify safety trends; 4) Include electronic reports of all annual listings of all serious adverse reactions to provide more representative data on safety of IMPs	**CTFG pharmacovigilance subgroup & Eudravigilance Expert WG** 1) Clarify MS legislation to ensure all SUSARs are reported electronically to Eudravigilance CTM. Identify by agreement whether sponsor or NCA to enter SUSAR reports. 2) Include Eudravigilance Medicinal Product Dictionary in legislation. 3) Implement link from EudraCT to Eudravigilance CTM using IMP codes from EVMPD; 4) Obtain expert advice on content and format of reports to help identify safety trends for IMPs; 5) Add function to EVCTM to receive annual listings of all serious adverse reactions electronically. 6) Organise training for academic sponsors to report electronically (free of charge).

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?

Comments	Suggestions
Substantial Amendments **(Applications to CA and EC ENTR CT1 Oct 2005)** 1) NCAs, ethics committees and sponsors not harmonised on what is substantial amendment; 2) Current guidance not clear enough 3) Sponsors submit non-substantial amendments overloading NCAs and RECs; 4) Sponsors need to keep application form updated without submitting a substantial amendment.	**CTFG applications subgroup** 1) Identifying differences and plan to identify harmonised criteria. 2) From (1) aim to clarify guidance and provide examples. 3) From (1) and (2) work with stakeholders on procedure to submit substantial amendments only. 4) Agree harmonised approach and provide clear guidance including comparison tables of substantial and non-substantial amendments. 5) Organise joint meeting CTFG/stakeholders.
Safety information: expedited reports **(Pharmacovigilance guidance ENTR CT3 Apr 2006)** 1) Some sponsors not reporting electronically; 2) Some MS require reporting to NCA and Eudravigilance; 3) Sponsors reporting all serious events instead of SUSARs; 4) NCAs and Ethics Committees overloaded with unhelpful reports	**CTFG pharmacovigilance subgroup** 1) Identify barriers to electronic reporting; 2) Identify MS requirements for PhV reporting; 3) Explore reasons for over-reporting with stakeholders; 4) Clarify guidance on what should be reported – agree NCAs and RECs should return inappropriate reports.
Safety information: annual safety reports (ASR) 1) Difficult to assess line listings of all serious adverse reactions (SARs); 2) Sponsors have different SOPs for determining "expectedness" 3) ASRs generally not concise enough.	**CTFG pharmacovigilance subgroup** 1) Discuss usefulness of line listings and identification of SUSARs; 2) Provide definition for procedure for 'change of expectedness'. 3) Improve guidance on content and format of ASRs.
Databases: EudraCT **(Guidance on EudraCT database ENTR 5.1 & 5.2 May 2004)** 1) Validation of quality of data not adequate; 2) Need to send alerts to all NCAs instead of only concerned NCAs; Need ability to search database and make standard and customised reports	**CTFG applications subgroup & EudrCT TIG/JOG** 1) Agree algorithm for validation of essential fields; 2) Add additional alert functionality to EudraCT; 3) Agree content and format of standard reports and add functionality

WRITTEN SUBMISSION FOR SESSION 3

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
Databases: Eudravigilance **(Guidance on electronic PhV reporting ENTR CT4 April 2004)** 1) Need for all SUSAR reports to be entered electronically; 2) Link EudraCT application to Eudravigilance reports by identification of IMP using codes; 3) Provide standardised reports that help identify safety trends 4) Include annual listings of all serious adverse reactions to provide more representative data on safety of IMPs	**CTFG pharmacovigilance subgroup & Eudravigilance Expert WG** 1) Identify barriers to electronic reporting and plan to remove them; 2) Implement link from EudraCT to Eudravigilance CTM using IMP codes from EVMPD; 3) Obtain expert advice on content and format of reports to help identify safety trends for IMPs; 4) Add function to EVCTM to receive electronic listings of all serious adverse reactions.

What should a new legal framework look like?	
Comments	**Suggestions**
Substantial Amendments	1)No change
2) Safety information: expedited reports	1) Clarify that MS legislation must require that all SUSARs reported electronically to Eudravigilance CTM 2) Allow simplification of SUSAR reporting to RECs and allow NCAs to be responsible for informing RECs of SUSARs when necessary
3) Safety information: annual safety reports	1) Allow NCAs to be responsible for informing RECs of ASRs when necessary 2) Creating possibilities for worksharing by NCAs for assessment of ASRs.
4) Databases: EudraCT	1) Allow the publication of a European public registry.
5) Databases: Eudravigilance	1) Include Eudravigilance Medicinal Product Dictionary in legislation 2) Mandate EVCTM to receive electronic listings of all serious adverse reactions

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Name of Organisation	Country
Clinical Trials Facilitation Group	All Member States and EEA countries

Subject Headings for Session 3

Scope of legislation
Definitions
Clinical Trial Authorisation and IMP Dossier

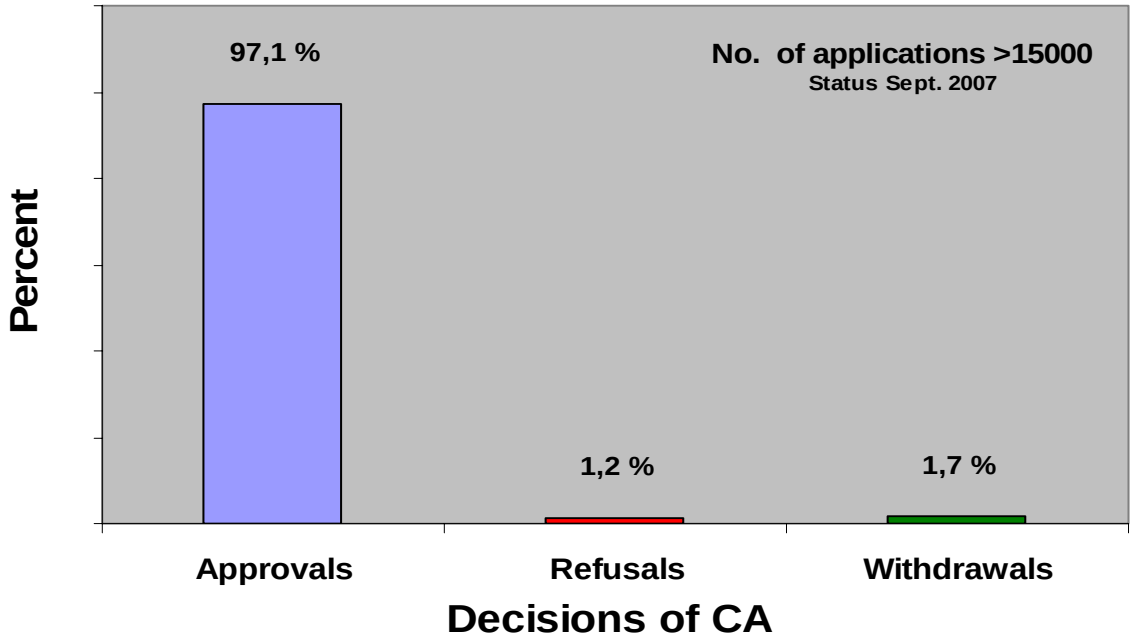
- To Ethics committee
- To Competent Authority

IMP related issues (definitions, labelling, GMP etc)
Ethics committee structures and processes
Competent authority processes
Roles of ECs and NCAs
Trials conducted in third countries, including developing countries

Aspects of the Directive 2001/20/EC that work well	
Topic	**Suggestions**
Scope of legislation Article 1 (1-4)	1. Specific provisions regarding the conduct of clinical trials All clinical trials, shall be designed, conducted and reported in accordance with the principles of good clinical practice.
Definitions Article 2 ▪ clinical trial / multi-centre clinical trial ▪ non-interventional trial ▪ investigational medicinal product ▪ sponsor ▪ investigator ▪ investigator's brochure ▪ protocol ▪ subject ▪ informed consent ▪ ethics committee ▪ inspection ▪ adverse event ▪ adverse reaction ' ▪ serious adverse event or serious adverse reaction ▪ unexpected adverse reaction	**Additional guidance given in guidelines under:** **EUDRALEX Volume 10 - Clinical trials** chapters 1- 5 e.g.: ENTR CT 1 **- Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial** October 2005 Revision 2 **- Chapter III : Information on the Quality of the Investigational Medicinal Product** **- Recommendation on inspections** - Guidance on IMP and other MP used in CTs (May 2007) ENTR CT 3 **- Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use** April 2006 Revision 2
Clinical Trial Authorisation(CTA) and IMP Dossier	- Approval required from EC and CA - Content of the application for CTA and IMP-Dossier defined in guidance documents - Transparent time lines for approvals - defining specific conditions for CTA for biological products/GMO
IMP related issues (definitions, labelling, GMP etc)	- IMP dossier usable in several MS for multinational trials / Common requirements for IMP dossier as defined in Guidance CT1 - transparent MS specific requirements as defined in CT1 Attachment 1 additional guidance given Vol 10 Chapter III : Information on the Quality of the Investigational Medicinal Product

Competent authority processes	- transparent timelines / dossier requirements -deficiencies of applications (formal and scientific) will be communicated in writing. Possibility to amend the content of the application when grounds for non-acceptance are given
Roles of ECs and NCAs	- Defined responsibilities of CA and EC - EC and CA can work in parallel - single opinion per MS

The systems works well: leading to more than 97% approvals on the basis of more than 15000 decisions



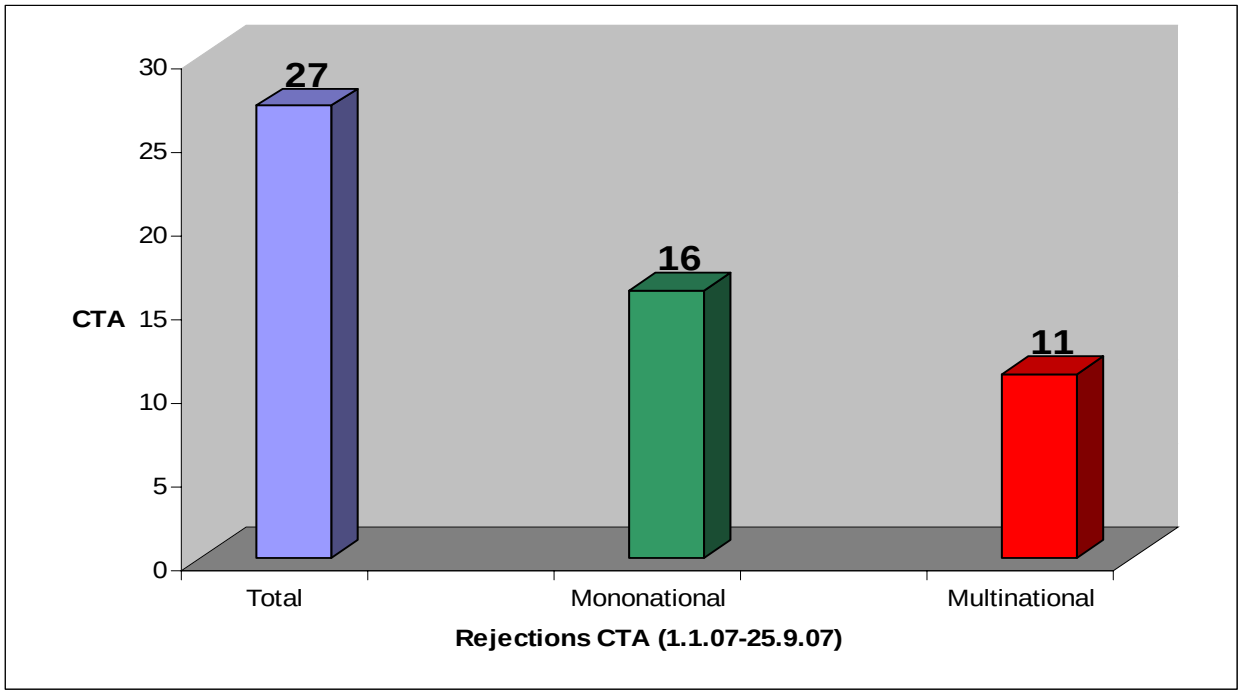
Aspect of the Directive 2001/20/EC that do not work well? But can be remedied within the present legal framework	
Topics/Problems	**Suggestions**
Scope of legislation No problems seen by CTFG	No suggestions
Definitions - Non IMP - Definition of Non-IMPs and back-ground treatments are divergent in MS (particularly because of divergent status of NIMP (with MA in the MS concerned or not)) Different understanding of Non-interventional-studies in different MS	- Further harmonisation in the ad hoc Group 2001/20 EC of examples given by applicants - Guidance on definition of IMP and NIMP published by Commission; - update of EudraCT Database to address NIMPs diagnostic or monitoring procedures are not the same in all MS, and one specific study could be considered a non interventional study in some MS and a CT in others **discussion of diverging decisions between MSs and in CTFG**
Clinical Trial Authorisation and IMP Dossier - additional national requirements for CTA diverging decisions of MS on the same CTA	- regular update of Attachment 1 of ENTR CT1 - -development of harmonised documents with core requirements by **CTFG applications subgroup**sponsor discuss critical issues with concerned MS before CTA ("advice Meeting" via written procedure and/or teleconference and/or "breakout session" during CTFG meeting -develop a suggestion for sharing assessments by **CTFG scientific harmonisation subgroup** discussion of diverging decisions between MSs and in **CTFG** after or during CTA
IMP related issues (definitions, labelling, GMP etc) - -Lack of clarity or agreement on role and responsibility of QP in releasing clinical trialGMP documentation for third country manufacturing - Different labelling requirements	**meeting/ discussion according EFPIA proposal with *European Commission, the Clinical Trials Facilitation Group, the EMEA GMP Inspection Services working group on a harmonised understanding of GMP requirements for IMPs***
Competent authority processes - diverging decisions of MS on the same Clinical Trial Application	- discussion of critical issues **before CTA** with concerned MS ("advice Meeting" via written procedure and/or teleconference and/or "breakout

- Different time lines between the MS	session" during CTFG meeting - harmonised procedures and sharing of assessments by **MS and/or CTFG scientific harmonisation subgroup** - **implementation of voluntary harmonised CTA** - **Harmonised start of CTA or Amendment submission** - **Consolidated list of Questions (GNA) for CTA** - **Consolidated opinion of MS** - **Approval according national regulations**
Roles of ECs and NCAs EC and CA do not work in parallel but EC vote is pre-requisite for CTA	- discussion of topic in 2001/20/EC ad hoc group after the details by sponsors and MS are given - further clarification in guidance documents

Topics of Harmonisation

Examples

Rejections of CTA submitted between 1.1. -25.9.2007
2-8 MS in the 11 multi-national trials (no unanimous decision)



FIM Studies

Status 3.4.2007

Total	784
Mono-national	680
Multi-national	38 (2-11)

What should a new legal framework look like?

Is a new legal framework needed to address the mentioned problems?

Presently, CTFG sees no need for a new legal framework, but is open to learn from you!

Rejections of CTA submitted between 1.1. -25.9.2007
2-8 MS in the 11 multi-national trials (no unanimous decision)

Summary CTFG

- Major advances in the approvals of multi-/ national CT have been reached by 2001/20/EC
- Further harmonisation of documentation (IMPD etc) is possible and under way
- Further harmonisation of scientific assessments and decisions of multi-national CT is needed, but achievable within the current legal framework (e.g. CTFG)

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Please note that the written submissions and the presentation slides from the meeting will be included in appendix to the report of the meeting will be published at the same time as the report.

Name of Organisation	Country
State Institute for Drug Control	Czech Republic

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
The aspects that are considered to work well are not specifically addressed. Comments + suggestions for improvement are made in the respective tables.	

Aspects of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
Non-commercial (academic) studies	The requirements should be minimised - e.g. labelling of IMP in phase IV studies: no requirements on labelling provided that the product is used in compliance with its SPC and the outer packaging has not been interfered with. *ECs agree.*
PIS/ ICFs (+ the way patients are being informed) - very frequently subject to comments raised by both the CAs and ECs	Guidance on various aspects of informed consent/ assent is needed. More attention should also be paid to specifics of informing currently compromised subjects ("sequential" consent), minors (taking account of age groups, approach to long-term studies when subjects come of age during the study etc.). *ECs agree.*
Situations can arise where giving informed consent may be compromised due to the immediate condition of the subject (e.g. acute myocardial infarction, acute psychosis etc).	*It would be useful to elaborate on a system of informing these patients (e.g. kind of "sequential informed consent" - very brief information at the beginning, followed by a detailed informed consent as soon as possible.*
ASSENT - sponsors´ interpretation of the term "assent" and approach to informing minors shows variability	Art. 2 - Definitions: the term "assent" should be specified. *EC agree with a greater focus of the Directive (or guidelines) on informing paediatric trial populations, the difference between "consent" and "assent" should be clear*
The term substantial/ non-substantial amendment is being interpreted differently (sponsors vs CAs/ ECs, differences between member state CAs)	The guidance should be more specific and provide examples.
SAFETY REPORTING - sponsors frequently misinterpret the term SUSAR: CA/EC receive reports on expected cases, cases with impossible causality (e.g. patient still in run-in and IMP not yet administered); reports on cases where causality is assessed towards a non-IMP etc.	
ECs are overloaded with SUSAR reports, line-listings etc.	*ECs suggest that only urgent safety issues should be reported with measures to be taken (proposed by the sponsor)*

Aspects of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
Sporadic cases of GCP non-compliance: this refers (not exclusively) to academic sponsors.	Currently, the opinion of the ECs on investigators is predominantly based on the investigator qualification per se, knowledge of trial related duties (and GCP principles) may be considered, but is not a pre-requisite. Certification of investigators (based on training in GCP principles) should be considered. EC comment: similarly, certification of EC members (at least some) would be useful
TIMELINES given by the Directive are very tight and the restriction on amending the documentation (Art. 9 (3) - "...on one occasion only") seems to be counterproductive. The review of the CTA comprises pre-clinical, clinical and pharmaceutical components and the respective lists of comments are usually finalised separately at different points in time. Adhering to this requirement results in very short deadlines for response (e.g. not sufficient for amending the protocol) and frequent withdrawal of CTAs by sponsors. Resubmissions are sometimes made in very short intervals after withdrawal made upon the CA´s recommendation.	The restriction on amending the documentation on only one occasion should ideally be left out. In cases, where the sponsor needs more time for response and where the CA anticipates that the documentation could be amended and reviewed within an additional period (e.g. 30 days at the most), both parties (CA and sponsors) should be allowed to agree on an extension of the review period. Alternatively, the CA could be allowed to give "conditional" approvals of the study and impose additional requirements on the applicant.
Currently, the synopsis of trial results is available only upon CA/EC´s request. The EC suggest that this summary should be submitted automatically after the study has been finished globally.	Amendment to Art. 10 (c)
Art 13 (1) - is focused on "holding of authorisation"; In some cases authorisation has expired, is not complete or is not available for all manufacturing sites.	The wording of the article should reflect the fact that the applicant is obliged to prove GMP status of the IMPs used in the clinical trial, i.e. to submit valid GMP documents for all manufacturing sites.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
The term substantial/ non-substantial amendment is being interpreted differently (sponsors vs CAs/ ECs, differences between member state CAs)	The guidance should be more specific and provide examples.
PIS/ ICFs (+ the way patients are being informed) - very frequently subject to comments raised by both the CAs and ECs	Guidance on various aspects of informed consent/ assent is needed. More attention should also be paid to specifics of informing currently compromised subjects ("sequential" consent), minors (taking account of age groups, approach to long-term studies when subjects come of age during the study etc.). *ECs agree.*
Situations can arise where giving informed consent may be compromised due to the immediate condition of the subject (e.g. acute myocardial infarction, acute psychosis etc).	*It would be useful to elaborate on a system of informing these patients (e.g. kind of "sequential informed consent" - very brief information at the beginning, followed by a detailed informed consent as soon as possible.*
ASSENT - sponsors´ interpretation of the term "assent" and approach to informing minors shows variability	Art. 2 - Definitions: the term "assent" should be specified. *EC agree with a greater focus of the Directive (or guidelines) on informing paediatric trial populations, the difference between "consent" and "assent" should be clear*
NIMPs - labelling of non-IMPs provided by sponsors and not authorised in the concerned MS.	If not prescribed by the investigators, non-IMPs should be labelled "for use in a clinical trial only". Clarification regarding language requirements (local vs original language).
	ECs would appreciate if the insurance related requirements were specified in a greater detail (e.g. clarification on whether commitment to make a contract after the trial has been approved by the CA would be sufficient)

What should a new legal framework look like?	
Comments	**Suggestions**
The timelines given by the Directive are very tight and the restriction on amending the documentation (Art. 9 (3) - "...on one occasion only") seems to be counterproductive. The review of the CTA comprises quality, clinical and pharmaceutical components and the respective lists of comments are usually finalised separately at different points in time. Adhering to this requirement results in very short deadlines for response (not sufficient for amending the protocol) and frequent withdrawal of CTAs by sponsors. Resubmissions are sometimes made in very short intervals after withdrawal made upon the CA´s recommendation.	The restriction on amending the documentation on only one occasion should ideally be left out. In cases, where the sponsor needs more time for response and where the CA anticipates that the documentation could be amended and reviewed within an additional period (e.g. 30 days at the most), both parties (CA and sponsors) should be allowed to agree on an extension of the review period. Alternatively, the CA could be allowed to give "conditional" approvals of the study and impose additional requirements on the applicant.
Art. 4 - the requirement on consent of parents (i.e. both parents – per SUKL´s interpretation of the Directive) may have a negative impact on the enrolment of paediatric population (the other parent may not be available, etc.)	Consent of one parent should be sufficient, provided that it represents the minor´s presumed will (assent) and a positive opinion of another investigator/ physician on the child´s enrolment has been obtained). *EC agree*
Sporadic cases of GCP non-compliance: this refers (not exclusively) to academic sponsors.	Currently, the opinion of the ECs on investigators is predominantly based on the investigator qualification per se, knowledge of trial related duties (and GCP principles) may be considered, but is not e pre-requisite. Certification of investigators (based on training in GCP principles) should be considered. *EC comment: similarly, certification of EC members (at least some) would be useful*
In Art. 10 - Conduct of a clinical trial, reference is made only to amendments to the protocol. Amendments to the IMPD may also impact on the safety of the patient.	The article should cover the pharmaceutical amendments (their notification)
Currently, the synopsis of trial results is available only upon CA/EC´s request. The EC suggest that this summary should be submitted automatically after the study has been finished globally.	Amendment to Art. 10 (c)
Art 13 (1) - is focused on "holding of authorisation"; In some cases authorisation has expired, is not complete or is not available for all manufacturing sites.	The wording of the article should reflect the fact that the applicant is <u>obliged to prove GMP status</u> of the IMPs used in the clinical trial, i.e. to submit valid GMP documents for all manufacturing sites.
ECs are overloaded with SUSAR reports, line-listings etc.	*ECs suggest that only urgent safety issues should be reported with measures to be taken (proposed by the sponsor).*
ECs feel that a system of EC accreditation (continual education of the EC members, system of self-evaluation) should be established.	
* *the comments in italics refer to the ECs.*	

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

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Name of Organisation	Country
ECRIN (European Clinical Research Infrastructures Network)	EU
EORTC (European Organization for Research and Treatment of Cancer)	EU
ESF-EMRC (European Science Foundation - European Medical Research Councils)	EU
CPI (Coordination des Promoteurs Institutionnels)	France
INSERM (Institut National de la Santé et de la Recherche Médicale)	France
VISEAR (Vienna Initiative to Save European Academic Research)	Austria
ESICM (European Society of Intensive Care Medicine)	EU

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1) The EU legislation resulted in a partial harmonisation of clinical trials on medicinal products in the EU.	1) There is now a need to extend the harmonisation process to all the categories of clinical research in the EU, beyond clinical trials on medicinal products.
2) The EU legislation also led to the integration of clinical trial identification (through the unique EudraCT number and database) and of adverse event reporting in clinical trials (through the EudraVigilance database).	2) Such databases should now be used to promote transparency, and particularly to develop a European tool for open study registration and reporting.
3) The EU legislation promoted a single opinion from ethics committees at the national level, and defined the roles and responsibilities of the sponsor and of the state (through the competent authority) in the conduct of clinical trials.	3) There is now a need for a better definition of the respective roles of ethics committees and of competent authorities, and for streamlining their interaction.
4) As a consequence of the Directive, some EU countries have invested in the development of a clinical research infrastructure and promoted training programmes, whereas some public institutions have strengthened their capacity to fulfil the sponsor's tasks. This resulted in an improvement in the conduct, in the quality and in GCP compliance of clinical trials.	4) The development of such clinical research infrastructures (at clinical sites, at clinical research centres, at clinical trials units undertaking design, conduct and analysis of clinical research) should now be supported in all the EU member states and coordinated at the EU level.

Aspects of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) ***Harmonisation / integration*** The 2001/20/EC Directive and its transposition into national legislation failed to efficiently harmonise the regulatory framework and to facilitate EU clinical trials. It made the initiation and conduct of national, and also of multinational clinical trials on medicinal products more difficult than before the implementation of the Directive. The increased administrative workload and expensive monitoring raised the cost of academic clinical research by 2 to 4 times, and made it impossible to conduct some studies. Moreover, acting as a single sponsor in the EU is impossible for most academic institutions.	1) Considering the failure of the 2001/20/EC Directive to efficiently harmonise the regulatory framework of clinical trials, and the failure of national legislations and national competent authorities to implement harmonised regulation and practice, we would recommend, whenever possible, an integrated approach (i.e. for the competent authority). When integration is not possible (i.e. for ethics committees), coordination, guidance, and accreditation should assist and enforce harmonisation. In addition, implementation of such legislation should be coupled to a strengthening of the clinical research infrastructure and of training programmes at both the national and the EU levels.
2) ***Directive / regulation*** Some EU member states took advantage of the flexibility in the transposition of the Directive to escape part of its negative impact on clinical research. This resulted in divergent national regulations that made multinational cooperation even more difficult.	2) In an ideal situation where the new EU legislation would foster rather than hamper clinical research, the issue of a real harmonisation should be addressed by the new legislative framework, either through a Directive, a regulation, with clear implementation guidance. Most participants consider that the regulatory framework for clinical research can be covered by regulation, avoiding divergent interpretation while transposed into national legislation – in such case, a Directive should be maintained for ethic committees, as ethics is left to the competence of the member states and cannot be covered by an EU regulation.
3) ***Field of the Directive*** Clinical research is not restricted to clinical trials on medicinal products – this is particularly true for academic research. There is a major disharmony between national regulations regarding clinical research other than clinical trials on medicinal products. This leads to consider the need for extension of the EU legislation to areas of clinical research not covered by the Directive. However some countries fear that such an extension would hamper rather than facilitate such research.	3) The ideal solution would be a single EU legislation designed to facilitate clinical research in the EU, prepared by DG SANCO, DG Research and DG Enterprise and Industry, adequately and equally protecting the participants in every category of clinical research across the EU (a situation equivalent to the national one where the Ministry of Health is usually responsible of such legislation). If such a solution is not possible, we would suggest : 3.1 to extend the field of an improved version (assuming that it really facilitates clinical research) of the EU legislation on medicinal products to all the clinical

	trials on health products (including medical devices, diagnostic products, herbal medicines, nutritional supplements), as they require a common regulatory framework in which the competent authority supervises the health product and the preclinical requirements, and the ethics committees supervise the protection of participants. 3.2 to write a new legislation (also assuming that it really facilitates clinical research) covering all clinical research not involving health products (also reviewing the preclinical development of know-how and procedures), either interventional or observational, in order to ensure harmonised adequate protection of participants and to facilitate clinical research in the EU. This new legislation should involve DG Research and DG SANCO.
4) ***Competent authorities*** The task of the competent authorities is to supervise the medicinal product, which is the same throughout the EU. There is still a considerable disharmony between requirements for clinical trial authorisation from the competent authorities. The practices differ between countries. There is a redundant assessment of the same product by many agencies, resulting in waste of time, money, and expertise for the agencies, and in multiple submissions for the applicant, and most importantly in a delay for a new therapy to benefit patients.	4) For multinational trials, the easiest way to circumvent this difficulty would be to obtain a single clinical trial authorisation through a centralised procedure (or a mutual recognition) in which the clinical trial application is managed by one single competent authority, instead of up to 27 national competent authorities. This would save a lot of time and human resources, avoid duplication of protocol and investigational medicinal product (IMP) dossier review, strengthen expertise, and reduce the administrative burden for academic sponsors and investigators. This is merely an extension of what is proposed for first-in-man studies. For national trials, the clinical trial authorisation could be left to the national competent authority; however, in the long term integration of clinical trial authorisation will make sense (as EudraCT and SUSAR reporting are already integrated) also for national trials. The governance of EMEA (and/or a new EU competent authority) should be modified towards more consideration of the interests of consumers, public health issues, and research issues – in the member states, the medicines agencies depend on Ministries of Health, not on the Ministries of Industry.
5) ***Ethics committees***	5) The EU legislation should promote harmonisation of the activity of ethics committees through either guidance or a change to the Directive implementing an

Ethics committees ensure the protection of participants in clinical trials. There is a major disharmony in the assessment of clinical protocols and informed consent forms by ethics committees. This reflects cultural differences in ethical review of clinical research but additional, unnecessary disharmony is due to the lack of coordination, training, and quality assurance systems.	appeal procedure and an accreditation system for ethics committees, ensuring appropriate training and quality assurance, based on EU-wide specification. In addition, a European coordination of ethics committees (under the responsibility of DG SANCO) should promote harmonised training, tools, and practice, including a common template for the informed consent requirements in the EU.
6) ***Multiple sponsors*** A single clinical trial authorisation, and a single EudraCT number, should not necessarily require a single sponsor in the EU, only a single applicant at the EMEA/EudraCT level. The requirement for a single sponsor is a major bottleneck to multinational clinical research for academic institutions that lack the capacity to fulfil sponsor's tasks in multinational studies. This is also true for small and medium-sized enterprises (SMEs). In addition, some countries allow multiple sponsors.	6) There is an absolute need to allow multiple sponsorship for multinational as well as for national trials, in order to share, on a contractual basis, the roles and responsibilities in the various EU member states, this multiple sponsorship being under the coordination of a single applicant for European regulatory authority.
7) ***Definition of categories of research*** Some definitions are open to divergent interpretation, resulting in national differences in the categorization of the same clinical study, particularly the border between interventional and observational studies. The Directive defines intervention as treatment intervention, diagnostic intervention, or change in follow-up ('monitoring') procedures. This led to divergent interpretations between countries, as some consider diagnostic procedures as intervention in any case, other only if they increase the risk for the patient, whereas other have defined an intermediate category of 'minimally interventional' studies. As a result, the same post-marketing safety study, without treatment intervention but with collection of a blood sample, may be regarded as a clinical trial on a medicinal product covered by the Directive in some countries, and as an observational study in other.	7) 7.1 There is a need to clarify the border between interventional and observational studies. Therefore, a workshop should be organised to discuss this point and the potential relevance of defining a category of 'minimally interventional' studies, without treatment intervention and with only low-risk intervention regarding diagnostic or follow-up procedures, for which approval from ethics committee is required, without full clinical trial application. 7.2 There is also a need to harmonise the interpretation on psychological assessment as an intervention. 7.3 In a more general perspective, there is a need to refine the definition of categories of clinical research, beyond the phase I-IV classification. The regulatory requirements should take into account the lower risk associated with studies using marketed drugs within their labelled indication for treatment optimisation or combination trials, or trials on off-label use of marketed drugs.

The Directive fails to differentiate categories of research on medicinal products, and does not consider the lower risk associated with some of them, (particularly post-marketing studies, which represent a major part of academic clinical research). Instead, it proposes adaptation for 'non-commercial trials'.	This is of utmost importance for the academic community as a considerable part of its clinical trial activity falls into these categories. Developing regulatory requirements based on the risk associated to these categories would be an alternative way to the 'specific modalities for non-commercial trials' that tend to suggest that there are two levels of quality. We strongly oppose the idea that clinical trials should come in different forms regarding their quality, depending on who initiated the trials. If clinical trials are to differ in any regard, this ought to be decided based exclusively on a thorough risk assessment (hazards to the participants, to the trial's data, to public health). A workshop should be organised to help further discuss this critical point. 7.4 There is a need to clarify the border between medicinal products, nutritional supplements, and nutrition studies. A workshop should be organised to help further discuss this critical point. 7.5 The Directive uses the wording 'subjects' for individuals participating in a clinical trial. This should be changed to 'participants', which better highlights their active role and is non-derogatory.
8) ***Definition of 'non-commercial' trials*** The concept of commercial compared to non-commercial trial should be replaced by a better wording (avoiding 'commercial'). In addition, the need for support and for regulatory adaptation may be different for 'non-commercial trials' and for 'trials sponsored by a non-commercial institution'.	8) There is a need to organise a workshop on the definition of clinical research run by academic institutions (e.g., investigator driven clinical trials), and to determine, with representatives of the academic research community, which adaptation could be proposed, for which type of trial. Defining 'specific modalities for non-commercial trials' tends to suggest that there are two levels of quality. This should be avoided, and in turn risk-based strategies should be used to improve the cost-effectiveness of clinical trials, especially for monitoring. Therefore developing regulatory requirements adapted to the risk associated to defined categories of clinical trials would be an alternative way. As stated in (7), most clinical trials sponsored by academic institutions correspond to categories of research associated with a lower risk: studies using marketed drugs within their labelled indication for treatment optimisation or combination trials, trials on off-label use of marketed drugs, pharmacoepidemiology studies. Academic institutions are also involved in the development of drug treatments for

	rare diseases, where market incentives fail to drive industry investment. Public-private partnership is frequently used for co-funding or co-development. Specific modalities should be defined for all these categories of research, not for 'non-commercial trials' as a whole.
9) ***Adaptations for academic research ('non-commercial trials')*** Academic institutions acting as sponsors in clinical research face major difficulties in either national or multinational trials, that may be dampened by measures ensuring an appropriate level of quality, and based on support and on regulatory adaptation depending on the risk associated with the category of study (hazard to the patient, hazard to the institution, hazard to the study, hazard to public health).	9) 9.1 The guidance document on 'specific modalities for non-commercial trials' mentioned in recital 11 of the 2005/28/EC Directive states that data from non-commercial trials cannot be used for registration, which is a major obstacle to academic-sponsored research and to the development of new indications for marketed medicines, especially in rare diseases. In the future, this may be a threat to all diseases due to the development of personalised treatments. 9.2 In some countries, non-commercial trials (or sponsors) are waived to pay fees to competent authorities and to ethics committees. Other countries do not implement such a waiver, or only reduced fees. This waiver system should be harmonised. 9.3 Similarly, some countries have implemented a waiver for the sponsor to purchase the IMP (investigational medicinal product) in non-commercial clinical trials, not other, and this initiative should be generalised. 9.4 In some countries, the insurance coverage for non-commercial trials is provided by the public health system, by the public hospitals or the university hospitals. This system should be implemented in all the EU member states, with the capacity to cover also investigator-driven trials sponsored by a foreign institution in an EU member state. 9.5 National competent authorities should provide free support to academic sponsor in SUSAR reporting and MedDRA coding. 9.6 Adaptation of the requirements should be allowed for marketed drugs regarding IMP dossier, and labelling. Alternative methods should be allowed to ensure traceability. Independence of academic trials should not be restricted by the need to ask the marketing authorisation holder to cross refer to an existing IMP dossier.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
1) ***Interaction between ethics committees and competent authorities*** Various models have been implemented for the interaction between ethics committees and competent authorities: no interaction, a streamlined cross-talk, or a close cooperation in which the competent authority, not the sponsor, directly interacts with the ethics committee.	1) A guidance is needed to further define the respective tasks of ethics committees (protection of participants) and of competent authorities (assessment of the medicinal product), and how ethics committees and competent authority (either national, or a single EU competent authority) should cooperate in the clinical trial application process and during the conduct of the trial (for instance the model of a direct communication between the competent authority and the ethics committees, resulting in a one stop-shop system for the applicant that interacts only with the competent authority, has to be further discussed). This could reduce redundant work and increase clarity and responsibility.
2) ***SUSAR reporting to ethics committees*** SUSAR reporting to ethics committees and to investigators is a major issue raised by ethics committees, investigators, and sponsors.	2) We consider that an improved and streamlined communication between ethics committees and competent authorities could help solve this issue. SUSARs and AER should be reported by the sponsor only to the competent authority, while ethics committees and investigators could have access upon request to the data collected by the competent authority. In addition, a workshop should help discuss how best to make information on risk and benefit also available to participants in order to ensure the long-term validity of the informed consent..
3) ***Information on national and EU requirements***	3) Information on national and EU requirements for clinical trial authorisation should be available, in English, to sponsors and investigators through a dedicated and updated website (at EMEA, or DG SANCO ?), and a helpdesk should be developed to support sponsors in multinational studies. In addition, electronic documents (pdf), not only paper documents, should be authorised for clinical trials application and submission to ethics committees.
4) ***Investigational medicinal product (IMP) definition***	

In the current guidance, only some background treatments are considered as IMP, and this requires case-by-case examination leading to divergent interpretation.	4) A simple and unambiguous definition of IMP should be provided. This is of particular importance for academic trials, as this has an impact on labelling and traceability, on SUSAR reporting, and as in some countries the academic sponsor still has to purchase the IMP.
5) ***Definition of substantial amendments*** The definition of substantial amendments is open to varying interpretation resulting in different status across the EU member states.	5) A guidance should provide unequivocal definition.
6) ***GMP (good manufacturing practice) requirements for biotherapy***	6) There is a need to harmonise the requirements for GMP manufacturing of biotherapy products.
7) ***Education and training of investigators, nurses and other specialised staff***	7) A guidance should be developed for education and training for investigators and staff in clinical trials, with accreditation of educational programmes. Continuous education of investigators and staff should be promoted. The issue of a qualification for investigators and staff should be discussed during a workshop.
8) ***Methodological assessment by ethics committees and competent authorities.*** The competent authorities and ethics committees play a critical role in controlling the methodology of the protocol and in reducing the risk of errors – risk of design errors, risk of random errors ('play of chance'), risk of systematic errors ('bias'). There is currently a lack of quality assurance requirements and accreditation ensuring that the methodological review of protocols is adequately performed.	8) Clinical trials methodology should be part of guidance documents, quality assurance, and accreditation processes for ethics committees and competent authorities.

What should a new legal framework look like?	
Comments	**Suggestions**
1) A single and comprehensive legislation (directive and/or regulation) covering all clinical research should be prepared, ensuring adequate and equivalent protection of participants in any biomedical research in the EU,	1) All the biomedical research on human beings, with or without health products, interventional or observational, should be covered by a single, legislative framework prepared under the umbrella of DG SANCO with the contribution of DG Research and DG Enterprises. In order to ensure harmonisation, a Regulation would be preferred to a Directive (whenever possible).
2) facilitating high-quality clinical science in the EU and protecting the participants according to the risk associated to the category of study (not according to its 'commercial' or 'non-commercial' objective),	2) Categories of research should be carefully and unambiguously defined, each being associated with regulatory and quality requirements adapted to the risk (instead of adaptation to 'non-commercial trials'). In turn, support should be provided to public institutions acting as sponsors in clinical research (possible co-sponsorship, support to MedDRA coding and SUSAR reporting, information and helpdesk on regulatory requirements, public insurance coverage, waiver of purchasing the IMP, development of the clinical research infrastructure). Workshops are needed to reach an agreement on the definition of, and borders between categories of research, the associated risk, and the resulting requirements.
3) with centralised assessment by a single competent authority (at least for multinational trials),	3) Instead of duplicating efforts, assessment of the health intervention should be conducted by a single agency (either centralised, or specialisation of the national competent authorities in a given type of health product, or mutual recognition).
4) with accredited and co-ordinated ethics committees,	4) Implementation of a quality assurance and accreditation system, and of an EU coordination under the responsibility of DG SANCO, leading to harmonised training and practice.

5) with clear guidance on their respective roles, and on the harmonised interaction between ethics committees and competent authority,	5) The national ethics committees should protect the participants in every category of clinical research, whereas the competent authority should assess the health intervention (including a health product if any), using a streamlined and harmonised procedure for interaction between both,
6) and promoting trust, transparency and optimal use of data in clinical research through open study registration, study reporting, and data sharing.	6) A clinical trial registration tool, in line with the requirements of the WHO international clinical trials registration portal (ICTRP) and of the ICMJE (International Committee of Medical Journal Editors) is lacking in the EU. The new EU legislation should state that data from the EudraCT database (and/or equivalent) will be used to build a public EU clinical trial register for all interventions (open access to information from EudraCT is already planned in the paediatric regulation). In addition, the EU should take advantage of this registration tool to give open access to study reporting, and to create a repository for anonymised clinical trial data.

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Please note that the written submissions and the presentation slides from the meeting will be included in appendix to the report of the meeting and be published at the same time as the report.

Name of Organisation	Country
European Group for Blood and Marrow Transplantation (EBMT)	Europe

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1) Improved standards of conduct for non-commercial studies which will improve the quality of the research	1) A significant number of non-commercial studies have been able to find an overall sponsor, which has prevented studies from taking place. There should be some mechanism whereby individual institutions can sponsor themselves and then collate the data.
2) There has been some standardisation of paperwork	2) Consensus should be sought within countries and between countries to further standardise submission requirements, this should result in better harmonisation, a significant improvement in the speed of the process, and should be achievable.
3) The implementation of an European trial is extremely complex, time consuming and expensive, which at least means that only important or very relevant questions will be addressed in new trials.	3) Some questions even if they are of high scientific interest and have potential to improve patient care, may not get done if there is no funding and/or an overall sponsor cannot be found
4) The minimal requirements for monitoring	4) Monitoring is very expensive, keeping it to a minimum is a help but still need to address how you fund the monitoring of non funded studies
5) The shortened timeframes at the authorities have speeded up procedures	5) This has been a benefit at least in Sweden. However, some additional allowed clock-stops could be included since for non-commercial studies, the time frames might have become too tight..

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) Harmonization across Europe could never be achieved by a Directive(s)open to local interpretation in each country and this has clearly been identified	1) Harmonisation could still be achieved to a greater degree by seeking consensus between the Competent Authorities of the member states. There are no truly essential differences in what they want so it should be possible to gain consensus
2) National ethics approval does not work well in most countries. The desired objective would have been to implement the "French system" whereby one ethics committee reviews and local review is confined to local resource evaluation by each institution. Instead in most countries the national ethics committee exists alongside local ethics and in many instances national review must precede local review leading to more paperwork and longer approval times.	2) Again it should be attempted to gain consensus. In addition, most local committees appear to be mainly resource focused in which case this should be clarified and be processed simultaneously with the main ethics review
3) Countries differ in their requirements of SAEs reporting to national health Authorities thus making the role of the "promoter" of an academic study even more difficult.	3) Harmonisation should be sought on the subject among the different States.
4) The directive has resulted in skyrocketing costs for performing academic non-commercial studies.	4) There should be a simpler form of trial regulations for non-commercial studies. Registration studies of new products need to be performed rigorously but a lot of studies are comparing licensed products to each other alone or in combination and a lot of the basic knowledge already exists for these products. Either a large injection needs to be made into research funding to permit close trial monitoring or a lower standard of monitoring should be accepted. This could be managed without reducing trial governance or safety.

5) The directive is too inclusive	5) The basic idea is to safeguard the patients from poorly conducted trials. Many studies now running under the directive are actually quite simple and could be excluded from the directive and only be regulated by ethical committees.
6) Very difficult to get sponsors to accept responsibility for trials which cross national boundaries.	6) This area needs exploration – can it be made easier to share sponsorship responsibilities?
7) The definition of an IMP differs between the Directives and guidelines for Pharmacovigilance reporting	7) Clarify and address the issue of standard of care drugs being used in a non-licensed indications

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
1) Try and gain consensus as to submission requirements, safety reporting and annual/progress reports	1) Create a working party with representatives form each Member State to try and gain consensus
2) Publication of definite lists of submission requirements from each CA in local language and the official language of the EU, English	2) Impose on CAs the requirement to publish such information and keep it up to date in real-time
3) Clarify definition of IMP	3) Define an IMP as a medicinal product that is being tested
4)	4)
5)	5)
…	…

What should a new legal framework look like?	
Comments	**Suggestions**
1) It should clearly differentiate between non-commercial and commercial studies and ensure that the requirements of the directive are not only desirable but achievable.	1) Ensure participation of representatives from all areas of research, industry, research organisations, academic groups, pharmacists etc are all involved preferably during the drafting of any proposals, but at the very least during the review process. Ensure wide dissemination throughout all stake holders in research during the consultation period.
2) It should clearly differentiate between trials with high patient numbers in a single institution and situations where even large centres can recruit only one or two patients per year.	2) Must be a system that allows studies of rare disease to be run without paralysing the study with paperwork, then patients can be entered in a rapid way. It is nonsense when all institutions must submit the study to their ethics protocol and do all the paperwork when there is a big risk that they will never see such a patient.
3)	3)
4)	4)
5)	5)
…	…

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Please note that the written submissions and the presentation slides from the meeting will be included in appendix to the report of the meeting and be published at the same time as the report.

Name of Organisation	Country
European Commission – Directorate General for Research and Technology Development (DG-RTD) – Directorate "Health"	EU

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
Legislative harmonisation.	
EudraCT and *EudraVigilance* integration of trials' identification and adverse events' reporting.	
Clear identification of the roles of Sponsors, Competent Authorities and Ethical Committees within the conduct of a clinical trial.	
Dissemination and Implementation of the Good Clinical Practice rules.	
Enhancement of the level of quality of management of private and public institution (sponsor's duties).	
Triggering of investment in clinical research.	

Aspects of the Directive 2001/20/EC that can be improved	
Comments	**Suggestions**
Lack of definition of "Non Commercial Clinical Trial"	Careful evaluation of the specificities of RTD-F funding activities in "non commercial clinical trials" run with Academia only in the interest of the patient and where SMEs are involved in research projects. An inadequate definition could seriously reduce the capacity of RTD-F to fulfil the mandate within the FP7. The potential equivalence of data obtained in "non commercial clinical trials" in comparison with those obtained in "commercial clinical trials" for legislative purposes could be considered.
Lack of comprehensive consideration of the specificities regarding the involvement of Small and Medium Enterprises	An inadequate consideration could have a negative impact especially in the development of new innovative therapies whereas SMEs have a key role. The potential role of SME as sponsor of "non commercial clinical trials" could be considered.
Single Sponsorship	RTD-F is aware of the burden single sponsorship has put in the planning and management of multinational academy-driven non-commercial clinical trials. Multiple sponsorships should be considered.
Excessive Reporting/Administrative Requirements	Simplification measures could be considered.
Payment of medicines used "in label" by a "non-commercial" sponsor	*A waiver system could be considered.*
Complex traceability (incl. manufacturing / packaging / labelling procedures)	*Simplification measures could be considered*

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Name of Organisation	Country
European Forum for Good Clinical Practice (EFGCP)	Belgium

The comments and recommendations provided here result from 2 meetings with experts from academia, industry, industry associations, ethics committees and patients organisations from many different European countries, organised by EFGCP in order to identify and discuss areas for improvement in the Clinical Trials Directive (CTD). The proposals presented below are aspects that were agreed among all participants.

In addition, several recommendations were made which received strong support but not approval from all participants; however, these proposals should be further considered:

- A recommendation to include a revision of the GCP Directive 2005/28/EC into this upcoming CTD review process
- A recommendation to define specific facilitating conditions for academic treatment optimisation trials
- A recommendation to consider adding clinical trials with medical devices to the CTD
- A recommendation to include a request for publication of the results of all clinical trials performed in a peer-reviewed journal.

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1) Achievement of a single ethics opinion per country is a real improvement	1) However, there is a need to agree on the exact content of Module 2 of the application form.
2) An agreed IMPD format is very helpful	2) However, the content of the CTA dossier should be made identical in all EU member states.
3) 1 CTA and 1 ethics opinion per Member State submitted in parallel or sequentially is a good opportunity to reduce the overall timelines for approval of clinical trials.	3) However, the interaction between Competent Authorities and Ethics Committees is not well enough established and varies, country by country. This frequently leads to delays in study start due to the need for approval of substantial amendments, or requests for protocol changes, by one of the two parties.

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) Article 2 – Definitions Change in the definition of 'sponsor' Especially in multinational academic clinical trials, there is a need for the organisation of co-sponsorship	1) EFGCP Proposal: 'sponsor': an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial; **co-sponsorship should be permitted where appropriate and must be covered by a contractual agreement which specifies the roles, responsibilities and liabilities of each sponsor.**
2) Article 2 – Definitions Change in the definition of 'subject' The two different types of subjects should be mentioned for clarification purposes.	2) EFGCP Proposal: 'subject': an individual **– a patient or a healthy volunteer –** who participates in a clinical trial as either a recipient of the investigational medicinal product or a control;
3) Article 2 – Definitions Additional definition of 'SUSAR'	3) EFGCP Proposal: (q) suspected unexpected serious adverse reaction (SUSAR): an adverse event assessed as serious and unexpected and for which there is a reasonable suspected causal relationship with an investigational medical product
4) Article 6 – Ethics Committee	4) EFGCP Proposal: 1. For the purposes of implementation of the clinical trials, Member

EFGCP considers a need for formal accreditation of Ethics Committees to ensure their proper establishment, function and supervision.	States shall take the measures necessary for establishment, **accreditation** and operation of Ethics Committees.
5) Article 8 – Detailed Guidance EFGCP considers that there should be a requirement for adequate education and training to be provided for all personnel involved in the clinical trials process. Experience of EFGCP members revealed that there is no established dialogue between Ethics Committees and responsible Health Authorities about clinical trials approval during the CTA process. This should be formally established to avoid prolongation of the approval process due to substantial amendments required by one of these two parties in the clinical trial approval process.	5) EFGCP Proposal: The Commission, in consultation with Member States and interested parties, shall draw up and publish detailed guidance on the application format and documentation to be submitted in an application for an ethics committee opinion, in particular regarding the information that is given to subjects, and on the appropriate safeguards for the protection of personal data. **All personnel involved in clinical trials including Competent Authorities, Research Ethics Committees, sponsors and investigators should be qualified by means of education and training.** **Guidance should be produced to clarify and encourage appropriate dialogue between all Ethics Committees and Competent Authorities involved in the approval of a clinical trial.**
6) Article 9 - Commencement of a clinical trial 1. For consistency reasons, 'Competent Authority' should be spelled with 'C' and 'A' 2. EFGCP is of the opinion that the efforts for the preparation of a multinational clinical trial could be substantially reduced if there were only the need for **1** CTA from the EMEA to avoid duplication of efforts for submitting the same	6) EFGCP Proposal 1. Member States **and the Agency** shall take the measures necessary to ensure that the procedure described in this Article is followed for commencement of a clinical trial. The sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion and inasmuch as the **Competent Authority** of the Member State concerned **or the Agency** has not informed the sponsor of any grounds for non-acceptance. The procedures to reach these decisions can be run in parallel or not, depending on the sponsor. 2. EFGCP Proposal: (2) Before commencing any **national** clinical trial, the sponsor shall be

documentation to all Competent Authorities of the countries involved in the trial and to reduce the workload of the national Competent Authorities who all review the same documentation at the same time. Such an approach would also help to truly reduce the approval period to 60 days as substantial amendments approval due to different opinions of the national Competent Authorities could be avoided. Another possibility could be the sole approval from one national authority e.g. the national authority of the coordinating investigator. The national authorities would have to be informed about the single specific CTA to enable them to fulfil their obligations of clinical trial supervision and reporting of SUSARs. Whichever system would be adopted would have to allow for one Member State to refuse the CTA without blocking the clinical trial from being performed in the other Member States.	required to submit a valid request for authorisation to the **C**ompetent **A**uthority of the Member State in which the sponsor plans to conduct the clinical trial **or to a dedicated CTA Committee for multi-national trials at the Agency.** (3) If the **C**ompetent **A**uthority of the Member State **concerned, or the Agency,** notifies the sponsor of grounds of non-acceptance, the sponsor may, on one occasion only, amend the content of the request referred to in paragraph 2 in order to take due account of the grounds given. If the sponsor fails to amend the request accordingly, the request shall be considered rejected and the clinical trial may not commence. (4) Consideration of a valid request for authorisation by the **C**ompetent **A**uthority **concerned** as stated in paragraph 2 shall be carried out as rapidly as possible and may not exceed 60 days. The Member States may lay down a shorter period than 60 days within their area of responsibility if that is in compliance with current practice. The Competent Authority can nevertheless notify the sponsor before the end of this period that it has no grounds for non-acceptance.
7) Article 10- Conduct of a clinical trial The definition of 'substantial' is not clear and permits considerably different interpretations by sponsors, Competent Authorities and Ethics Committees. Also the term 'otherwise significant' does not help with the understanding of the type of amendments that are expected to be submitted for approval. EFGCP therefore proposes to delete the terms 'substantial' and 'otherwise significant' in this article.	7) EFGCP Proposal: (a) after the commencement of the clinical trial, the sponsor may make amendments to the protocol. If those amendments ~~are **substantial and**~~ are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial~~, or if they are **otherwise significant**~~, the sponsor **will consider them substantial and** shall notify the **C**ompetent **A**uthorities of the Member State or Member States

Again for consistency purposes, Competent Authorities and Ethics Committees should be spelled with capital letters.	concerned **or the Agency** of the reasons for, and content of, these amendments and shall inform the **E**thics **C**ommittee or **C**ommittees concerned in accordance with Articles 6 and 9.
8) Article 17 - Notification of serious adverse reactions EFGCP proposes to restrict expedited SUSAR reporting to the competent Health Authorities. During the EFGCP Annual Conference 2007 on *Ethics Committees in Europe – How to Work with Diversity?*, Ethics Committees members from 32 countries as well as the members of the EFGCP Ethics Working Party and the participants of the 2 EFGCP meetings on the Revision of the Clinical Trials Directive unanimously agreed to this suggestion. The reasons: Ethics Committees are 'flooded' with SUSAR reports from all over the world that require administrative handling. Ethics Committees have neither the capacities nor the competence nor digital means to do 'signal detection' or otherwise systemically identify a change in benefit and risk of the clinical trial. On the contrary, their capacities for protecting the patients are blocked by this administrative burden. Other ways need to be identified to enable Ethics Committees to make the required judgements, recognising that Competent Authorities already take appropriate action on receipt of such SUSARs.. A more efficient approach would therefore be a separation of responsibilities for Competent Authorities and Ethics Committees. EFGCP proposes that the sponsor submits safety reports at to be agreed minimum intervals of at least once a year throughout the lifetime of a clinical trial to the Competent Authorities involved including a listing of all SUSARs which occurred over the previous reporting period and a cumulative report of the subjects safety since the start of the clinical trial. The Ethics Committees concerned should receive a summary of these reports evaluating the benefits and risks for healthy volunteers or patients who have participated, are participating or will be participating in the respective clinical trial. EFGCP also considers it vital that other important safety information is reported expeditiously e.g. non-compliance of an investigational site (whereby "non-	8) EFGCP Proposal: Article 17 Notification of **suspected unexpected** serious adverse reactions **and other important safety information** **1.** (a) The sponsor shall ensure that all relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening is recorded and reported as soon as possible to the **C**ompetent **A**uthorities in all Member States concerned, in any case no later than seven days after the sponsor is made aware of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days. **Any change in the benefit-risk evaluation of the ongoing trial resulting in either a temporary hold or premature termination of this study should be reported immediately to the Competent Authorities and Ethics Committees in all concerned Members States, in any case no later than seven days after the sponsor has become aware of the change in the benefit- risk balance.** (b) All other suspected **unexpected serious** adverse reactions shall be reported to the Competent Authorities concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor. (c) Each Member State shall ensure that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are recorded.

compliance" should be defined). A special process needs to be introduced for the situation of temporary hold or premature termination of a clinical trial due to safety concerns: Established procedures for rapid information exchange, escalation and appropriate communication to all involved Health Authorities, Ethics Committees, investigators and study participants need to be in place to avoid potential harm to individual study subjects.	(d) The sponsor shall also inform all investigators. 2. At a minimum (to be agreed) interval or at least once a year throughout the lifetime of the clinical trial, the sponsor shall provide to the Member States in whose territory the clinical trial is being conducted a listing of all suspected serious adverse reactions which have occurred over the previous reporting period and a cumulative report of the subjects' safety since the start of the clinical trial. The Ethics Committees concerned should receive a summary of this report, evaluating the **benefits and risks** for healthy volunteers or patients who have participated, are participating or will be participating in the respective clinical trial. (…) **4. In the event of Competent Authorities of Member States or Ethics Committees becoming aware of any non-compliance having occurred at an investigational site during a clinical study, the Competent Authority or the Ethics Committee concerned shall notify the sponsor of that clinical study and all other sponsors conducting clinical studies at that site, of the specific concerns of non-compliance that have been identified.** **5. In the event that the Competent Authorities in concerned Member States, Ethics Committees or the sponsor consider that a temporary hold or premature termination of a clinical trial due to safety concerns is necessary, established procedures for rapid exchange of information, escalation and appropriate communication to all stakeholders including investigators and study participants need to be followed to avoid potential harm to the individual study subject.**
EFGCP is of the opinion that the Clinical Trials Directive should pay due regard to legislation that applies to the collection, preservation and transfer of human biological material within the context of clinical trials.	

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
1) EFGCP recommends that a change be made to the preamble of the Commission Directive 2005/28/EC concerning non-commercial clinical trials: the responsibility for special modalities should not be left to the Member States level as this will lead to considerable diversification of conditions for multinational non-commercial clinical trials. Instead the European Commission should provide concrete guidance on how far requirements for non-commercial clinical trials can be softened without compromising GCP and quality standards.	1) EFGCP Proposal (…) (11) Non-commercial clinical trials conducted by researchers without the participation of the pharmaceutical industry may be of great benefit to the patients concerned. Directive 2001/20/EC recognises the specificity of these non-commercial clinical trials. In particular, when trials are conducted with authorised medicinal products and on patients with the same characteristics as those covered by the authorised indications, requirements already fulfilled by these authorised medicinal products, as far as manufacturing or importation are concerned, should be taken into consideration. However, it could also be necessary, due to the specific conditions under which non-commercial trials are conducted, that Member States foresee specific modalities to be applied to these trials not only when conducted with authorised medicinal products and on patients with the same characteristics, in order to comply with the principles imposed by this Directive, in particular as far as the manufacturing or import requirements for authorisation and the documentation to be submitted and archived for the trial master file are concerned. The conditions under which the non-commercial research is conducted by public researchers and the places where this research takes place, make the application of certain of the details of good clinical practice unnecessary or guaranteed by other means. Member States will ensure in these cases, when providing for specific modalities, that the objectives of the protection of the rights of patients who participate in the trial, as well as, in general, the correct application of the good clinical practice principles, are

	achieved. **Although no distinction should be made between commercial and non-commercial / academic trials as far as GCP and quality requirements are concerned, some deviations from the general rules could be considered for non-commercial trials. The Commission will prepare a new draft with guidance in this respect.**
2) Creation of a global, easily accessible database, containing all national requirements in English should be added to the Guidance on CTA approval.	2)
3) The request to establish support for administrative and regulatory advice by providing a helpdesk for commercial and non commercial clinical research at the European level should be added to the Guidance on CTA approval.	3)

What should a new legal framework look like?	
Comments	**Suggestions**
1) EFGCP strongly recommends that the Clinical Trials Directive should be converted into a Regulation and that a single central Clinical Trial Authorisation for multinational clinical trials should be introduced by the EMEA.	1)

efpia
European Federation of Pharmaceutical Industries and Associations

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Name of Organisation	Country
European Federation of Pharmaceutical Industries and Associations (EFPIA) including the EFPIA specialised groups: European Vaccines Manufacturers (EVM) and European Biopharmaceutical Enterprises (EBE)	Belgium

efpia

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
A harmonised application form for Clinical Trial Applications (CTAs) to Competent Authorities (CAs) and Ethics Committees (ECs) and harmonised requirements for core scientific information across Member States (MSs). The acceptance of a simplified Investigational Medicinal Product Dossier (IMPD) for Investigational Medicinal Products (IMPs) known to the concerned CA.	Evaluate further areas for harmonisation between MSs for both CAs and ECs.
The possibility of cross-referring to the Investigator's Brochure for generation of the IMPD avoids duplication in the CTA to the CA. Acceptance of a simplified IMPD for IMPs known to the CAs.	Maintain and further support this possibility.
Harmonised timelines for CTA review by CAs and ECs. Parallel assessment by CAs and ECs. Statutory role for ECs and provision of a single EC opinion in the MS. Implicit approval mechanism for CAs.	Parallel submissions should be made possible in the minority of MSs where this is currently not the case. Timelines need to be respected and not extended (e.g. by validation time). Further improvements are needed to ensure all MSs are operating in the same way.
Having a EU-wide legal framework for clinical trials is a first step in creating an understanding within CAs, ECs and investigators about the global nature of clinical research required for development of innovative medicinal products.	Establish a forum for continuous dialogue between all stakeholders (CAs, EC, European Commission, Academia and Industry) to further promote clinical research in Europe.
All countries seemingly require SUSARs to be reported within 7/15 days to the national CAs, albeit with some variation in specific local requirements for what should be sent and discrepancies in unblinding procedure (see below). Harmonisation of the reporting timelines is considered to be positive however some aspects of the expedited reporting requirements remain open to interpretation and hence could be improved by clarification within the ENTR/CT3 guideline: - For the definition of 'seriousness', there is no standard for assessing 'important medical events' - For 'expectedness', the reference document requires clarification: is it the entire Investigator's Brochure (IB) or should sponsors follow the CIOMS III/V recommendations that they assess Adverse Drug Reactions (ADRs) against a specific section within the IB?	Within the ENTR/CT3 guideline: 1. Provide further examples of 'important medical events' that should usually be judged as serious when not fulfilling other criteria for serious adverse events 2. Clarify whether sponsors should assess expectedness against mention of an ADR anywhere within the IB or against mention in a specific section of the IB.

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
<u>CTA Approvals and Country-Specific Requirements</u> The need for "a valid request" before commencing a clinical trial is stated in Directive 2001/20/EC (Article 9; paragraph 2). For multinational trials, divergent CTA assessment outcomes are difficult to incorporate into a single international clinical trial protocol. Currently, there is no process established for conflict resolution. Ways for sponsors to handle these situations are either post approval amendments to incorporate different requests into one international clinical protocol or to withdraw certain MSs from the trial. It is further recognised that most of the scientific "core" documentation in the CTAs (including the IMPD) is to a great extent standardised for the majority of MSs and associated states. Unfortunately however, study sponsors of multinational trials face with a multitude of national administrative requirements. Attachment I of the relevant EU Guideline (ENTR/F2/BL D CT 1; Rev. 2, October 2005) lists over 40 potential information items (plus a few additional preferences added as footnotes) that may or not be needed depending on MS. Many of the documents are also frequently requested by both the CA and the EC in the same country. The administrative requirements should not be confounded with more scientifically based (but likewise divergent) requirements, e.g., "*Method of contraception*" (several CAs refuse as "*Exclusion criteria*" statements such as "*women of childbearing potential not protected by effective contraceptive method of birth control*". Instead, they request a specific method of contraception to be stated. Other CAs accept a general statement). "*Right to publish*" (several CAs refuse a statement that publication of trial results shall be delayed by the investigators until approval of publication is given in written by the sponsor. Other CAs accept such statements) In addition to the disharmony displayed in Attachment I of the referenced Community guideline, sponsors face with a number of other administrative obstacles and national particularities that are not explicitly mentioned or justified in Attachment I of the Community guideline. These requirements may in some cases reflect "preferences" of individual assessors or administrative decisions by the CA. Illustrative examples are: *Application form in national language, national applications forms, application forms in both electronic and paper format, proof of fee payment, copy of notification letter to hospital scientific board, signed declaration by head of healthcare institution, import licenses/notifications, sponsor proof of establishment in the Community, Certificates of Analysis, samples of IMP and placebo, Good Manufacturing Practices (GMP) certificate, contact point for "further information" to be provided to patients, copy of application to EC, EC approval letter, written confirmation by investigator that study will be conducted in accordance with protocol and regulatory requirements, a justification for gender distribution of patient population to be recruited, a declaration that the sponsor will inform the patients regarding methods used to securely transmit personal data to CA and EC, for subjects under age of consent: a statement that study will be conducted in accordance with CPMP/ICH/2711/99), justification of global evaluation of risks and benefits of the trial, applicant agreement or refusal to include trial in national public register of authorised trials, completed declaration form for biological samples, protocol statement that preclinical and clinical studies have been conducted in accordance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP), respectively, a letter from the IMP supplier authorising the sponsor to use data relating to the IMP (when supplier is not the sponsor), additional local insurance policy, valid GCP training certificates for investigators and sub-investigators, CV of independent*	For suggestions, please refer to the next table titled 'What can be remedied within the present legal framework'

physician to whom subjects can address questions, comparative table of changes versus previous IB/protocol version. When taken individually, some of the national administrative specificities here exemplified may not seem unreasonable. In the context of a multi-country trial, however, the cumulative effect can become very burdensome for the sponsor (without adding to patient safety)	
Variation in Application of Safety Reporting Requirements 1. Despite consistent application of the requirement to report Suspected, Unexpected Serious Adverse Reactions (SUSARs) within 7/15 days to national CAs, there remains some variation between MSs with regards to which SUSARs should be reported, based on country of origin of the SUSAR, application of the definition of IMP, whether or not the trial generating the SUSAR is conducted within the MS etc. There have also been inconsistencies across MSs with regards to whether SUSARs should be unblinded or not before notification and whether SUSARs are considered as efficacy endpoints or not in specific clinical trials. This ultimately leads to inconsistent population of the EudraVigilance-Clinical Trials Module (EV-CTM), with duplicate and/or missing data, thereby hampering the protection of trial subjects. 2. There is significant variation in national requirements for notification of SUSARs to ECs: All SUSARs or local SUSARs, on paper or 'creative' electronic formats; Data presented as expedited Individual Case Safety Reports (ICSRs) vs. periodic line listings; some ECs want unblinded SUSARs only; All SUSARs associated with the IMP vs. only SUSARs arising from trials approved by the EC; Fees to cover the cost of managing the SUSAR reports/line-listings. 3. There is significant variation in national requirements for notification of SUSARs to investigators: Expedite all SUSARs as individual ICSRs; Expedite local SUSARs with periodic line listings for foreign SUSARs; Periodic line listings only; Not specified in some countries. 4. Inconsistent application of annual safety reporting requirements across MSs. Lack of clarity of the requirements for line listings and summary tabulations: Periodic or cumulative? Local or global serious ADR reports? By trial or all-inclusive? Blinded or unblinded? 5. There are several issues remaining with regards to electronic transmission of individual SUSAR case reports to EudraVigilance (EV): ▪ High duplication rate – some MSs report the same ICSRs to EV without informing the sponsor(s), leading to duplicate reports from the MS(s) and the sponsor(s); ▪ No reports at all: some MSs act as 'sponsors' on behalf of non-commercial investigators but then do not report the SUSARs to EV; some MSs do not require reporting to EV and are not equipped to report to EV-CTM; ▪ Data quality issues, for example: cases transmitted by some MSs do not include narratives, even though the sponsor reported the ICSRs to the MSs with narratives; inconsistencies in data reported by MSs e.g. the outcome is fatal but no death is reported in the appropriate section; the IMP is not identified, as the EudraVigilance-Medicinal Product Dictionary (EV-MPD) is not populated at the time of SUSAR reporting	For suggestions, please refer to the next table titled 'What can be remedied within the present legal framework'
No Common Understanding of IMP Scope Significant differences in national interpretation of what constitutes an IMP still exist. This is in spite of: ▪ Directive 2001/20/EC which includes a single definition of IMP, ▪ The Commission Guidance on IMPs and other medicinal products used in Clinical Trials and	For suggestions, please refer to the next table titled 'What can be remedied within

▪ Annex 13 of EU GMPs which unequivocally describes products, which do not fall within the definition of IMP. The issues seem to arise because of differing interpretations and national legal implementation of the definition of IMP included in the Directive, and the fact that it does not differentiate the requirements as applied to different types of IMP. Inconsistent approaches to the designation of background and "standard of care" therapies used in multi-country clinical trials, have also been taken leading to the same product in the same trial being listed as an IMP in one MS but not in another, especially when the product is not approved in all participating MSs. Some MSs have concerns about the ability to trace these products, leading to requests for such products to be designated as IMPs. This particularly is the case for products with a MA whose use is required by the study protocol but that the sponsor does not regard as IMP. Differences in interpretation have implications for provision of information in the CTA, as well as for labelling, logistics, traceability, pharmacovigilance and release by the Qualified Person (QP). In addition, the guideline on IMPs seeks to impose a number of requirements for products that are not considered to be IMPs that are disproportionate to their use in clinical trials, and which have questionable benefit to study subjects. In particular, having the general requirement that information to be provided on products not considered to be an IMP should be in accordance with the Commission Guidance on applications to the competent authority (i.e. nothing more than a SPC should be required for authorised products)."	the present legal framework'
National GMP Requirements EFPIA member companies are experiencing significant differences in interpretation of GMP requirements for IMPs by individual MSs. Examples of different requirements: (not in prioritised sequence): ▪ Requests for QP audits of IMP manufacturing sites ▪ Requests for QP declaration in country specific format ▪ Requests for supporting GMP documentation for 3rd country manufacturing sites ▪ Re-analysis of comparators from 3rd countries Requests for import notification/license in addition to import authorisation ▪ Different IMP labelling requirements Legalised Transmissible Spongiform Encephalopathy (TSE) statements	For suggestions, please refer to the next table titled 'What can be remedied within the present legal framework'
Inconsistency of Amendment Notification Although Directive 2001/20/EC attempted to prevent the notification of trivial changes to clinical trials, there is a problem of over-notification or inconsistent notification of minor changes to CTAs as substantial amendments. This particularly concerns changes to study protocols. The probable causes of this are: ▪ Divergent interpretation of the guidance driven by organisations' or individuals' differing tolerance to risk ▪ The interpretation that the International Conference on Harmonisation (ICH) on GCP guideline requires all protocol amendments to be notified to the ECs	For suggestions, please refer to the next table titled 'What can be remedied within the present legal framework'

▪ Some ECs and CAs being uncomfortable with not being notified of every change to CTAs ▪ Retroactive challenges to the Sponsor's decision on non-substantial amendments when the change is communicated to the CA or EC at a later date The consequences of this are: ▪ Additional burden on the resources of Sponsors, Applicants, Investigators, national CAs and ECs ▪ For multi-country trials, it can lead to a divergence in the information submitted to CAs and ECs in support of the trial (within a given MS or between MSs) ▪ Delay to clinical trials thereby slowing down the pace of medical research.	
<u>Repeated assessments of the science and methodology by CAs, central and local institutional ECs, respectively</u> The protection of patients participating in a clinical trial is of paramount importance and the role that institutional ECs assume in this context is well recognized. The process described in the clinical trials Directive suggests that different roles and responsibilities are allocated to the EMEA, national CAs, central or national institutional ECs and local (at the investigators' site) institutional ECs. Division of roles between EMEA and national CAs works well. However, when a CA approves a protocol but subsequently the corresponding national/central institutional EC raises issues about the protocol design that should have been raised by their CA this results in delays, at best, or more complex protocol designs to satisfy an isolated request by a national institutional EC. It is undisputed that an institutional EC must have the right of identifying weaknesses in protocol design that have the potential to harm patients or impact on their rights but this role should not lead to a repeat of the assessment performed by the CA. The issue is further compounded when local institutional ECs overturn the decision of the national/central institutional EC or make their approval depending on the implementation of changes to the protocol requested only by this particular institutional EC.	For suggestions, please refer to the next table titled 'What can be remedied within the present legal framework'

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
Short/Medium Term Objective	We need less disparity between the MSs - Certain key issues (i.e. those described below) need to be addressed urgently and cannot wait a legal revision of the Clinical Trials Directive. We believe the consensus-building work currently conducted in the Clinical Trials Facilitation Group (CTFG) and Commission working group will need to be accelerated and given a higher priority by the Heads of Medicines Agencies (HMA) (and their full endorsement). A greater transparency regarding the objectives and workplans of these groups and a systematic involvement of the stakeholders are also needed. In some areas, national disparities (e.g. safety reporting, approach taken to comparators and combination therapies) are particularly obstructive to research. Certain issues (e.g. SUSAR and annual safety reporting assessments) could also be addressed by a work sharing approach. However, if all harmonisation attempts between the MSs fail, the EU Commission may have to take a more directive stance (e.g. by issuing recommendations or communications).
CTA Approvals and Country-Specific Requirements For comments, please refer to the previous table titled 'Aspect of the Directive 2001/20/EC that do not work well'	While a unified approach to the actual scientific assessment seems like a utopic goal within the present framework, a reasonable aim is still for a single and unique CTA dossier (which includes the IMPD) that is acceptable to all the EU/EEA national CAs. There seems to be no scientifically valid reason why the documentation contained in the EU CTA should differ between MSs. Indeed, the core IMPD is to a large extent identical for all EU/EEA States (while the administrative requirements are not). While there may be a number of reasons why the administrative requirements vary between MSs (we acknowledge there may in some instances be legally defined obligations) we strongly argue that it should be in everybody's interest to rapidly remove all or as many as possible of the differences. ▪ As a short-term measure, as a matter of efficiency and transparency, information about all national requirements should be made available in English, i.e. spelt out in an updated Attachment I (of the guidance documents on CA and EC applications) The definitive list will provide clarity and avoid a cumulative build-up of ad hoc requirements. ▪ Mid-term, country-specific administrative forms and requirements not justified by science or safety should be phased out. ▪ However, the ultimate goal must be to have identical information requirements and formats, applicable to all MSs and associated states (i.e. a removal of Attachment I from the guideline). [We realise and acknowledge that removal of some MS-specific requirements may require changes in national legislation]
Variation in Application of Safety Reporting Requirements For comments, please	The following issues can and should be addressed within the current framework: 1. MSs should be consistent in their application of expedited reporting requirements to ensure that EV-CTM is populated in a manner that facilitates rather than impairs the protection of trial subjects. EFPIA suggests that, in the short-term, expedited reporting requirements should be applied across all MSs as specified in Directive 2001/20/EC i.e. SUSARs should be notified within 7/15 days in an unblinded manner to all concerned CAs regardless of the country or

refer to the previous table titled 'Aspect of the Directive 2001/20/EC that do not work well'	trial of origin of the SUSAR or the suspect drug involved (study drug or active comparator), and that this should be emphasised within ENTR/CT3 accordingly. An alternative (and a simple) solution would be that the sponsors report all the SUSARs occurring in any of the trial sites worldwide to a single database EV which all the MSs have an access to. 2. The current requirements for the notification of SUSARs to ECs as presented in the guidance ENTR/CT3 should be applied across all MSs i.e. immediate (7/15 days) notification of SUSARs of local origin out of a concerned trial to all concerned ECs that approved this clinical trial on the IMP within that MS, as unblinded ICSRs in paper format: ▪ periodic notification of 'foreign' (i.e. occurring in all other countries worldwide) SUSARs to all ECs that have approved clinical trials on the IMP, as unblinded 6-monthly line listings; ▪ fees should not be charged to sponsors for the administration of these reports by ECs. In due course, Directive 2001/20/EC should be amended to clarify this requirement accordingly. 3. The current requirements for the notification of SUSARs to investigators as presented in the guidance ENTR/CT3 should be applied across all MSs i.e. periodic notification SUSARs as blinded 6-monthly line listings. In due course, Directive 2001/20/EC should be amended to clarify this requirement accordingly. 4. The annual safety reporting requirements are clarified in the guidance ENTR/CT3, to indicate: ▪ Periodic line listings, presenting all serious ADRs (Suspected Serious Adverse Reactions (SSARs)) reported during the 1 year under review; data should be unblinded for all SUSARs from ongoing studies and all SSARs from completed studies, but remain blinded for 'expected' SSARs from ongoing trials; ▪ Cumulative summary tabulations, covering all serious ADRs reported during each clinical trial up to the most recent data-lock point. 5. To strengthen and clarify the guidance documents ENTR/CT3 and ENTR/CT4 on the reporting rules to EV ▪ All the sponsors should follow the same reporting rules and particularly: To be able to transmit electronically the cases to EV-CTM; To include a narrative for all serious cases; To be compliant with the business rules defined in EV; To populate the EV-MPD with the IMPs. ▪ Elaborate new set of business rules to ensure consistent data in the ICSRs.
No Common Understanding of IMP Scope For comments, please refer to the previous table titled 'Aspect of the Directive 2001/20/EC that do not work well'	▪ Ensuring that the guidance on IMPs presents a truly harmonised approach to be applied by all MSs; the current guidance still allows opportunities for different interpretations between MSs. ▪ In particular, it should be made clear that a comparator with a marketing authorisation within the EU shall only be classified as an IMP if it is used in a modified form and/or it is not used in conformance with its marketing authorisation terms ▪ Appropriate and simplified approaches should be developed, in conjunction with stakeholders, to ensure the traceability of medicinal products with an MA whose use within a clinical trial is required by the protocol, without unnecessarily classifying all such products as IMPs; such approaches should not add to the burden in the creation and review of the CTA and the conduct of the trial, but should be assessed as part of inspection procedures. ▪ Unless voluntary harmonisation efforts are successful, amending Directive 2001/20/EC should be considered in order to describe specific, relevant, risk-based requirements for three defined groups of medicinal products for interventional clinical trials, such as the

	"test" products (i.e. the product(s) which is/are the subject of the study), active and placebo comparators, and standard treatments, concomitant treatments and established procedures
National GMP Requirements For comments, please refer to the previous table titled 'Aspect of the Directive 2001/20/EC that do not work well'	▪ A joint meeting involving representatives of the European Commission, the CTFG, the GMP/GDP inspectors working group, HMA representatives and industry to discuss the issues. Meeting objective: to accomplish a harmonised understanding of GMP requirements for IMPs between regulators and industry. ▪ Improve GMP requirements/legislation for IMPs on the following points: - Introduce harmonised requirements for administrative aspects of GMP for IMPs in Commision's detailed guidance. Remove or align national legislation/guidelines for GMP requirements, which exceed Community requirements. - Define/agree on QP role and responsibility in releasing IMP across all MSs. - Provide clarity on GMP for IMPs of other annexes in EU GMP guidelines, e.g. Annex 19 on Reference and Retention samples.
Inconsistency of Amendment Notification For comments, please refer to the previous table titled 'Aspect of the Directive 2001/20/EC that do not work well'	▪ The sponsor's responsibility for the decision on whether a change constitutes a substantial or non-substantial amendment, as provided in the legislation, must be respected by all ECs and CAs. ▪ It should be made clear by the Commission that the 2005 EU guidance (ENTR/F2/BLD/2003 as revised) has precedent over the 1996 ICH GCP guidance in the areas of apparent contradiction. ▪ Although the above guidance satisfactorily sets out the criteria for decisions on substantial amendments, some additional guidance on best practice and process may assist some sponsors, particularly on how to proceed with non-substantial amendments. In addition, it may be useful to consider examples of changes that would categorically be considered as non-substantial amendments, as long as it was stressed that the examples were not an exhaustive list.
Repeated assessments of the science and methodology by CAs, central and local institutional ECs, respectively For comments, please refer to the previous table titled 'Aspect of the Directive 2001/20/EC that do not work well'	Guidance should be issued that defines roles and responsibilities of CAs, national / central and local institutional ECs, respectively. The aim is to clarify that the CA is responsible for assessing the medical and scientific merit of a trial, whether the design and methodology to be applied will allow reaching sound conclusions. The national / central institutional EC should verify whether the protocol is in line with the medical practice of a given country, whether the protocol meets ethical standards and preserves the rights and integrity of patients. Should the national / central institutional EC identify weaknesses in the trial design and methodology these should be brought to the attention of the CA within the stipulated time frame. The CA will determine and decide whether the objections raised require the protocol to be amended. Similarly, the local institutional ECs should only assess whether the investigator and his institutions are capable to execute the protocol, i.e. whether they have the resources, competency and patients to conduct the protocol as planned. Should a local institutional EC identify weaknesses in trial design and methodology they are required to raise these through the national / central institutional EC.

What should a new legal framework look like?	
Comments	**Suggestions**
Medium/Longer Term Objective: ***A Dual Pathway Towards an Improvement*** It seems reasonable to assume the general framework of the Clinical Trials Directive will apply to clinical research in Europe for many years to come. A hypothetical revision of the Directive would necessitate a long parliamentary review process followed by a complex national implementation process. Even a "simplified" Directive would again be subject to national interpretation. A fundamental flaw in the current system is the multiple assessment of the same documentation in each involved MS - without any mechanism for arbitration or for reaching a consensus	**1. The following safety reporting issues should be addressed in modifying the current Directive:** - EFPIA suggests to clarify the reporting rules in the Directive and revise the Article 17, 3(a) "*Each MS shall see to it…*" that has lead to a confusion with regard to the role and responsibilities of each stakeholder. - Directive 2001/20/EC should be amended so that the sponsor only needs to report all SUSARs (and more broadly all SSARs) involving the IMP(s) and regardless of their origin to a single database, preferably **EV** at the EMEA, who shall then place the case reports on EV-CTM for all other CAs to have access to. This rule would have the advantage to allow for a safety assessment, immediately for SUSARs since they will be reported unblinded, and at the end of the studies when the SSARs will be unblinded at the time of the ASR. - Directive 2001/20/EC should be amended to establish a. A better use of EV-CTMas the safety database used by all CAs for the protection of trial subjects in Europe. b. Uniform reporting rules to ECs as described above in the suggestions of what could be done within the current legal framework c. Uniform reporting rules to investigators as described above in the suggestions of what could be done within the current legal framework d. Mandatory population of the EV-MPD by sponsors and CAs, as appropriate e. Work sharing amongst CAs for assessment of SUSARs and ASRs. **2. A new addition to current legal framework** We need a new (optional) alternative for CTA approvals and supervision - There are some <u>fundamental</u> weaknesses of the Clinical Trials Directive that can not be remedied via further consensus-building: ▪ Duplication – multiple CTA reviews. Many (but not all) of the commercial sponsor difficulties are not linked to the Directive requirements *per se*, but to a divergent interpretation of the requirements between the MSs. Moreover, it is doubtful if repeated technical reviews of the same background and product information significantly add to patient safety, nor may it be the best use of scarce resources. ▪ No streamlined "from CTA to marketing authorisation application" process for centralised products – with extended mandatory - and optional scopes for the centralised procedure, a majority of all new medicines already follow the centralised registration pathway. Clinical trial design issues and the subsequent evaluation of the results from the same trials are addressed at Community level (via EMEA scientific advice and the centralised marketing authorisation application assessment, respectively). Yet, the clinical trial protocols are instead evaluated by, approved by and reported to national CAs. ▪ Protecting public health: it seems unrealistic to assume that all MSs and associated states have access to the necessary assessment

decision. Many of the difficulties arising from the principle of multiple assessments cannot be addressed by further guidance. For the above reasons, we believe that efforts to improve the regulatory environment for clinical trials in Europe instead have to be pursued via two co-existing and mutually non-exclusive pathways (i.e., amending the safety reporting sections of the current Directive and by a new addition to the current legal framework; see the right-hand column)	expertise to cover all types of products and trials designs at national level (e.g. advanced therapies, adaptive trial designs). Indeed, in certain areas the European expertise has by necessity already been pooled (e.g. orphan products, paediatric medicines). A co-existing, optional, procedure applicable to multicenter trials, which provides a single approval would: ▪ *only require one single Community CTA,* ▪ *avoid the current duplication of assessments, discordant decisions and allow a better resource utilization,* ▪ *provide a better predictability for marketing authorisation application review outcome (scientific advice linked to study design).* Some of the key issues to resolve with such a procedure include: ▪ *Which body would be responsible for the scientific review of the CTA?* ▪ *How would this review be resourced and financed?* ▪ *How would the review be transposed to an "approval" that applies in all concerned MSs in which the trial was to be conducted?* ▪ *Could this procedure be adapted for the ethical review of the CTA?* We propose to develop these ideas further shortly and look forward to fruitful discussions with the regulators and other stakeholders.

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Please note that the written submissions and the presentation slides from the meeting will be included in appendix to the report of the meeting and be published at the same time as the report.

Name of Organisation	Country
European Genetic Allliance's Network (EGAN)	UK

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) The initial experiences suggest a decline in the number of new studies both in the industrial and academic research sectors. Not only the number of new studies is falling, but also the number of subjects included in the sector. This development, this delay is certainly not in the interest of patients who are looking for possible new or improved treatments, especially in the area of incurable diseases	A good survey in a short period to really investigate the suggested decline
2) Another issue is whether the opinion of trial subjects themselves about the new regulations is heard and in particular, if they feel that the stricter rules actually afford them more protection. Between trial subjects there is a difference between those who are organized in patient organizations and those – most probably the larger part – who are not organized in patient organizations. The organized patient organizations in Europe can raise their voice at meetings with the EU, EMEA and so on. But at the national level there is almost no platform to hear these voices. The non-organized trial subjects are represented in most countries in medical ethical review committees by lay persons, but also the opinion of these lay-persons is not heard or is unknown.	2) Better communications between the trial subjects, patient organizations and the medical ethical review committees (research ethic committees) at the local and national level in EU member countries.
3) Especially in the rare disease area there is an increasing number of comments received by EGAN that REC's are unfamiliair with the type of research that is being done in the rare disease area. And especially confusion over the boundary	3) REC's should have better developed mechanisms for letting families express their views about the desirability of the project proposal, of their hopes for outcome, and of their willingness to balance the risk and benefits associated

between research and clinical practice also compounded to the problem. Also there is a problem for REC's when funding for the research project had been raised by patients, the research question discussed and agreed with the PI and the (affected) family members were queuing up to participate. People familiar with research in the rare disease area will know that this is not an uncommon situation with rare disease support groups and there is frequently a close relationship between families and specialist clinicians/researchers by virtue of the small world of interested people they populate. In this context, REC demands for confidentiality, for example, are unreasonable because they are impossible to fulfil – everyone know everyone in the field and can recognise this very easily. This is also apparent in multi-state trials, where researchers, clinicians and patient groups know each other very well.	with their participation as research subjects. As an educational tool EGAN-member - the Genetic Interest Group (GIG) and the Ethox Centre at Oxford University produced a booklet of guidance for REC's. This booklet can be downloaded at www.gig.org.uk/docs/GIG-OGKP.pdf

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
2)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

What should a new legal framework look like?	
Comments	**Suggestions**
1) In future, the medical ethical review committees or REC's – at least at the national and European level – should have input (membership) from the patient community directly. The past decades have seen increasing involvement and collaboration in scientific research on the part of patients'organisations. In many cases, the combination of traditional knowledge gained through scientific channels and the experiental knowledge or expertise acquired by patients'organisations provides added value. The question therefore arises as to why the REC's do not take greater account of the knowledge possessed by patients' organisations. And especially, when considering the appointment of lay members. The EU legal framework should contain guidance on this.	1)
2) See also before on the relationship between REC's and the requests from the rare disease groups	2)
3)	3)
4)	4)
5)	5)
…	…

The European Society for Developmental, Perinatal and Paediatric Pharmacology (ESDP) welcomes regulation number 1901/2006 on Medicinal Products for Paediatric Use. This regulation will hopefully encourage clinical trials in the paediatric population. This is important as many medicines are currently used off label.

We feel it is important that the EMEA through the Paediatric Committee ensures that the medicines studied are those that will benefit children and not just generate the biggest profits for the pharmaceutical industry. This has been a problem with the American legislation.

The legislation provides financial incentives for the pharmaceutical industry to study medicines in children and this is appropriate as paediatric clinical trials are more expensive than those performed in adults for a variety of reasons. It is important that the EMEA and the Paediatric Committee review both the financial benefits to the pharmaceutical industry and the benefits obtained by children through the provision of a greater evidence base for the use of medicines.

The European Paediatric Clinical Trials Database is an important development that should benefit the children of Europe. We welcome the fact that the results from all clinical trials submitted to the EMEA will be made public on this website. It is essential that information generated from clinical trials in children is freely available to public and health professionals.

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Please note that the written submissions and the presentation slides from the meeting will be included in appendix to the report of the meeting and be published at the same time as the report.

Name of Organisation	Country
Ethics Committee Medical University of Vienna	Austria

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1) From the perspective of an Ethics Committee, the requirements of article 7 (single opinion) have proven to be beneficial. It has led to less diversity and more capacity building in Ethics committees in Austria.	1) There are no defined training requirements for EC members (neither initially nor ongoing). There is a need for harmonized training of ECs in Europe.
2)	2)
3)	3)
4)	4)
5)	5)
…	…

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
Categories of Research The Directive is mainly tailored to the requirements of trials for registration of medicinal products. It does not differentiate types of clinical trials, in particular not with regard to their risk level. There is abundant research involving no or minimal risk, particularly in the academic sector. As any intervention in a study involving medicinal products tags this study as clinical trial on a medicinal product, the requirements of the Directive have to be met (insurance is often a substantial obstacle). Basic clinical research has severely suffered at our institution (minus 60% studies on medicinal products in the academic sector since the introduction of the Directive). To underline the problem, 3 recent examples: EXAMPLE 1: Patients on dialysis receive anticoagulation therapy during dialysis. The proposed study was to measure a blood platelet parameter with a new instrument in addition to the routine monitoring of coagulation. This involved the collection of an additional small amount of blood. Since the effect of an anticoagulant on a platelet parameter is measured, this constitutes a clinical trial on a medicinal product. The result of the study is of entirely academic interest and may only serve for hypothesis generation. EXAMPLE 2: Diabetic patients suffer from complications such as macular edema. Some of these patients are on dialysis and receive erythropoetin during their dialysis therapy. The project in question was ophthalmologic with the aim to check whether erythropoietin-therapy would change (improve? deteriorate?) the macular edema. This involved a non-routine split-lamp investigation of the eye. As the effect or erythropoietin on the course of a disease (macular edema) is measured and a non-routine intervention (split-lamp examination) takes place,	There is a need for better definitions which types of studies (and interventions) fall under the scope of the directive. This should be done on a broad basis (work groups, workshop). Whether – once a framework of definitions is established - a given study has to be considered truly interventional and requires full clinical trial application may be decided by the ethics committees.

the study constitutes a clinical trial on a medicinal product (i.e. the patients have to be insured). EXAMPLE 3 Patients with pulmonary hypertension are routinely treated with bosentan, an endothelin-antagonist. The aim of the project was to measure an endogenous substance in plasma with the hope to find a biomarker that would indicate outcome. Interventions involved a blood sample before and two times after initiation of bosentan-therapy. Because the influence of bosentan on a biochemical marker is studied, the project is a clinical trial on a medicinal product (with the "threat" that the "sponsor" has to carry the cost for the bosentan treatment). Again, the project was only of academic value and served only hypothesis generation.	
2)	2)
3)	3)
4)	4)
5)	5)
…	…

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
2)	1) Clarification of the term “non-interventional” may definitely help basic research involving registered medicinal products that are used within their labelled indications.
2)	2)
3)	3)
4)	4)
5)	5)
…	…

What should a new legal framework look like?	
Comments	**Suggestions**
3)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Please note that the written submissions and the presentation slides from the meeting will be included in appendix to the report of the meeting will be published at the same time as the report.

Name of Organisation	Country
EUCROF European CRO Federation	CRO Associations of EU Member States: Czech Republic France Germany Italy Spain The Netherlands UK

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1) The fact that there is a single CTA form for all Member States (MS) is a big plus compared to old legislation	1)
2) Overall, the time to receive clinical trial authorisation by the Competent Authorities of MS has been reduced (few exceptions only). For Ethics Committees, time to response has been reduced in some MS.	2) Please see under: Aspects of the Directive 2001/20/EC that do not work well Points 2 and 3)
3) Single Ethics Committee per Member State is very positive and works well in some MS, but not in all of them.	3) Please see under: Aspects of the Directive 2001/20/EC that do not work well Point 3)
4) The fact that batch release of IMPs which have to be imported from third countries can be performed by a sponsor QP is very positive and works well.	4)

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) The Detailed Guidance Documents ENTR CT1 and CT2 list the documents which need to be submitted per MS. From that list, it becomes obvious already, that there are quite some differences across Member States (MS). However, the listed documents only represent "core" documents and MS require additional documents as part of a CTA which are not listed (and therefore are maintaining a "list behind the list"). Without these additional documents a CTA is not considered complete and will not pass the (formal) validity check. For a single country trial, the effect might be acceptable, however, for a multi-national trial, the situation is very complex and the administrative burden is not acceptable. One goal of the Directive was to simplify administrative provisions. This goal is clearly not met when considering the work which has to be performed for the submission of a multi-national clinical trial. The above mentioned issue becomes even more cumbersome when countries are involved which require documents in local language. Example: • In Spain, the full protocol and the IB have to be translated into Spanish. This is a real disadvantage for Spain, because the translations are not only expensive, they are also very time consuming. In addition, Spain requires the local law being referenced (e.g. RD 223/04) in the trial protocol, even in case of an international protocol. This does not represent an EU approach.	1) Country specific documents should be abandoned. This could be reached by defining the documents needed for a CTA within the Directive. In addition, it should be stated that a CTA is considered valid as soon as all documents listed in the Directive are submitted. There should be agreement in the EU on the kind of documents which have to be submitted in local language (like informed consent form, IMP label, synopsis of the clinical trial protocol) and those which are allowed to be submitted in English.
The above Comments and Suggestions also match under the heading "What should a future legal framework look like?", however, for the sake of length of the document, will not be repeated there	

2) Some MS maintain national authority procedures on top of the procedures deriving from the implementation of Directive 2001/20/EC or have implemented the Directive in a very "regional" way. This is contradictory to the goals of the Directive 2001/20/EC, i.e. to • Reduce start-up time • Simplify and harmonise administrative provisions Examples: • Germany maintains extensive notification procedures on a federal state level (in addition to the procedures with the Competent Authority) which increases the administrative burden drastically, for example o Notification of starting and finishing involvement in a clinical trial for every investigator (not only principal investigator) o Notification of amendments to federal states • In Italy, each Region can and in fact does issue different administrative rules. The Competent Authority is represented by the General Manager of each Local Sanitary Unit (responsible person for administrative issues of a geographical area with one or more hospitals). The outcome is a variety of different procedures and timelines. Overall start-up time of clinical trials is impacted very negatively by these regional requirements.	2) The Directive should clarify that any MS-specific (local) procedures should be either abandoned or – if not possible - must not interfere with the goals of the EU Directive, i.e. must not affect timelines defined in the EU Directive 2001/20/EC. It is realized that the removal of MS-specific procedures will require legal changes in the respective MS.

The above Comments and Suggestions also match under the heading "What should a future legal framework look like?", however, for the sake of length of the document, will not be repeated there	
3) Submissions to Ethics Committees still suffer from a whole variety of different procedures across MS, starting with different forms, different documents (see point 1) and different interpretation as to the requirement of "one single opinion per Member State". The result is "no harmonisation" whatsoever, in particular for multi-national trials. Also, it could take much longer than the allowed timelines to receive the EC opinion and the sponsor is not able to do anything about it as the EC procedure is no "implicit" procedure. Examples: • In Italy, the vote of the lead EC has to be submitted to local ECs, and they can decide whether it is accepted or not on a local basis. This procedure does not represent a single opinion per MS and the total response time often exceeds the legal provisions for timelines for ECs. • In Spain, local ECs use a large variety of different documents and procedures which must be complied with even if the lead EC does not demand them. This increases the workload of sponsors and CRO and makes the submissions tremendously complicated. Additionally, local ECs evaluate not only local aspects of the trials (as suitability of investigator or site) but also methodological part of the protocol or CRF and can reject a project even if the lead EC approves it. This again, is an incorrect implementation of the Directive Furthermore, in Spain submissions to ECs can only be made between the 1st and the 5th day of a month. This is not in accordance with the Directive as the clock should start ticking once a valid application is submitted, independent of the day of the month.	3) It is realised that it is more difficult to reach harmonisation for EC procedures than for Competent Authority procedures. However, the Directive could be more stringent regarding the requirement of a single opinion, stating that timelines have to be kept even when local ECs are involved or requiring the involvement of one single Ethics Committee per trial and MS (which would be most advantageous). An EU application form for ECs (Module 1 plus Module 2) should be required on a Directive level in order to reach harmonisation of the EC application across all MS.

The above Comments and Suggestions also match under the heading "What should a future legal framework look like?", however, for the sake of length of the document, will not be repeated there	
4) "Free movement of product" after batch release by a QP is not guaranteed in all MS Examples: • Finland is asking to distribute study medication through a central point in Finland • Portugal and Austria are requiring import licenses	4) EU Commission to control adherence of implementation of EU Directive and EU principles (free movement of product once batch release is available by an EU qualified person (QP) for GMP).
5) Not all MS are following Annex 13 in their local requirements for labeling Example: • Germany requires the CRO on the label in addition to the sponsor	5) Label requirements for study medication should be defined in the Directive to make it legally binding

The above Comments and Suggestions also match under the heading "What should a future legal framework look like?", however, for the sake of length of the document, will not be repeated there	
6) Procedures for SUSAR reporting are outlined in the Guidance Document ENTR CT3, i.e. they are not legally binding. This results in a diversity of procedures across MS. Example: • Germany asks for expedited reporting of all SUSARs to all involved parties (CA , EC and investigators), i.e. no periodic line listings are allowed for ECs and investigators. This also means that for a marketed IMP, all spontaneously reported SUSARs are forwarded to all ECs and all investigators in an expedited manner. The amount of paper fills whole halls, however ECs and investigators are not able to digest the information. Many sponsors try to find procedures for their Pharmacovigilance Departments which satisfy all MS (and other countries), i.e. they are looking for a conservative approach. This results in the maximum approach: i.e. reporting every SUSAR (notwithstanding the source or the status of the IMP (authorised / not authorised)) to everybody (CA, EC, investigators) in an expedited manner. The outcome is a tremendous over-reporting which decreases the chance to detect real signals. Another issue is the duplication of reporting within one country. Example: • In Spain, in addition to the SUSAR reporting via Eudrovigilance, it is requested to report all SUSARs which occurred in Spain to the local Autonomous Communities on a country specific paper form	6) The procedures outlined in the Detailed Guidance Document ENTR/CT3 under 5.1.1 (What must be reported?), 5.1.6.5 (How to inform the Ethics Committee?) and 5.3 (How to inform the investigators?) should be included in the Directive in order to reach harmonisation across MS. However, the expedited SUSAR reporting to ECs should not be limited to SUSARs having occurred in that particular MS, but all SUSARs from the concerned clinical trial. Additional reporting to regional communities within one country should be abandoned. It is realized that the removal of MS-specific procedures will require legal changes in the respective MS.

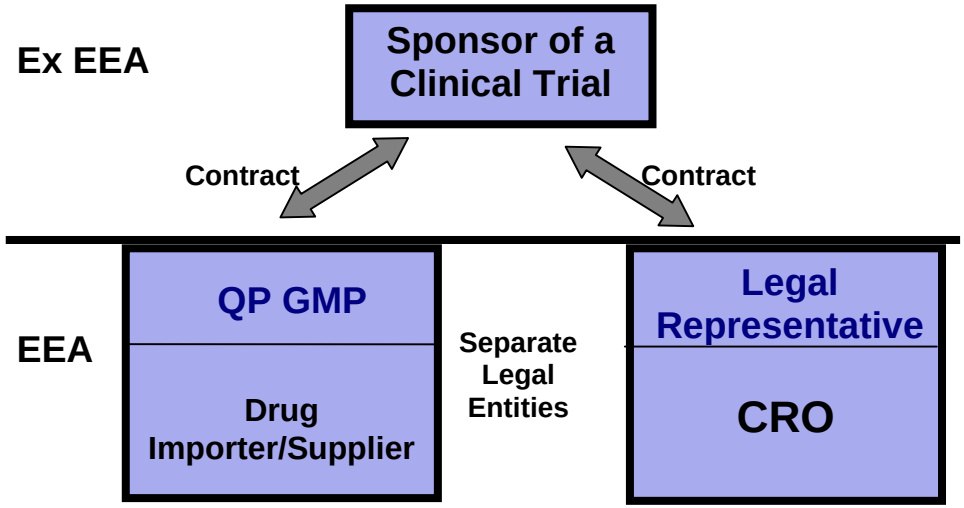
The above Comments and Suggestions also match under the heading "What should a future legal framework look like?", however, for the sake of length of the document, will not be repeated there	
7) Eudravigilance is extremely complicated and contains a number of flaws Examples: • The sponsor has to sign a form saying that all studies are covered by the same legal representative, however the legal representative is clearly a function defined per trial and a sponsor is allowed to have different legal representatives for different trials. • The website explains that, in order to avoid duplications, CAs of MS are not entering data. This is incorrect for Germany For non-commercial trials the administrative burden is considered not acceptable.	7) Incorrect information / flaws should be corrected. Non-commercial trials should be generally exempted from the use of Eudravigilance (like, for example, in Germany). The requirement to use the database often leads to the supporting industry taking over this task (not being the sponsor) and then the discussion starts on "how much support can industry give without becoming the sponsor of a non-commercial trial?" The limits are not clear. Lowering the administrative burden for non-commercial trials would reduce the potential of conflict as (non-commercial) sponsors would be better able to fulfil the sponsor tasks themselves.
The above Comments and Suggestions also match under the heading "What should a future legal framework look like?", however, for the sake of length of the document, will not be repeated there	
8) Sponsor Definition (Article 2 (e)) "An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial". The "or" is a problem because a pharmaceutical company supporting a non-commercial trial becomes a sponsor per definition	8) Drop the "or" in the definition as did some MS in their local law (e.g. UK, Germany)

The above Comments and Suggestions also match under the heading "What should a future legal framework look like?", however, for the sake of length of the document, will not be repeated there

9) Legal Representative (Article 19)

„This Directive is without prejudice to the civil and criminal liability of the sponsor or the investigator. To this end, the sponsor or a legal representative of the sponsor must be established in the Community"

This definition addresses liability. Who is liable in the scenario illustrated below in case of quality issues with the IMP? The drug supplier (with a QP at its disposal) or the CRO (being the legal representative)? This is not clear, however this is very important for CROs taking on the role of a legal representative for a sponsor not established in the EU (EEA).



9) Guidance is needed on the role and responsibilities of a legal representative.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
2)	
2)	2)
3)	3)
4)	4)
5)	5)
…	…

What should a new legal framework look like?	
Comments	**Suggestions**
1) Competent Authority Authorisation: It would be very desirable to follow the idea of a central approach also for the authorisation of a multi-national clinical trial (similar to the central approach of marketing authorisation). The central approach was possible for the marketing of medicinal products, why should it not be possible for the conduct of clinical trials?	1) Limit the assessment of a multi-national clinical trial to two MS (similar to rapporteur and co-rapporteur). As soon as all issues which these two MS brought up are solved, the clinical trial should be authorised for all MS.
2) Substantial Amendments: A multi-national clinical trial becomes very cumbersome as soon as different MS categorise amendments in different ways. It could be that an amendment is seen as "substantial" in one MS, in others it is accepted as "non substantial". Substantial amendments are sometimes authorised in some MS but not in others. The situation is extremely confusing and difficult to handle.	2) A central approach could also solve the difficult situation regarding amendments. There should not be more than two MS reviewing substantial amendments. As soon as an amendment is authorised by two MS (rapporteur, co-rapporteur), the amendment should be authorised for all MS.
Additional suggestions for changes of the Directive 2001/20/EC are listed under the heading "Aspects of the Directive 2001/20/EC that do not work well" and were not repeated here.	

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

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Name of Organisation	Country
European League Against Rheumatism (EULAR)	Switzerland (Headquarters)

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1) Standardisation of clinical trial conduct with clear lines of responsibilities and transparency of processes, including non commercial investigator initiated studies (paragraph 14).	1) Some aspects of non commercial trial conduct could be modified to ease the burden of administration for investigators with limited resources. Partly addressed in directive 2005/28/EC (paragraph 11).
2) The establishment of a "sponsor" i.e. a single legal entity responsible for all aspects of trial conduct.	2) Should be clearly separated from the common use of the word " sponsor" meaning the entity which finances a study.
3) Compulsory registration of all clinical trials to avoid suppression of negative results.	3) Re-consider of all small " proof of principle" pilot studies need to be so registered.
4) Standardisation of adverse event reporting.	4) Common forms throughout Europe to reduce paperwork.
5)	5)
…	…

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) "Off- label" use of therapeutic agents in clinical trials. Investigator initiated clinical trials using agents already registered for other indications often lead to important new treatment options for patients. The current situation is not clear regarding the "commercial" status of such studies.	1) Directive 2005/28/EU and the later "specific modalities" paper in part addressed this issue with the wording "patients with the same characteristics". Needs further clarification.
2) Industry participation and definition of a "non commercial clinical trial" are too rigid.	2) More detailed and pragmatic definitions allowing industry, academia and regulatory bodies collaboration without loss of quality.
3) Multiplicity of regulatory authorities (local, national and EMEA) involved in trial conduct. Already difficult for fully funded commercial studies, it may become prohibitive for less resourced non- commercial studies.	3) "One for all" national review board decision process and a centralised EMEA guidelines / template document to ensure international minimal European standards.
4)	4)
5)	5)
…	…

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
1) **"Off –label" use trials**. The current position (directive 2005/28/EU) uses the words "patients with the same characteristics". This is confusing and restrictive. Very often a proven registered agent is successfully tested in another similar setting, often with some passive industry participation such as free drug supply e.g. anti CD 20 monoclonal antibody , registered for rheumatoid arthritis , applied to vasculitis.	1) A more biologically meaningful definition such as "patients with similar pathophysiological characteristics" could better define a potential off -lable new target group.
2) **Particiption with industry in non commercial trials.** Unrestricted grants or supply of free drug from industry to assist non -commercial investigator initiated studies are a major source of support. Currently, under section 3, under 3.1.1 point 3 of directive 2005/28/EU, "no agreements between the sponsor and third parties etc." is inflexible. This does not mean that the industry runs or controls the study, but if the outcome is favourable for their product, it could support an extension of the labelling. An example is a running EULAR / EBMT study using rabbit ATG in hematopoietic stem cell therapy of severe scleroderma which is part of the protocol and could be supportive data if the study confirms this.	2) A more precise and restrictive definition of a commercial study would then leave non commercial studies with a more flexible status. e.g. a commercial study is one which is "a fully funded registration trial initiated by and sponsored by an industry". Any other kind of study would then be possible to be called non-commercial, with precise details of part industry support and degree of control being part of the transparency of the protocol including the investigators' conflicts of interest.
3) **Bureaucracy versus quality**. Clearly many of the tedious aspects of purely commercial trial GCP are necessary due to potential conflict of interest issues i.e. need to get product to market in the shortest time. However, some non-commercial investigator initiated studies become almost impossible to perform under the same conditions for cost reasons, and equally clearly, no conflict of interest issues exist. For example EULAR is currently supporting a study testing the role of methotrexate (a generic drug) in the treatment of polymyositis and dermatomyositis (a rare condition). The study has almost foundered due to complex EU regulations not directly related to safety or quality in this case.	3) A solution to this could be a structured platform or committee whereby EMEA and the learned societies e.g. EULAR could regularly interface on such issues to find a less formal but still high quality (with respect to safety in particular) solution. It should be noted that the EU experts consulted by EMEA in specific fields are often also members of such societies. A regular forum for dialogue between such societies and EMEA would ensure a "unité de doctrine" in the EU for non commercial trials , and formal conflict of interest statements by the clinical trial sub committee members would ensure transparency.

What should a new legal framework look like?	
Comments	**Suggestions**
1) Precise definition of what constitutes a non- commercial trial, or better what constitutes a purely commercial trial.	1) May not be legally possible by simple modification of the existing Directives 2001/20/EU and 2005/ 28/ EU.
2) Precise definition of what constitutes industry **participation** as opposed to **control** of a clinical trial.	2) ”
3) Precise definition of which aspects of commercial trials (no matter how defined) may be waived or modified (e.g. site visit number) in the case of non commercial trials, with safety being the major parameter.	3) ”
4) EMEA generated guidelines for defining minimal standards for ethics committee/ institutional review board requirements for all studies, in particular non-commercial trials.	4) A formal cross consultation process with industry, academia and learned societies e.g. EULAR to ensure a realistic and fair process in order to give patients access to effective and safe therapeutic agents in the shortest time possible.
5)	5)
…	…

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

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Name of Organisation	Country
EUREC (European Network of Research Ethics Committees)	

The enclosed comments and proposals result from an exchange of opinions between members of the EUREC core group, representing REC national networks from 8 Member States, and Switzerland. The proposals presented below have been agreed upon by all members of EUREC.

Aspects of the Directive 2001/20/EC that work well Session 2	
Comments	**Suggestions**
1) The directive 2001/20 has contributed to improving the overall protection of human subjects in Europe by offering a common framework for all CTs. It has also had an impact on the quality of the ethical review for other types of research using human beings. For instance, researchers in non-profit making organisations have had to learn to work in compliance with the GCP requirements.	1) Efforts should be made to better coordinate this directive with other sets of legislation on a European and national level. For instance, it would greatly facilitate the work of researchers, as well as the RECs and the competent authorities, if there is more systematic coordination with the Council of Europe Convention on Human Rights and Biomedicine and its additional protocol on biomedical research (see comments on research in emergency clinical situation). It would also be important to better coordinate the EU legislation applicable to other fields of research, for instance CTs on medical devices.
2) Article 6 concerning the functions and obligations of RECs is very explicit and has certainly helped to improve the situation is some Member States by giving a clearer legal framework than before.	
3) Having a single ethics opinion per country is a real improvement.	3) The role of local RECs still needs to be defined for excluding or terminating a CT on specific sites as mentioned at paragraph 9 of the directive's preamble.

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) There is a lack of effective coordination between the RECs and the competent authorities and among the RECs themselves. This results in the unnecessary duplication of the review process by the RECs and the competent authorities.	1) The directive should specify more precisely the role of the competent authorities (see article 6 for the RECs) and impose better coordination between them and the RECs. Article 6 paragraph 4 could be completed to become a specific provision. Indeed it is very hard for RECs to estimate the correct level of insurance cover in a given case and if there are enough guarantees, even when a national insurance scheme exists.
2) The directive 2001/20 confers far-reaching responsibilities on the RECs in comparison with the competent authorities. However, the resources required for the RECs to meet their responsibilities remain at the discretion of the Member States and the competent authorities.	2) More guarantees are needed to ensure the protection of human subjects and the quality of CTs within the EU. The costs of the ethical review should be better evaluated and should be entirely covered by the Member States, with a mechanism to charge the sponsors for this. The directive should be more explicit on the need to guarantee the independence of the RECs (including financially) by providing them with the necessary means to meet their responsibilities and also by offering RECs members the necessary education and continuing education.
3) The set up, organisation, function and supervision of the RECs could be improved at the European level.	3) Taking into account national specificities the directive should impose clear guidance on the minimal requirements concerning the composition, qualification, basic and continuing education of the members, organisation, and standard operating procedure of the Ethics Committees
4) The deadlines set out in the directive do not always allow the RECs to complete the ethical review of a protocol in detail, especially when RECs need consulting experts.	4) Mechanisms to facilitate exchange of information and opinion, thereby ensuring the quality of the ethical review should be put in place, especially for smaller Member States and new Member States.
5) The directive makes it very difficult to conduct research in emergency, even if this is necessary in terms of the patients' best interests and public health reasons.	5) The directive should be completed by adopting a similar requirement on research in emergency clinical situation to that set out at article 19 of the Council of Europe additional protocol on biomedical research (ETS 195).
6) There is a need for more sharing of information among RECs at the national and international level (i.e. review of specific protocols, misconduct by researchers or sponsors, emerging ethical issues, etc.)	6) The directive should allow for the exchange of information taking into account confidentiality and data protection issues.
7) Sometimes RECs receive unnecessary or excessive amounts of information.	7) The notification of Severe Unexpected Serious Adverse Reaction should be

Article 16 and 17 should be revised to make sure that the RECs only receive the information directly of use in view of their responsibilities vs. those of the competent authorities.	revised, the RECs should only receive direct information when the change of the benefit-risk evaluation of an ongoing CT results in a temporary hold on or the premature termination of the CT. Concerning other situations, the RECs should receive a summary of the yearly report with the evaluation of the ratio benefit-risk.

What can be remedied within the present legal framework (modification of guidelines or clarifications)?	
Comments	**Suggestions**
1) There is a lack of effective coordination between the RECs and the competent authorities and among the RECs themselves. This ends up in the unnecessary duplication of the review process by the RECs and the competent authorities.	1) Efforts should be made to develop guidance on this at the European level. For instance, template forms could be drafted for CTA application and ethical review application.
2) **Article 2 definitions** (f) investigator	2) **Article 2 definitions** (f) investigator: a doctor … The investigator who is the leader responsible for a multi-centre clinical trial may be called the coordinating investigator.
3) **Article 2 definitions** (q) (new)	3) **Article 2 definitions** (q) (new) Suspected unexpected serious adverse reaction (SUSAR): an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship to an investigational medical product.
4) **Article 3 protection of clinical trial subjects** This provision should include as principles paragraph 1 and 2 of article 2 of the commission directive 2005/28.	4) **Article 3 protection of clinical trial subjects** paragraph 2 (g) the rights, safety and well being of the trial subjects prevail over the interest of science and society; paragraph 3 Each individual involved in conducting a trial shall be qualified by education, training, and experience to perform his task. The medical care given to, and medical decisions made on behalf of, subjects shall be the responsibilities of an appropriately qualified doctor or, where appropriate, of a qualified dentist.
5) **Article 4 Clinical trials on minors** The littera (i) can be deleted in accordance with the proposed article 3 paragraph 2 littera (g) (see above)	5)

6) **Article 5 Clinical trials on incapacitated adults not able to give informed legal consent** The littera (h) can be deleted in accordance with the proposed article 3 paragraph 2 littera (g) (see above)	5)
7) **Article 6 Ethics Committee** This provision should better take into account the need to guarantee that RECs have the necessary means to fulfil their responsibilities.	7) **Article 6 Ethics Committee** For the purposes of implementation of the clinical trials, Member States shall take the measures necessary for establishment, financing and operation of Ethics Committees.
8) **Article 8 Detailed guidance** As mentioned above, there is a need for improved coordination between the RECs and the competent authorities as well as among the RECs themselves. Some have suggested that accreditation would be a solution to assure some minimal standards in Europe, but such system would create duplication in many countries where the RECs are regulated by law and operate under control of the State. The key issue may not be accreditation but its objectives: RECs working according to the best practices and following the same standards in Europe. Accreditation is one way to achieve this, but there are other ways linked to the financing, training, providing proper guidance, etc. EUREC therefore proposes to adopt standards at the European level that deals with those issues. For those countries which have not yet adopted them, this should help clarify the situation in a coordinated way.	8) **Article 8 Detailed guidance** The Commission, in consultation with Member States and interested parties, shall draw up and publish detailed guidance on the application format and documentation to be submitted in an application for an ethics committee opinion, in particular regarding the information that is given to subjects, and on the appropriate safeguards for the protection of personal data. Guidance shall define as well the minimal requirements concerning the composition, qualification, basic and continuing education of the members, organisation, and standard operating procedure of the Ethics Committees Guidance should be produced to clarify and encourage appropriate dialogue between all Ethics Committees and Competent Authorities involved in the approval of a clinical trial.
9) **Article 10 Conduct of a clinical trial** The definition of 'substantial' is not clear and gives large room for different interpretations by sponsors, Competent Authorities and Ethics Committees. Also the term 'otherwise significant' does not help with the understanding of the type of amendments that are expected to be submitted for approval. EUREC therefore proposes to delete the terms 'substantial' and 'otherwise significant' in this	8) **Article 10 Conduct of a clinical trial** (a) after the commencement of the clinical trial, the sponsor may make amendments to the protocol. If those amendments are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, the sponsor will consider them substantial and shall notify

article.	the competent authorities of the Member State or Member States concerned of the reasons for, and content of, these amendments and shall inform the **E**thics **C**ommittee or **C**ommittees concerned in accordance with Articles 6 and 9.

10) **Article 17 Notification of serious adverse reaction** Ethics Committees are 'flooded' with SUSAR reports from all over the world that require administrative handling. Ethics Committees have neither the capacity nor the competence or the information systems to carry out 'signal detection' or otherwise systemically identify a change in the benefit and risk of the clinical trial. In addition their capacities for protecting the patients are reduced by this administrative burden. Other ways need to be identified to enable Ethics Committees to make the required judgements. A special process needs to be introduced for the situation of temporary hold or premature termination of a clinical trial due to safety concerns: Established procedures for rapid information exchange, escalation and appropriate communication to all involved Health Authorities, Ethics Committees, investigators and study participants need to be in place to avoid potential harm to individual study subjects.	10) **Article 17 Notification of suspected unexpected serious adverse reactions and other important safety information** **1.** (a) The sponsor shall ensure that all relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all Member States in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days. **Any change in the benefit-risk evaluation of the ongoing trial resulting in either a temporary hold or premature termination of this study should be reported immediately to the Competent Authorities and Ethics Committees in all concerned Members States, in any case no later than seven days after the sponsor has become aware of the change in the benefit- risk balance.** (b) All other suspected unexpected serious adverse reactions shall be reported to the competent authorities concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor. (c) … (d) … 2. At a minimum (to be agreed) interval but at least once a year throughout the lifetime of the clinical trial, the sponsor shall provide to the Member States in whose territory the clinical trial is being conducted a listing of all suspected serious adverse reactions which have occurred over the previous reporting period and a cumulative report of the subjects' safety since the start of the clinical trial. The Ethics Committees concerned should receive a summary of this report, evaluating the **benefits and risks** for healthy volunteers or patients who have participated, are participating or will be participating in the respective clinical trial. (…)

	4. In the event of competent authorities of Member States or Ethics Committee becoming aware of any non-compliance having occurred with an investigational site during a clinical study, the competent authorities or the Ethics Committee concerned shall notify the sponsor of that clinical study and all other sponsors conducting clinical studies at that site, of the specific concerns of non-compliance identified. 5. In the event that the competent Authorities in concerned Member States, Ethics Committees or sponsor consider a temporary hold or premature termination of a clinical trial due to safety concerns is necessary, established procedures for rapid information exchange, escalation and appropriate communication to all stakeholders including investigators and study participants need to be followed to avoid potential harm to the individual study subject.

What should a new legal framework look like?	
Comments	**Suggestions**
1) EUREC recommends that the present revision be not limited to the directive 2001/20 but covers all aspect of the European CT regulation, in particular the directive 2005/28.	1)
2) EUREC does not feel that the Directive should become a Regulation as cultural differences across Europe mean there will be diversity and not complete harmonisation. Even more CTs with therapeutic products are only part of all biomedical research. This could have a negative impact on other types of research for which the present directive is not adapted. In the point of view of the protection of human subjects and the quality of research, a Regulation is not a solution. Yet standards should be high and universal. A better coordination with existing EU legislation as well as other pieces of legislation of the Council of Europe and at the national level is therefore a priority.	

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Please note that the written submissions and the presentation slides from the meeting will be included in appendix to the report of the meeting and be published at the same time as the report.

Name of Organisation	Country
EuropaBio EuropaBio is the European Association for Bioindustries. It represents 83 corporate members operating worldwide, 12 associate members including 5 bioregions and 25 national biotechnology associations. Through its national associations EuropaBio is also the voice of over 1800 small and medium-sized enterprises involved in research and development, testing, manufacturing and commercialisation of biotechnology products.	Belgium / EU

Executive Summary

EuropaBio welcomes the opportunity to submit these comments on our experience to date with the operation of the Clinical Trials Directive. In light of this experience, we wish to offer recommendations for reform of the regulatory environment for the approval and conduct of clinical trials in the European Community.

In October 2006 the BIA and EuropaBio submitted to the European Commission and the Clinical Trials Facilitation Group a White Paper entitled "Promoting Consistency of Implementation and Interpretation of the Clinical Trials Directive across EU Member States". This paper describes the regulatory impact on the conduct of clinical trials following implementation of the Clinical Trials Directive, highlighting aspects of the current system which cause bottlenecks in the development of biopharmaceutical products in the EU. For ease of reference, we summarise the salient points of this paper below.

The Directive was an important first step towards harmonisation of the requirements and processes between EU Member States. The Directive could provide potential for synergies and time savings. However, these potential benefits have not been realised. The challenges stemming from the uneven and inconsistent implementation do not fully support the Lisbon agenda, which aims to turn Europe into the most competitive and dynamic knowledge-based economy in the world by 2010.

We believe that there is an urgent need to address the following related issues:

· Lack of harmonisation for applications for clinical trial authorisations as a result of different national dossier requirements and/or discrepant application of Community law,
· Increased bureaucracy and uncertainty as a result of variable national requirements placed on industry, particularly in respect of multicentre clinical trials conducted in two or more Member States,
· Different interpretation of the definition of Investigational Medicinal Product,
· Other GMP related issues in some Member States, and
· Varying requirements for safety reporting across the Member States.

The general consensus of our members is that the Clinical Trials Directive fails to achieve any significant harmonisation. This is notwithstanding that the objective of the Directive is to ensure harmonisation of the national rules governing conduct of clinical trials based upon the single market principle. Individual Member States have imposed different requirements – some of which go beyond those set out in the Directive, others that appear disproportionate to the objective of protecting safety of trial subjects – resulting in different regulatory standards being applied by the Member States in granting clinical trial authorisations. Such differences have adversely impacted on the ability of our member companies to initiate and continue to carry out multicentre and multinational trials across Europe. The situation is more exacerbated for clinical trials with products designated for the treatment of orphan or rare diseases, which affect a small fraction of the population.

It should be emphasised that small and medium-sized enterprises (SMEs) do not have sufficient financial and manpower resources to effectively deal with different national requirements imposed by the Member States. The administrative burden to identify and comply with additional local requirements is significant, and Europe is now regarded as less attractive to undertake clinical development. Indeed, some member companies have already decided not to conduct their clinical studies in the EU. If the current situation is not addressed and improved, it will be particularly damaging to the continued viability of the bioscience sector in the Community.

We believe that the Clinical Trials Directive (and its national implementing legislation) should be reviewed in order to achieve harmonisation, transparency and consistency in the approval and conduct of clinical trials across EU Member States. This will facilitate efficient development of biopharmaceutical products in Europe, which would in turn have a direct benefit of improving access by patients to innovative medicines.

EuropaBio in conjunction with its member associations and companies look forward to continuing to work with the European Commission, National Competent Authorities and EMEA to address the issues faced by the bioscience industry and ensure harmonisation of the regulatory requirements and processes. This will make Europe a more competitive environment for clinical research and a leading region for innovation.

Aspects of the Directive 2001/20/EC that work well	
Key points	**Suggestions**
The aim and spirit of the Directive To provide an attractive environment for the approval and conduct of clinical trials whilst ensuring that the rights, safety and well-being of trial subjects are protected. (see Recitals 2, 8, 9, 10, 11, 12, 15 and 18, Article 2) **Standardisation of review processes and documentation** Recital 10 states that it is necessary to simplify and harmonise the rules and administrative provisions governing clinical trials by establishing a clear, transparent procedure and creating conditions conducive to effective coordination of such trials in the Community by the authorities concerned. **Principle of parallel processing of clinical trial applications by the competent authority and the ethics committee** This greatly reduces the cumulative time for granting of clinical trial authorisations and issuance of ethical opinions. **Improving Ethics committee review process** Establishing a procedure for the adoption of a single opinion for the Member State in which clinical trials will be carried out. **Clear and consistent approval timelines** The Directive sets out timelines which bring more predictability for companies.	EuropaBio supports the Clinical Trials Directive which came into force in May 2004 with the aim of harmonising the national rules governing clinical trials in the EU. Prior to the adoption of the Directive the rules on commencement and conduct of clinical trials varied considerably from one Member State to another. Biotechnology derived products faced a wide divergence in the approach towards risk/benefit assessment as well as variable processes and timelines applied by National Competent Authorities. The Directive was an important first step towards harmonisation of the requirements and processes between Member States, as illustrated by the key points on this page. Indeed, the spirit of the Directive is now recognised within the Community since its adoption in 2001. However, the potential benefits for synergies and time savings have not been realised because of the uneven and inconsistent implementation by the Member States. This has resulted in different regulatory standards being applied by the Competent Authorities in granting clinical trial authorisations. Such differences have adversely impacted on the ability of companies to initiate and carry out multicentre and multinational trials, in particular SMEs which do not have the financial and manpower resources to cope with the administrative burden. We believe that the Clinical Trials Directive (and its national implementing legislation) should be reviewed as discussed below, to establish a proportionate regulatory environment without unnecessary bureaucracy, whilst ensuring public health protection.

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
Lack of harmonisation for applications for clinical trial authorisations, increased bureaucracy and proliferation of Member State specific requirements 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. Member companies have experienced additional national requirements in a significant number of Member States on a consistent basis. Member States have adopted different requirements for defining the characteristics of the Investigational Medicinal Product Dossier. It should be noted that the Commission guidance for the request for authorisation of a clinical trial to the competent authorities, notification of substantial amendments and declaration of the end of the trial (revised October 2005) recorded divergent Member State requirements and additionally did not take into account the actual national requirements currently in practice. The lack of certainty is affecting the conduct of trials in Europe and may also adversely impact on investment decisions.	It is of importance that these operational issues are addressed at an EU level. We strongly recommend that Member States adhere to the Commission guidance for the request of clinical trial authorisation (CTA). It is unclear why the documentation in the CTA application should differ between Member States. In the short term, we urge greater transparency and request that all national requirements are documented in the Commission guidance. **These additional national requirements should be justified taking full account of the objectives of Community law**. This will allow companies to make applications that fulfil the country requirements as well as show the Commission that some countries have retained requirements that are against the spirit of the Directive and therefore should be dropped. The next goal that sponsors wish to achieve is having a **unique CTA application and harmonised data requirements for all Member States that are proportionate with the protection of the rights, safety and well-being of trial subjects**. We believe that EudraCT database could provide the opportunity for a single point of entry for submission of CTA applications to the concerned Member States. This will help to overcome the administrative burden experienced by companies, especially SMEs which do not have the resources to deal with variable requirements. Moving forward, greater harmonisation and consistency in data assessment will enhance the research environment in Europe. The ultimate goal is of course a single opinion on data. To achieve this, we should consider strengthening the mandate of the HMA Clinical Trials Facilitation Group. This should not be construed as requesting a single European assessment. We recognise and respect the rights of Member

	States to oversee clinical activities within their territory under current EU legislation. The Facilitation Group could be an arbitration body between Competent Authorities.
Ethics Committee review Some Member States introduced an additional level to the Ethics Committee structure when implementing the Directive. However, local/site specific ethics committees are still in place and conduct a full review of the protocol, resulting in serious delays. The impact of the multiple, complex Ethics Committee structure in Europe should be addressed and reduced in order to increase effectiveness, reduce fees and time while ensuring public health protection.	A harmonised approach to ethics committee review, based upon a common set of guiding principles, across EU Member States would be welcomed. It would be helpful to clarify the scope of responsibilities of the central Ethics Committee versus local Ethics Committees. We would welcome a common application form for all Ethics Committees. Most critically, a clarification of the roles and responsibilities of the Competent Authority and Ethics Committee in the approval process is requested. Appropriate allocation of responsibilities will increase efficiency during the assessment process and improve timelines for initiation of clinical trials in the EU. Overlap of responsibilities and a lack of clarity can lead in our experience to duplication of review and sometimes to differences in opinions.
Different interpretation of the definition of Investigational Medicinal Product (IMP) Member companies have experienced differences in interpretation of the IMP definition in Article 2 (d) of the Directive by National Competent Authorities and Ethics Committees. This issue is causing our member companies confusion and has a high impact on the conduct of clinical trials in terms of costs, resources and timelines. Member companies reported that multicentre trials conducted in more than one Member State pose practical difficulties. This is because some Member States may consider products such as challenge agents and concomitant and background treatments as an IMP, while others do not. In addition, the interpretation of IMP raises a potential ethical conflict. This could be viewed as a financial inducement for the sites (and in some cases the patients) to participate in the studies if companies are required to pay for comparator products and other concomitant medications.	The guidance on IMPs and other medicinal products used in clinical trials is certainly open to interpretation and has not met the purpose of presenting a common understanding across EU Member States on the definition of an IMP. We would welcome clearer guidance as to which products used in a clinical trial are classified as IMPs. There is a need for pan-European agreement on definitions in respect of terms used in the Directive.

It should be noted that non-investigational medicinal products (NIMPs) have not been defined in the Directive. The concept was introduced by the Commission guidance for the request for authorisation of a clinical trial to the competent authorities (revised October 2005) and expanded in the guidance on IMPs and other medicinal products used in clinical trials (May 2007). The latter guidance imposes a number of requirements which are disproportionate with the objective of safeguarding clinical trial subjects, resulting in over-regulation.	
GMP requirements for IMPs Member companies are experiencing operational difficulties in relation to certain aspects of GMP requirements as discussed below. These issues impact significantly on company resources, timelines and costs. <u>Non-acceptance of QP declaration for third country manufacturers</u> Certain Member States require GMP certification for third country manufacturers, which is not aligned with the provisions of the Directive or the requirements of other Member States. <u>Scope of Manufacturing Authorisation (IMP) requirements</u> There is a lack of clarity and consequently a divergence between the Member States regarding the scope of requirements to hold a Manufacturing Authorisation (IMP) for certain operations commonly undertaken at trial sites. Article 9(2) of Directive 2005/28/EC states that authorisation shall not be required for reconstitution prior to use or packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member States to carry out such processes if the investigational medicinal products are intended to be used exclusively in those institutions. <u>Different IMP labelling requirements</u> Some National Competent Authorities consider that re-labelling operations (as occasionally required for extension of shelf-life) must be performed in licensed facilities. This appears inconsistent with the provisions of the Directive and the GMP guidance in Annex 13 of Volume	We need to have a real harmonisation of GMP requirements for IMPs across EU Member States. We believe that the requirements imposed by certain Member States go beyond those set out in the Directive. The administrative burden which resulted from the uneven and inconsistent implementation of the Directive is significant for the bioscience sector. We recommend the involvement of the EMEA GMP Inspectors Working Group in order to address these issues. To achieve harmonisation: - For the purpose of importation batch release, a QP declaration certifying that the IMP has been manufactured in accordance with GMP should be acceptable. Article 13 of the Directive expressly states that a certification by a QP as satisfying the requirements of GMP. - These national labelling requirements are not justified with the objectives of Community law and should be removed. Compliance with labelling requirements in the GMP guidance should be acceptable. - Import licences for IMPs manufactured within the EU should be eliminated.

4 – Good Manufacturing Practice of the Rules governing medicinal products in the EU, which states that re-labelling may be conducted at the trial unit by the trial monitor or a pharmacist. Moreover, certain Member States require that the label for all immediate packaging, including vials and ampoules, carries the statement "for clinical trial use only" without exception. <u>Import licence</u> An import licence for products from other EU Member States has been	
Quality data requirements for biopharmaceuticals It is acknowledged that biopharmaceutical products are often inherently more complex than small chemical entities from a quality perspective. However, this should not automatically lead to a higher regulatory hurdle beyond what is scientifically justified and appropriate for the stage of development. In our experience certain National Competent Authorities requested compliance with manufacturing guidelines that would normally be applicable to a marketing authorisation application submission, while other Competent Authorities interpreted the CMC requirements very strictly. For example, a Member State required the submission of a separate viral validation application with large amounts of data. This adds to the timelines considerably - both in terms of preparation of the CTA application and the review timelines.	We believe that the quality data requirements for biopharmaceutical products should be transparent, harmonised and consistently applied taking account of the type of IMP, the disease being studied and the specifics of the development programme. We would welcome clear guidance on the requirements concerning the quality data supporting the IMPD for biotechnology products and biologicals.
Substantial amendments to clinical trial authorisations Member companies have found the interpretation of substantial amendments to be consistently different across all Member States. The Commission guidance for the request for authorisation of a clinical trial to the Competent Authorities, notification of substantial amendments and declaration of the end of the trial (revised October 2005) is very limited and open to interpretation. Many companies have reported that Competent Authorities would differ in opinion on which amendments they consider to be substantial or not.	Further guidance would be welcomed, including the process for notification, as this issue is causing our member companies major difficulties, especially for multinational trials carried out across the Community. We believe that guidance on what constitutes a substantial amendment should be discussed and agreed by all the Competent Authorities to achieve harmonisation of implementation. In the case of substantial amendments, it would be helpful to clarify

This is a big issue for our members and has a significant impact on resources and timelines.	whether approval is required from Competent Authorities and/or Ethics Committees.
Different requirements for safety reporting Article 17 (1) of the Directive requires sponsors to notify all information about suspected unexpected serious adverse reactions (SUSARs) to Competent Authorities and Ethics Committees within defined timelines. It should be noted that the Commission guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials (April 2006) recommends that sponsors report SUSARs from other Member States and third countries periodically as line listings to Ethics Committees. In our experience, some Member States requested quarterly line listings of SUSARs from third countries while 6-monthly line listings of SUSARs are acceptable for other Member States. Some Member States have not set up "Concerned Ethics Committees" allowing sponsors to report to one Ethics Committee per trial; instead sponsors must report to local Ethics Committees. Article 17 (1) (d) does not provide recommendations when sponsors should inform all investigators. The Commission guidance states that the information can be aggregated in line listing of SUSARs and sent periodically. Again some Member States will not allow investigators to be informed of SUSARs via line listings and require that fatal / lifethreatening SUSARs are submitted within 7 calendar days and all other SUSARs within 15 calendar days to investigators. Consequently, there are different requirements among Member States as to when and who needs to be informed, resulting in over-reporting to Ethics Committees and investigators. The lack of consistency in interpretation of reporting requirements impacts considerably on time, costs and resources. It should be noted that small companies which conduct blinded clinical trials in the Community have difficulties in meeting the request for unblinded safety reporting.	We would welcome clarification on the regulators expectations. Harmonised requirements would facilitate safety reporting. Therefore we would welcome: - Common rules for SUSAR reporting applied by all EU Member States. - Harmonised requirements concerning the line listing reports to Competent Authorities and Ethics Committees - to have the same periodicity, same content and format. We would strongly recommend that safety reporting is centralised using the EudraVigilance database with a system integrated for notifying all concerned Competent Authorities in order to overcome the administrative burden. We believe that sponsors should provide a single consolidated package of safety information in respect of the IMP for all clinical trials conducted in Europe. We believe that the anniversary date to submit the annual safety report should be set according to the first approval of the clinical trial worldwide (and not only the first approval of the clinical trial within the Community).

There is disharmony in the implementation of electronic submissions across member States. The process for submitting safety information varies between Member States - some countries requiring that this is provided electronically whereas others accepting paper form. For example, certain Member States require that local and third country SUSARs are submitted directly to the Competent Authority, while others require that third country SUSARs are submitted using the EudraVigilance database. In addition, some countries have no requirement for direct electronic submissions. **Annual Safety Reports** Some Member States have introduced additional requirements for the Annual Safety Report.	

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
Transparency in documentation and data requirements for CTA applications	Updating Commission guidance for the request for authorisation of a clinical trial to the Competent Authorities. Publication on Competent Authority websites of local data requirements and interpretation of the Directive/Commission guidances would help sponsors prepare approvable CTA dossiers. Consideration of guidance on the data requirements for Phase I, II and III trials, providing clarity on the requirements which are specific for biological IMPs.
Harmonisation of scientific assessment	Providing pan-European training to assessors will help to achieve consistency in the approach to assessment across Member States.
Guidance on substantial amendments to clinical trial authorisations to ensure consistent implementation	Providing clarity on what constitutes a substantial amendment, including the process for notification and circumstances when approval is required from both Competent Authorities and Ethics Committees.
Transparency of approval timelines	Publication of approval metrics will help sponsors in planning their clinical programmes.
Improving communication between Ethics Committee and National Competent Authorities	Greater coordination of review processes between Ethics Committees and Competent Authorities.

What should a new legal framework look like?	
Comments	**Suggestions**
Reviewing Directive 2001/20/EC The entire Directive does not need to be repealed and replaced by a different legal instrument. However, the Directive should be updated in light of the discussions at the forthcoming European Commission and EMEA Conference.	It is necessary to reduce the current flexibility by modifying the language in the provisions of the Directive which are open to misinterpretation and misapplication of the law by Member States.
Clear provisions and definitions in the body of the Directive Whilst Commission guidelines have been developed to assist applicants and competent authorities in interpreting the legal requirements, we have observed that certain Member States choose to depart from the recommendations made in these guidelines.	**Agreement between Member States on the definition of an investigational medicinal product** is required for a harmonised EU approach to regulation of clinical trials. **Agreement between Member States on what constitutes a substantial amendment.** **Harmonisation of the format, content and submission of an application for a clinical trial authorisation is required.** This will reduce the administrative burden, facilitate assessment and shorten the time to commence clinical trials.
Streamlining review processes to accelerate the initiation of trials and allow patients faster access to innovative treatments We believe that the current regulatory and ethics review processes could be streamlined whilst ensuring the protection of rights, safety and wellbeing of trial subjects remains paramount. This also applies to the process of notification of substantial amendments.	Introducing **mutual recognition of assessment carried out by National Competent Authorities**. **Strengthening the role of the Clinical Trials Facilitation Group** so as to provide a broader remit to oversee the application of the rules and coordinate the Competent Authorities review process. It should be emphasised that we do not request that a single body is established at EU level to review and approve all clinical research, as this is neither feasible in the medium term, nor necessarily desirable. The Facilitation Group could play an important role in promoting mutual recognition of assessments and arbitrating between Member States if there is any discrepancy in decision by Competent Authorities. The Facilitation Group could provide a venue for sponsors to appeal a Competent Authority rejection. The creation of an appeal process would be a potentially valuable addition to the European procedural framework.

	Given that biotechnology products are authorised under the centralised procedure and sponsors go to the EMEA for scientific advice and protocol assistance, we believe that representation from the EMEA on the Facilitation Group could be beneficial in ensuring a continuum in the assessment process for such products in a decentralised clinical development environment. **Identifying the roles and responsibilities of the National Competent Authorities and Ethics Committees so that certain aspects of the approval process are not unnecessarily duplicated**. This will reduce the documentation requirements for authorisation applications. We believe that the Competent Authority has primary responsibility for assessing the safety of trials, reviewing the technical data pertaining to the pharmaceutical and non-clinical testing. The Ethics Committees responsibilities should focus on ethical issues, ensuring informed consent of trial subjects, safety measures are in place to minimise potential risk exposure, suitability of investigators and adequacy of facilities, and taking account of, or subject to, the risk/benefit assessment performed by the Competent Authority.
A single point of entry for submission of CTA applications	The original EudraCT vision was a single point of entry into a centralised database for all CTA applications that National Competent Authorities would access as necessary, thus reducing the administrative burden and cost of compiling multiple applications for submission using national processes. This original vision was abandoned because of budgetary constraints and challenges from Competent Authorities with regard to the change of process. The original vision of EudraCT should be reconsidered. We believe that EudraCT database could provide an ideal opportunity to overcome the administrative burden and improve the conduct of trials in Europe.
Harmonisation of safety reporting requirements	**Harmonised electronic reporting via EudraVigilance database** with a system integrated for notifying all concerned Competent Authorities. This would ease the administrative burden given the local variations in requirements for SUSAR reporting.

	Periodic reporting of SUSARs to Ethics Committees and Investigators We believe that SUSARs should be reported to Ethics Committees periodically as line listings. This is because Ethics Committees informed us that they cannot cope with the volume of reports and do not have the resources to analyse them. It would also be beneficial for all investigators to receive a summary of SUSARs periodically.
Promoting Europe's competitiveness for clinical development of innovative medicines	**Collaboration on inspections between EU and US FDA and mutual recognition of results** so as to avoid duplication of inspection by both FDA inspectors and inspectors from National Competent Authorities. **Harmonisation of approval timelines**: 60 days in the EU versus 30 days in the US. The US provides the opportunity to set up the trial faster and getting the first patient in, which is a significant consideration for companies.
Promoting innovation: Industry and academia relationships	It is our view that dialogue between biopharmaceutical companies and academia could be improved. They share a common objective, which is to conduct research to meet unmet medical needs and provide safer medicines to patients. For SMEs this connection to academia is especially critical. The feedback from academic sponsors is that their trial activities have been weighed down, delayed or that it is impossible to launch certain studies because of the lack of support (financial or technical). We would welcome guidance providing clarity on how support can be given by a biopharmaceutical company without affecting the scientific, technical and procedural autonomy of the investigators. Furthermore, the modalities for non-commercial clinical trials need to be defined more homogenously and consistently across Member States. As non-commercial studies can be conducted in more than one member State it would be helpful to have a clear and common guidance to strengthen multinational collaboration within the medical community.

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

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Name of Organisation	Country
European Association of Nuclear Medicine	

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
In general, the principles at the basis of this directive are clear and straightforward. Articles related to protection of the clinical trial subjects, role of the ethics committee, authorization requirements, allow for safe trials conduction, without prejudice for efficiency and flexibility.	When applied to radiopharmaceuticals, the principles of the Directive are generally interpreted in a way which is not taking into account their small scale preparation. Due to the short half-life of radioisotopes emitting ionizing radiation, which is utilized in radiopharmaceuticals, these radiopharmaceuticals are often prepared "in house" i.e. in the hospital where they are used within minutes or hours after preparation. Hence, additional regulations for radiopharmaceuticals may be necessary to assure scientific progress in the area of new radiotracers.

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) The major problem of the directive is that requirements for large clinical trials conducted by large pharmaceutical players are virtually the same as for small academic units in hospitals or at universities. This is a specific problem for radiopharmaceuticals, that in many cases are used within clinical trials not as an investigational medicinal product themselves, but as a diagnostic biomarker to observe therapeutic effects or physiological changes in the conduct of the trial. With the development of Positron Emission Tomography (PET) and the technological progress in imaging technology the variety of radiolabelled tracer agents has dramatically increased in the last years. However, due to the specific properties of radiopharmaceuticals with very short half lives, a local, often hospital based production and preparation is required. The small market (especially in economic terms) leads to the fact that only few radiopharmaceuticals have obtained a marketing authorisation. Therefore most (especially with short lived isotopes) radiopharmaceuticals are considered as Investigational Medicinal Products (IMPs), even if their efficacy and safety has been shown in numerous clinical studies. It should be stressed that radiopharmaceuticals have shown an excellent safety profile, are injected in tracer amounts usually as a single dose in a hospital environment and are highly special in nature due to an extremely short shelf life, radioactivity etc. Even for therapeutic applications the efficacy and side effects are driven by the associated radiation and not the carrier used in tracer amounts. The introduction of Directive 2001/20/EC with all subsequent guidelines has introduced a high administrative burden, which has led to a severe challenge in clinical research activities with radiopharmaceuticals in Europe endangering the competitiveness of European research institutions. This aspect is also of importance as PET is more and more introduced as biomarker technology in drug development.	1) The legal framework should make it possible, that radiopharmaceuticals, for which clinical data on clinical and pharmaceutical safety and efficacy are existing, but have not gained a marketing authorization, may be used outside the framework of the Directive 2001/20/EC and the appendant IMP-regulations, e.g. by specifying exemptions from Directive 2001/83 EC article 3, as already existing for magistral or officinal preparations.

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
2) Another major problem of the directive is the need for full GMP compliance in the manufacturing of IMPs, including radiopharmaceuticals as stated above. In general, the logistic (e.g. size of the facility, number of available radiochemistry labs), personnel and economic availability in a typical PET Centre or Nuclear Medicine Dept. are not compatible with a full GMP compliance.	2) the EANM radiopharmacy Committee has published after public consultation specific guidelines for Good Radiopharmaceutical Practice (cGRPP) for small scale production of radiopharmaceuticals especially in a hospital environment (published on-line at the EANM web-page: www.EANM.org). These guidelines should be used instead to "current good manufacturing practice" of drugs adopted by the industrial environment.
3) Requirements for the qualified persons are, in practice, the same for radiopharmaceuticals as required in pharmaceutical industry (matching completely with requirements of 2001/20/EC and, in turn 75/319/EEC directives). Again, the specific nature of radiopharmaceuticals requires specific training, personel with qualifications both as qualified person in the pharmaceutical sense as well as experience in the small scale extemporaneous preparation of radiopharmaceutical is practically non-existing.	3) the EANM radiopharmacy Committee has published after public consultation specific guidelines for Good Radiopharmaceutical Practice (cGRPP) for small scale production of radiopharmaceuticals especially in a hospital environment (published on-line at the EANM web-page: www.EANM.org). These guidelines should be used instead to "current good manufacturing practice" of drugs adopted by the industrial environment.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
	1) For radiopharmaceuticals a specific guideline could be drafted containing a clarification, that if radiopharmaceuticals are used within clinical trials, not having the aim to gain a marketing authorization, they should not be considered as an IMP. A specific definition for such products may be required
	2) As there are no specific European guidelines for the small scale, non commercial, extemporaneous preparation of RP, the EANM radiopharmacy Committee has published after public consultation specific guidelines for Good Radiopharmaceutical Practice (cGRPP) for small scale production of radiopharmaceuticals especially in a hospital environment (published on-line at the EANM web-page: www.EANM.org). These guidelines should be used also in the context of clinical trials instead of "current good manufacturing practice" of drugs adopted by the industrial environment.
	3) Specific guidelines for precursors for radiopharmaceutical preparations should be introduced. The term precursors include each active pharmaceutical ingredient (API) and API starting material for production of RP that are intended for use in early Phase Clinical trials. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. Important is to not limit the supply of the precursor to commercial GMP material as it would limit the use of PET especially if used in drug development.
1) Toxicological information of radiopharmaceuticals usually concern only microdoses as defined in the "Final Position Paper on non clinical safety studies to support clinical trials with a single microdose" (EMEA/CPMP/SWP/2599/02/Rev 1). It will not concern higher dose of radiopharmaceuticals for which the toxicological information required are those described for any active substances in the "Note for Guidance on Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals needed to support human clinical trials of a given scope and duration (EMEA/CPMP/ICH/286/95). Considering the tracer principle of radiopharmaceuticals the microdosing concept should be extended for radiopharmaceuticals.	4) If RP belongs to a well-known chemical class for which genotoxicity data are available the following tests may be sufficient: mutation test in bacteria (Amest test), chromosome aberration test, mouse lymphoma test or in vitro micronucleus test. A specific guideline might be introduced in this respect.

What should a new legal framework look like?	
Comments	**Suggestions**
	1) A major point in a new directive should be a clear distinction between "classical" clinical trials aiming at a marketing authorization of a medicinal product and trials that especially in an academic environment with clear scientific, non-profit aims i.e. a physician sponsored trial with an explicit scientific hypothesis.
	2) A specific definition of radiopharmaceuticals used in clinical trials e.g. as "biomarkers" or diagnostic tools for evaluation of therapeutic efficacy with specific exemptions (GMP, production, non-IMP, see above) taking into account the particular nature of radiopharmaceuticals (tracer amount, single dose, short shelf life, etc.) should be introduced.

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Name of Organisation	Country
EUROPEAN HEMATOLOGY ASSOCIATION (EHA)	

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1) OVERALL POSITIVE	1)
2) IMPORTANT FOR THE HARMONIZATION OF COMMERCIAL AND NON-PROFIT STUDIES	2)
3) MORE CUMBERSOME AND EXPENSIVE FOR ACADEMIC STUDIES	3) SIMPLIFY
4)	4)
5)	5)
…	…

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) PROBLEM OF SINGLE ETHICS COMMITTEE OPINION (ARTICLE 7). THIS INDICATION OF THE DIRECTIVE HAS NOT BEEN ACCEPTED AND IMPLEMENTED BY ALL MEMBER STATES. THIS MAKES THE PROCESS MUCH MORE CUMBERSOME AND TIME CONSUMING, AS WELL A NON-UNIFORM PROCESS WITHIN DIFFERENT MEMBER STATES.	1) THIS INDICATION SHOULD BE RE-INFORCED. CAN MEMBER STATES NOT FULLFIL THESE INDICATION? HOW CAN THIS PROBLEM BE OVERCOME IN ORDER TO UNIFORM THE PROCESS THROUGHOUT MEMBER STATES?
2) ROLE AND LEVEL OF MONITORING. SOMETIMES THIS CAN BE VERY EXPENSIVE.	2) MORE PRECISE GUIDELINES FOR MONITORING, PARTICULARELY FOR ACADEMIC STUDIES, WOULD BE A HELP.
3) SAE AND SUSAR MANAGEMENT. SOMETIMES, BUT CERTAINLY NOT ALWAYS, THIS CAN BE HANDLED BY THE PHARMA COMPANIES ALSO IN ACADEMIC STUDIES. IF NOT, THIS IS HIGHLY CUMBERSOME AND REQUIRES AN ORGANIZATION THAT FEW CENTERS HAVE.	3) IS A CENTRAL FUNCTION FOR THIS PURPOSE POSSIBLE? PERHAPS THROUGH EMEA CONNECTED TO A DEDICATED COMPANY. ALTERNATIVELY, ORGANIZATIONS SUCH AS EHA AND EBMT COULD JOIN ACTION TO CONTRACT A COMPANY FOR THIS PURPOSE. THE POSSIBILITY OF UTILIZING EXISTING ORGANIZATIONS FOR REGISTERED DRUG SAFETY (PRESENT IN ALL COUNTRIES) COULD ALSO BE CONSIDERED.
4) OVERALL, THE DIRECTIVE IS COMPLICATED FOR ACADEMIC STUDIES (see also below).	4) CONSIDER THE POSSIBILITY OF SIMPLIFYING PROCEDURES FOR ACADEMIC STUDIES.
5) PROBLEM OF LACK OF A SINGLE AND STANDARDIZED LAYOUT OF PROCEDURES INCLUDED WITH THE PROTOCOL. THIS CAUSES AN INCREASE IN PAPER WORK, THUS OF COSTS WHICH ARE RISING CONSIDERABLY WITHOUT A REAL BENEFIT FOR SCIENCE AND PATIENTS.	5) STANDARDIZE THE PROCEDURES AND DOCUMENTS TO BE SUBMITTED TO LEGAL ENTITIES FOR APPROVAL.

6) PHARMACOVIGILANCE AND ON SITE MONITORING ARE A REAL PROBLEM.	
7) TIME DEADLINES INDICATED IN DIRECTIVE OFTEN NOT APPLIED.	7) DEADLINES SHOULD BE RE-INFORCED. CONSIDER POSSIBILE SANCTIONS.
8) COSTS OF ETHICS COMMITTEES.	8) BY LAW, THERE SHOULD BE NO CHARGE FOR ETHICS COMMITTEE.
9) QUALITY ASSURANCE (QA) SYSTEM. GCP REQUIRES THAT ALL ORGANIZATIONS THAT PLAN TO CONDUCT AN EXPERIMENTAL TRIAL MUST APPLY STANDARD PROCEDURES, AND THAT THESE ARE ORGANIZED AND VERIFIED THROUGH A QUALITY CONTROL SYSTEM. THE SETTING UP OF A QUALITY CONTROL SYSTEM, AND MORE SO ITS MAINTENANCE, ACCORDING TO THE PRESENT STANDARD PARAMETERS REQUIRE THE AVAILABILITY OF HIGHLY DEDICATED RESOURCES, FORMATION OF PERSONNEL ON A WORKING PLATFORM WHICH DIFFERS FROM THE ONE USUALLY UTILIZED AND THE INVESTMENT OF RELEVANT ECONOMIC RESOURCES.	9) IN ACADEMIC STUDIES, THESE PROCEDURES SHOULD BE LEFT LESS CUMBERSOME.
10) SYSTEMS DEDICATED TO DATA COLLECTION, BOTH IF BY E-CRF OR USING CLASSIC PAPER-BASED CRF, NEED TO BE VALIDATED. OTHERWISE, THE DATA ARE NOT CONSIDERED ACCEPTABLE BY THE COMPETENT ORGANIZATIONS. VALIDATION IS AN EXTREMELY SOPHISTICATED PROCESS, VERY COSTLY AND ONLY SOME/FEW ORGANIZATIONS ARE IN A POSITION OF CARRYING IT OUT.	10) AGAIN, IT WOULD BE A GREAT PRACTICAL STEP FORWARD IF MINIMUM CRITERIA CAPABLE OF GUARANTEEING THE SECURITY OF THE ELECTRONIC SYSTEM AND THE RELIABILITY OF THE DATA COLLECTED, WITHOUT REACHING THE COMPLEX VALIDATION SYSTEM DESCRIBED BY THE 21 CFR PART 11 OF FDA, COULD BE DEVISED.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
	1) SIMPLIFY PROCEDURES FOR NON-PROFIT STUDIES
2)	2)
3)	3)
4)	4)
5) GBG	5)
…	…

What should a new legal framework look like?	
Comments	**Suggestions**
	1) DIFFERENT STANDARDS FOR NON-PROFIT STUDIES
2)	2)
3)	3)
4)	4)
5)	5)
…	…

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Please note that the written submissions and the presentation slides from the meeting will be included in appendix to the report of the meeting will be published at the same time as the report.

Name of Organisation	Country
The Sub-Committee on Medical Research Ethics	Finland

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
2) The Directive does not allow the clinical trials in emergency situations where it is not possible to obtain consent in advance. This situation has had hugely negative and unethical input on the development of new or better treatments /medicines for emergency care.	2) Directive must be changed in this respect. The change can be done by adopting the principles of the Articles 17(2) and 19 of the Additional Protocol To The Convention On Human Rights And Biomedicine, concerning biomedical research (ETS 195, Council of Europe, 2005).
3) There is some inconsistency in defining the role and duties of the Ethics Committees. In the beginning of the Directive it is written that "the clinical trial subject's protection is safegarded through…[ ] ***screening*** by ethics committees…etc." The expression differs from the definition in Article 2(k) where the responsibility of the EC is ***to express an opinion*** on the trial protocol, the suitability of the investigators etc. The distinction between these two expressions may not seem clear or significant but different methods of interpretation may lead to many different and contradictory practices in European perspective.	3) Any reference to ECs role as a monitoring body should be altered or deleted and replaced with the definition from in the Article 2(k).
4) In accordance with previous notion the provisions of notification of the safety reports have caused a lot of difficulties and administrative burden for ECs as well as for the sponsors and investigators. It is not stated appropriately what ECs are expected to do with the reports and what is their mandate in case of safety updates of the individual trials. Safety reporting practices usually relate to remarkable volume of individual reports and reporting procedures and current unclear situation has not at all promoted the principle of Directive to simplify and harmonise the administrative provisions governing such trials.	4) Since Competent Authorities have relevant mandate and means for retrospective follow-up the safety aspects of the individual trials it is unnecessary to even inform ECs of such events. Therefore the obligation to report the ECs about individual SUSARs and the annual listings of all SUSARs should be deleted from the Article 17.
5) It is necessary to take account of the specific needs of non-commercial clinical trials, in particular in relation to manufacturing or import requirements for authorisation and the documentation to be submitted and archived for the trial master file and on criteria for classifying such trials as "non-commercial".	4)

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
4)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

What should a new legal framework look like?	
Comments	**Suggestions**
5)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

COMMENTS FROM NATIONAL AGENCY FOR MEDICINES TO THE CT CONFERENCE 2 OCTOBER 2007

Enclosed are comments from National Agency for Medicines (NAM), Finland, to be included in the conference report.

Aspect of the Directive 2001/20/EC that do not work well

Databases: EudraCT

EudraCT database and application form are far more extensive than required by the Article 11 of Directive 2001/20/EC. Data fields including free text in more than twenty languages cannot be used for any meaningful statistical or other purposes. NAM suggests revision of the database to include only pivotal information. Relevant data (except contact information) should be presented in pull-down menus, numbers, SI units or as international codes, such as ICD, MedDRA and INN. No form can replace the protocol, which is readily available for competent authorities.

Completion of the form is a laborious task (especially for non-commercial sponsors) and the form may include more than hundred pages, where most data fields are left blank. NAM proposes revision and reduction of the form to include only data requested by the Directive 2001/20/EC. Blank fields should be automatically deleted, when inclusion of these is inappropriate (for example, if the IMP is of chemical origin, sections D3, D4 and D5 are redundant).

Databases: EudraVigilance CT

It is suggested that all SUSARS should be reported electronically. Non-commercial sponsors may report SUSARs only a few times a year. It is not reasonable to require them to report SUSARs electronically; as electronic reporting requires training, regularly updated programs and protected data connections.

Safety information: annual safety reports (ASR)

Sponsors do not report the subject's safety in the trial, but ASR of the medicinal product. As a result, ASRs have hundreds of pages, where relevant information on subject's safety in the trial in question may include only one paragraph. Sponsors should consider the "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use" and revise their SOPs accordingly.

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

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Name of Organisation	Country
GCP inspections working group (GCP IWG)	All Member States and EEA countries

Table 1 : Aspects of the Directive 2001/20/EC that work well
Table 2A : What can be remedied within the present legal framework (by modification of guidelines or clarifications)?
Table 2B : What should a new legal framework look like?

Aspects of the Directive 2001/20/EC that work well (Table 1)	
Comments	**Suggestions**
1.3. National systems of GCP inspection **. Implementation of a GCP inspection system** Clear legal framework (Art. 15(1) Dir. 2001/20/EC; Art. 24-25 Dir 2005/28/EC) Guidance published in Vol. 10 **. Appointment of inspectors by Member States** Clear legal framework (Art. 15(1) Dir. 2001/20/EC, Art. 21 Dir. 2005/28/EC) **. Trials under the scope of inspection** Clear provisions (Art. 23(1) Dir. 2005/28/EC) **1.4. Cooperation between MS and with EMEA on GCP inspections** **. Mutual recognition of inspection results** Clear legal framework (Art. 15(1) Dir. 2001/20/EC; Art. 23(4) Dir.2005/28/EC) Implies harmonisation of inspections procedures to achieve identical quality levels **. Assistance request from a M.S. by another M.S.** Clear legal framework (Art. 15(1) Dir. 2001/20/EC; Art. 27(b) Dir. 2005/28/EC)	(See point 1.5. in Table 2.A.)

Aspects of the Directive 2001/20/EC that work well (Table 1)

Comments	Suggestions
. Request for inspections Clear legal framework for 1) request by the Agency (Art. 15(1) Dir. 2001/20/EC; Art. 23(2) Dir. 2005/28/EC) 2) request of a new inspection by Agency or a MS (Art. 15(3) Dir. 2001/20/EC) 3) request of an inspection in a third country (Art. 15(4) Dir. 2001/20/EC	
. Communication / Exchange of information **1) Support** • Constitution of a platform for inspectors (GCP IWG, hosted and chaired by EMEA)	1- GCP IWG at EMEA, implemented in 1997. Considered as an effective platform for harmonisation and exchange of information by MS inspectors 2- New mandate, objectives and rules of procedures published on 27/07/07
• Eudract: (Art. 11 (1(f) Dir. 2001/20/EC) - Provisions for inspections adequate - Entering data on inspections simple	
2) Operational issues • Inspection programs and planning: - Procedures coordinated by EMEA in the context of Marketing authorisation (Art. 15(1) Dir. 2001/20/EC; Art. 23(2) Dir. 2005/28/EC) : no comment	

Aspects of the Directive 2001/20/EC that work well (Table 1)	
Comments	**Suggestions**
1.5. Quality of inspections and harmonisation	
. Qualification and independence of inspectors	
Clear legal framework (Art. 15(5) Dir. 2001/20/EC, Art. 21 and 22, Dir. 2005/28/EC)	
Detailed guidance (Art. 15(5) Dir. 2001/20/EC), published in Vol. 10	
. Harmonisation, training	
. Procedures and guidelines on inspections (Art. 15.(5) Dir. 2001/20/EC and Art. 23(3)(4), 26 and 29 Dir.2005/28/EC)	
. General recommendation on inspection procedures published in Vol. 10	
. Inspection procedures	
- inspections coordinated by EMEA (Art. 15(1), Dir.2001/20/EC; Art. 23(2), Dir.2005/28/EC)	Adopted by the GCP IWG and to be published
. Training	
. Training sessions (Art. 23(4), Dir.2005/28/EC)	GCP IWG, case studies, review and discussion of inspection findings Annual training (3 days; 5th meeting in Athens, October 2007): illustrated lectures, case studies, role plays, group discussions National initiatives for training of EU colleagues (Adverse reactions management, bioequivalence)
. Sharing of experience (Art. 23(4), Dir.2005/28/EC)	GCP IWG, joint inspections

What can be remedied within the present legal framework (by modification of guidelines or clarifications)? (Table 2.A.)	
Comments	**Suggestions**
1.4. Cooperation between MS and with EMEA on GCP inspections **. Communication / Exchange of information** **1) Support** • Eudract: (Art. 11 (1(f) Dir. 2001/20/EC) - Validation of quality of data not adequate	GCP IWG, Workplan 2008 An algorithm for validation of essential fields to be agreed on Core set of mandatory data for inspections to be defined => a "Data entry manual" to be developed.
2) Operational issues Article 11 (f) of Dir 2001/20/EC mentions that a reference to the inspections carried out on conformity with GCP should be entered in the data base. This should include data related to inspections programs and results. • Inspection programs and planning: - To be improved for links between some national programs	Is currently the subject of draft guidance "Communication and cooperation between Regulatory Bodies / other organisations involved in assessing Good Clinical Practice requirements". GCP IWG, point TBD meeting Dec 2007, Workplan 2008
• Inspection outcomes: - Findings : meta analysis not easy, due to a current lack of harmonisation	. GCP IWG, Work plan 2008 A common schema for classification of findings is in progress

What can be remedied <u>within the present legal framework</u> (by modification of guidelines or clarifications)? (Table 2.A.)	
Comments	**Suggestions**
<u>1.5. Quality of inspections and harmonisation</u> **. Harmonisation, training** **. Procedures and guidelines on inspections** (Art. 15.(5) Dir. 2001/20/EC and Art. 23(3)(4), 26 and 29 Dir.2005/28/EC*)* . Inspection procedures - core inspection guidance for all inspections (Art. 29 Dir.2005/28/EC) . Training Joint inspections (Art. 23(4), Dir.2005/28/EC)	Adoption and publication planned for December GCP IWG meeting GCP IWG / joint visits programme in place (in addition, participation in PICS with EU~ and non-EU partners has started) This program should be strengthened in 2008, to be included in the GCP IWG Workplan 2008
1.6. Inspection results **. Report (**Art.15 (2) Dir. 2001/20/EC, Art. 30 Dir. 2005/28/EC) Inspection report to be available to: . sponsor . other MS, E.C. and Agency, at their reasoned request . recipients subject to any arrangements concluded between the Community and third countries . recipients in accordance with national regulations of the Member States (made publicly available in some MS).	
There are no explicit provisions for transmission of the report to: . the inspectee , . Ethics Committees (systematically, or at least information). .the MA Applicant/Holder	Availability of the inspection report should be more transparent and improved. Provisions for transmission of the inspection report to: . the inspectee . the MA Applicant/Holder, under specific conditions to be at least clarified. To be added in Article 15(2) of Directive 2001/20/EC if modification of the Directive.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)? (Table 2.A.)	
Comments	**Suggestions**
. Transparency	
Process to consult the GCP inspectors group by any clinical trial stakeholder not clear for sponsors, investigators, CROs	GCP IWG This process should be clarified on the EMEA website
Inspection findings and statistics / trends by categories not available to the public	GCP IWG System to be implemented, while safeguarding confidential aspects Requires harmonisation of thematic categorisation of findings (See 1.4).

What should a new legal framework look like? (Table 2.B.)

Comments	Suggestions
1. 1. Reference texts for GCP i) ICH GCP guideline is the international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials ⇨ "The objective of this ICH GCP guideline is to provide a unified standard for the EU, Japan and the USA to facilitate the mutual acceptance of clinical data by the regulatory authorities in these juridictions." ⇨ "ICH GCPs should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities" ⇨ "The principles of this guideline may also be applied to other clinical investigations".	
This recognised standard is not referred to as a reference guideline in Dir. 2001/20/EC. (it only has to "be taken into account", according to Recital 8 of Directive 2005/28/EC). The consequence is that there is no harmonisation of the transposition of ICH GCPs between Member States.	A legal solution for the inclusion of a reference to CPMP/ICH/135/95, agreed upon by the CPMP and published by the Agency, should be found. (See examples of wording from the directive 2001/83/EC modified: - Principle 2 of the annex of Dir.2003/63/EC for reference to ICH texts - Art. 47 for GMP guidelines (Dir. 2001/83 mod./EC))
ii) Detailed guidelines of good clinical practice are currently the subject of a draft guidance on 'specific modalities' for non-commercial clinical trials, in relation to manufacturing requirements and documentation (Recital 11 and Article 1.3. Dir.2005/28/EC). An explanatory / interpretation guidance adapted to the type of trial (purpose, characteristics…), not only to the type of sponsor, should be considered, especially for trials conducted with authorised products.	A system of annexes similar to that used for GMP could be a way forward These annexes should present details of GCP in the different contexts

What should a new legal framework look like? (Table 2.B.)	
Comments	**Suggestions**
iii) Ethics committee shall adopt relevant rules of procedures to implement the requirements set out in Articles 6 and 7 of Directive 2001/20/EC (Art. 6 (1) of Directive 2005/28/EC). Principles and guidelines for this rules of procedures are not detailed, therefore there is no provision in the Directives that ensure that Ethics committees work in accordance with ICH GCP.	The principles of the rules should be described in the Directives and details in a guideline
1.2. GCP inspections: Title of Art. 15	
Verification of compliance of investigational medicinal products with good clinical and manufacturing practice The title is inadequate.	Proposed wording : "Verification of compliance of clinical trials on medicinal products with good clinical and manufacturing practice"
1.3. National systems of GCP inspection	
Sites under the scope of inspection	
Clear provisions (Art. 15(1) and 2(l) Dir. 2001/20/EC), except for Ethics Committee: the principle of inspection of Ethics committee should be more explicit in the Directive.	A modification of the definition of the inspection (Art. 2(l)), which includes Ethics Committee, could be proposed. Identification of inspectors appointed by Member states for such inspections should remain the responsibility of Member States.
1.4. Cooperation between MS and with EMEA on GCP inspections.	
Request for inspections	
No provision for inspection request from one MS to another MS in 2001/20/EC. This provision exists in Art. 27, Dir. 2005/28/EC	(minor) This provision of Directive 2005/28/EC should be moved into Dir.2001/20/EC, Art. 15. Is currently the subject of draft guidance "Communication and cooperation between Regulatory Bodies / other organisations involved in assessing Good Clinical Practice requirements".

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

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Name of Organisation	Country
Good Clinical Practice Alliance – Europe	Belgium

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1) The Directive provides a strong framework for clinical trials on medicinal products in Europe, establishing a common legal and regulatory reference point for all member states, responsible parties, and citizens.	1).
2) The bringing together of Member State Competent Authorities for the purposes of adopting common measures and practices vis-à-vis the Directive.	2)
3) The establishment of an increasing array of academic collaboration in clinical trials at the Member State and, foremost, the European levels.	3)
4) Providing a public framework for engaging clinical trials, especially with regard to patients and patient and consumer organisations. The Directive has also provided a framework for establishing European collaborations between patients and researchers, and the beginnings of an important trend in promoting the collection of clinical trial and patient-related data as well as patient registries.	4)
5) The establishment of an improved ethical framework for clinical trials, including transparency toward Competent Authorities regarding clinical trial registration (Eudract) and pharmacovigilance (Eudravigilance). Assisting in standardising practices within ethics committees (timelines) and in establishing national ethical review systems (single opinion structures). Improved awareness of clinical trial participant vulnerabilities as well as improved approaches to informed consent practices.	5)
…	…

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) A thorough review of the implementation of the Directive into Member State laws, regulations, and administrative provisions to identify variances and provide guidance on corrective measures, as appropriate. The Directive led to growing amount of regulation and guidance for clinical trials, including Commission regulation and guidance, Member State law, regulation, and guidance, and clinical trial related organisations' internal standards and guidance. The Medicines for Children Regulation, the draft CHMP/EMEA Guidance on First-in-man Studies, and a number of other European guidances can be related to the development of the Directive.	1) The establishment of a permanent and ongoing clinical trial legal, scientific, and ethics observatory for the review of the implementation of the Directive into Member State laws, regulations, and administrative provisions to identify variances and provide guidance on corrective measures, as appropriate. The review should be mandated to consider all law, regulation, administrative procedures, standards, and guidance related to clinical trials in Europe.
2) Several tendencies to categorise clinical trials according to determinations other than design and methodology. In particular, the tendency to assume a distinction between industry and academic trials. Such distinctions have no scientific, ethical, or organisational value and tend to undermine the fundamental principles of Good Clinical Practice.	2)
3) A general failure to understand and appreciate the role of Third Country research and data in European medicinal product development.	3)
4) The lack of a clear definition of a sponsor in clinical trials.	4)
5) The failure to provide an appropriate GCP definition of an investigator and ethics committee. The general disappearance of the investigator's role within the Directive and the development of related regulation and guidances.	5)
…	…

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
1) The GCPA currently considers that modification of the present legal framework should be undertaken in a systematic fashion through the development and maintenance of a clinical trial legal, scientific, and ethics observatory established at the EU level.	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

What should a new legal framework look like?	
Comments	**Suggestions**
2) The GCPA currently considers that the development of a new legal framework for clinical trials (on medicinal products) in Europe is neither feasible nor desirable. Ongoing observation and modifications of the current framework established by the Directive would make an important contribution. The focus should now be on the development of the infrastructure needed to carry out clinical trials in the current and future global divisions of the economies, industries, and sciences needed to engage a significant portion of the annual clinical trials development.	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Name of contributor
EMEA/CHMP Working Group with Healthcare Professionals' Organisations (HCP WG)

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1) It makes working with Industry sponsors more streamlined.	1)

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) The necessity for denoting as "study drug" those medicines which are being used within a study in accordance with their licensed indication is onerous and increases pharmacy, monitoring, pharmacovigilance and data process related costs. An example would be a pharmacokinetic study where the patient is not given an unlicensed agent.	1) Remove the requirement for an agent given within a trial to be denoted as "study drug" as long as the subjects are being given the drug under the conditions of use of the marketing authorisation.
2) The increase in oversight and bureaucracy, resulting in a significant inflation in trial cost, without due foresight that there would be lack of such financial support for the actual implementation of the Directive at the level of (academic) clinical centres and governmental bodies in individual EU states, such as the MHRA in the UK. This has already and will continue to result in a severe decline in the number of non-industry-sponsored scientifically-independent studies, and take the ability to conduct studies out of the hands of most investigators.	2) Either, the Directive also guarantees that the needed funds to implement it are made available at governmental & clinical centre level, or for non-industry sponsored, investigator-initiated trials, requirements are made more lenient.
3) The complexity of the guidelines has prevented individual researchers from commencing studies and has diverted focus onto less robust methods to glean the answers to clinical research questions such as cohort studies and retrospective study analyses.	3) Move towards simplification of requirements in order to reverse this trend.
4) Extremely poor communication from the governmental agencies such as the MHRA on all aspects of interpretation and compliance with the EUCTD.	4) Clarify at EMEA level the answers to many common questions to provide the enacting agency in a member state to effectively implement the ECTD. Considering the possibility of issuing guidelines on how better implement at national level.
5) Requirement for IMPD for agents without a pharmaceutical sponsor e.g. for a new indication of an agent past or close to the end of its patent life effectively has ceased the evaluation of agents of known safety for novel use in other areas of medicines.	5) Remove the need to produces dossiers for agents which have already been licensed for use in the past unless serious concerns over the safety of the agent have not adequately been evaluated in the population to be studied.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
1) Clarify and maybe alter the definition of Sponsor.	1)
2) Provide much better guidance to bodies who implement or produce statutory instruments based on the EUCTD as to how it can work for the benefit rather than the prevention of quality clinical research.	2)
3) The EUCTD has destroyed the initiation of much innovative research in the EU in 3 short years.	3) Legislators should try to look at it from the perspective of those researchers who undertake studies outside of the pharmaceutical industry, most of whom do this in addition to heavy clinical workloads.

What should a new legal framework look like?	
Comments	**Suggestions**
1) This is for the meeting to advice on.	1) Fewer lawyers and more clinical researchers in the process might help

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Name of Organisation	Country
International Society for Pharmaceutical Engineering	UK

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1) Harmonisation of the CT Application form	1)
2)Harmonisation of the IMPD	2)
3)	3)
4)	4)
5)	5)
…	…

Aspect of the Directive 2001/20/EC that do not work well		
	Comments	**Suggestions**
1)	The requirements for certain member states to submit Certificates of analysis for each batch of investigational product to be used in a clinical trial.	This requirement should be removed as each batch is certified and released by a Qualified Person in accordance with the CTA and the IMPD. Therefore, there is no logic to member states approving the batches as well as they do not have the full manufacturing history of the batch.
2)	The requirement that some member states require their own inspectorate to inspect a third country site manufacturing prior to authorising a clinical trial in their country.	The majority of member states require a QP declaration of GMP to be submitted to the competent authority as part of the CTA submission. The local inspectorate can confirm at inspection that the QP declaration has been issued based on suitable evidence (e.g. audit). The EMEA could also produce guidance around this issue as to what level of evidence is required.
3)	There is a lack of harmonisation on the QP declaration statement.	EMEA to provide guidance on what the QP declaration statement should contain.
4)	There are differing approaches between member states in how updates to stability information and expiry dates are approved. In some member states, an amendment to the CTA is required, whilst in other member states a notification to the competent authority is required.	EMEA should provide guidance as to how updating of stability data and expiry dates should be handled.
5)	The EMEA requires QP to certify third manufacturing site are in compliance with EU GMP. However, there is no guidance in how this should be done.	EMEA should provide guidance on what is expected of a QP when certifying 3rd country manufacturing sites.
6)	The use of comparators from ICH regions are accepted for use in EU clinical trials (as stated in CHMP Guideline CHMP/QWP/185401/2004: The Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials, 31-Mar-2006 Chapters 3 and 4) Is there a uniform interpretation of the CHMP document that means we can import product from an ICH country without retesting or the need for some testing to be performed? There are some countries insisting on testing of these comparator products.	EMEA should ask these member states to stop the testing if comparators if they are obtained from third countries and comply with the guidelines. Testing of these product give no added benefit to the quality, safety and efficacy of the product.

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
7) Requirement in Eudralex Vol 10, Chapter 5 section 3.1.16 for investigators to have certificates of analysis in their trial master file. Discussions with EMEA representatives suggest that this is a typographical error and that it is only a requirement for an investigator to hold certificates of analysis when the investigator is the sponsor.	Update wording in this section as follows: **3.1.16 Certificate(s) of analysis of investigational product(s)** To document identity, purity, and strength of investigational medicinal product(s) to be used in the trial. File of the sponsor. (Note: Where the investigator is the sponsor, the investigator should hold copies of the certificates of analysis.)

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
1)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

What should a new legal framework look like?	
Comments	**Suggestions**
2)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Please note that the written submissions and the presentation slides from the meeting will be included in appendix to the report of the meeting and be published at the same time as the report.

Name of Organisation	Country
Irish Platform for Patients'Organisations, Science and Industry	Ireland

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) The indications are a decline in the number of new studies both in the industrial and academic research sectors. Not only the number of new studies is falling, but also the number of subjects included in the sector. This development, this delay is certainly not in the interest of patients who are looking for possible new or improved treatments, especially in the area of incurable diseases	Measure and collect information on the change in Clinical Trials activity throughout Europe

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
2)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

What should a new legal framework look like?	
Comments	**Suggestions**
The Medical Ethical Review Committees or REC's need to facilitate multicentre trials whereby processes are standardised across member states.	1) Look at ways of facilitating a single process across Europe, perhaps even mutual recognition of approval from one REC to another.

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

A) Directive 2001/20/EC and non commercial Clinical Trials
B) ICH-GCP; EU Clinical Trials Guidances

Name of Organisation	Country
Italian Medicines Agency - AIFA	Italy

Aspects of the Directive 2001/20/EC that work well Table I	
Comments	**Suggestions**
A) Directive 2001/20/EC and non commercial clinical trials. INTRODUCTION European Directive 2001/20 EC on GCP and clinical trials has been widely criticised by an important fraction of the scientific community more directly involved in the promotion and management of non commercial Academic (Ac.) clinical trial (CT). Since year 2003 several academic trialists stressed on Scientific International Literature difficulties derived from new EU Regulation specifically as far as it concerns 1) GCP compliance, 2) monitoring, 3) sponsorship, 4) Investigational Medicinal Product (IMP), 5) contents of authorization dossier, 6) notification of adverse event/reactions. In our opinion for the first 4 problems, provisions of Directive 2001/20/EC (Dir.20), read in conjunction with Directive 2005/28/EC (Dir. 28) (issued according to article 1.3 of Dir. 20), do not obstacle non commercial/academic (Ac.) clinical trials (CT) for following reasons:	
GCP IN AC. CT Neither Dir. 20 nor Dir. 28 oblige Ac. CT to be in compliance with E6, CPMP/ICH/135/95 (ICH-GCP) full text and details aimed to regulatory purposes, but they oblige to be in compliance only with GCP principles (art.1.4 Dir. 20) listed in chapter 2 of Dir.28 (this principles are the same of ICH-GCP) and with GCP Guidelines laid down in Dir. 28, which are very simplified if compared with ICH-GCP. Member States (MS) are allowed by Dir. 28 to take into account the specificity of Ac. CT as far as many issues are concerned (i.e. other means instead of certain GCP details, manufacturing and import authorization, Trial Master File (TMF) and archiving).	

MONITORING IN AC. CT 1) According to Dir. 20 (art. 1.3: *GCP detailed guidelines shall be adopted by EU Commission*) in conjunction with Dir. 28 (whereas 11: *For Ac. CT, the application of certain GCP details is unnecessary or guaranteed by other means;* and art. 4: *the protocol shall provide for monitoring policy*), Ac. CT are not obliged to face the same site monitoring and source data verification as are currently standard in industry, whose results can be guaranteed by other modalities.	
SPONSORSHIP IN AC. CT 2) According to Dir. 20 (art. 2 (e): S*ponsor definition*) in conjunction with Dir. 28 (art. 7: *A sponsor may delegate any of all his function*), each collaborating organization in Ac. CT is allowed to take responsibility for its part of CT when no one person or academic organization is willing or able to take responsibility for all aspects for the sponsor role.	
IMP PAYMENT IN AC. CT 3) According to Dir. 20 (art. 19, second sentence: *IMP shall be made available free of charge by the sponsor, unless precise condition established by Member States (MS)*), IMP already marketed, reimbursed and administered to patients under current medical practices, does not need to be paid by Ac. sponsor, but can be made available free of charge for the patients, by agreement between MS National Health Services and Ac. sponsors.	
IMP-TMF AND ARCHIVING IN AC. CT 4) According to Dir. 20 (whereas 14: *Simplified provision for IMP labelling and manufacturing in Ac. CT*) in conjunction with Dir. 28 (art. 1.3: *MS may introduce specific modalities for manufacturing or import authorization and the TMF and archiving in Ac. CT*), Ac. CT are exempted to be in compliance with some specific requirements foreseen	

for obtaining IMP manufacturing or import authorization and foreseen for TMF and archiving.	
INVESTIGATOR'S BROCHURE/IMP DOSSIER IN AC. CT 5) According to Dir. 20 (art. 9.8 (a)) in conjunction with Dir. 28 (art. 8.2), Ac. sponsors when using marketed drugs do not need, for the request authorization, to provide Investigator's brochure or IMP dossier that they don't have, but it is enough to refer to Summary of Product Characteristics, that Competent Authorities (CA) has.	

Aspect of the Directive 2001/20/EC that do not work well Table II	
Comments	**Suggestions**
B) ICH-GCP; EU Clinical Trials Guidances ICH-GCP IN REGULATORIES CT 1) Dir. 2001/20 does not foresee that GCP ICH is mandatory for CT whose results are utilized for Regulatory purposes.	1) See point 1 of Suggestions of the table IV "*What should a new legal framework look like?"*
EU GUIDANCE FOR CT AUTHORIZATION 2) Art. 9.8 of Dir. 20 provides that the Commission shall draw up and publish the detailed Guidance on the contents of the request for CT authorization, without taking into account the specificity of Ac. CTs. EU Commission published this detailed Guidance that has been judged "*red tape"* (i.e. excessive regulation, redundant and bureaucratic) by Ac. trialists.	2) In case of revision of Dir. 20, it should be necessary to foresee, for Ac.CT, simplified Guidance as far as it concerns CT authorization.
EU GUIDANCE FOR ADVERSE EVENTS/REACTIONS NOTIFICATION 3) Art. 18 of Dir. 20 provides that the Commission shall draw up and publish the detailed Guidance on the collection, verification and presentation of adverse event/reaction report, without taking into account the specificity of Ac. CTs. EU Commission published this detailed Guidance that it has been judged "*red tape"* (i.e. excessive regulation, redundant and bureaucratic) by Ac. trialists.	3) In case of revision of Dir. 20, it should be necessary to foresee for, Ac.CT , simplified Guidance as far as it concerns the notification of adverse event/reactions.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)? Table III	
Comments	**Suggestions**
EU GUIDANCE FOR CT AUTHORIZATION 1) See point 2 of Comments of the table II *"Aspects of Directive 2001/20/EC that do not work well"*	1) The EU Commission "Detailed guidance for the request for authorization of CT" could foresee specific simplification for Ac. CT.
EU GUIDANCE FOR ADVERSE EVENTS/REACTIONS NOTIFICATION 2) See point 3 of Comments of the table II *"Aspects of Directive 2001/20/EC that do not work well"*	2) The EU Commission "Detailed guidance on the collection, verification and presentation of Adverse Reaction Reports" and related EU Database (Eudravigilance) could foresee specific simplification for Ac. CT.

What should a new legal framework look like? Table IV	
Comments	**Suggestions**
ICH-GCP IN REGULATORIES CT 1) It needs to establish that CT for Regulatory purposes has to be in compliance with ICH GCP full text.	1) In case of revision of Dir. 20 it should be necessary to foresee: a) that CT whose results are used for Regulatory purposes shall be in compliance both with ICH GCP principles and details while Ac. CT shall be in compliance with ICH GCP principles to be either achieved by ICH GCP details or guaranteed by other means. Provisions of Directive 2005/28 will be applied as well; b) that only CT in compliance with ICH GCP principles and details shall be considered for Regulatory purposes while other CT can be used only as support, but non in substitution of the documentation required for the Marketing Authorization
EU GUIDANCE FOR CT AUTHORIZATION 2) See point 2 of Comments of the table II *"Aspect of the Directive 2001/20/EC that do not work well"*	2) In case of revision of Dir. 20, it should be necessary to foresee, for Ac.CT, simplified Guidance as far as it concerns CT authorization.
EU GUIDANCE FOR ADVERSE EVENTS/REACTIONS NOTIFICATION 3) See point 3 of Comments of the table II *"Aspect of the Directive 2001/20/EC that do not work well"*	3) In case of revision of Dir. 20, it should be necessary to foresee, for Ac.CT, simplified Guidance as far as it concerns the notification of adverse event/reactions.

“Notes from investigators on the operation of the clinical trial directive (2001/20/EC) and perspectives for the future.”

Istituto di Ricerche Farmacologiche “Mario Negri”

The Commission of the European Union has been very active in coordinating and harmonizing drug policy for the 15 Member States, now 27. This has resulted in the creation of EMEA (European Medicines Agency), located in London, with the mandate to approve new drugs and follow them during their entire life. Today most new drugs are approved not only by EMEA but also by national agencies although central authorization is mandatory for biotechnology products, orphan drugs, anti-tumoral, anti-HIV, anti-diabetics and others. Legislation is already available to establish good manufacturing practice (GMP) and good laboratory practice (GLP). The 2001/20/EC directive integrated by the 2005/28/EC directive also developed good clinical practice (GCP) in order to establish “a set of internationally recognized ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects” (article 1.2). These notes report the point of view of an investigator working in a non-profit institute.

What works well in 2001/20/EC directive?

The directive has the undoubted merit of having set in motion a process that may ultimately establish homogeneous rules throughout the EU Member States. This would in principle foster the exchange of information as well as the conduction of multi-centre international clinical trials to speed up the acquisition of data on drug efficacy and safety. The introduction GCP has certainly made academic clinical investigators aware of the importance of adequate rules for data collection, monitoring the centres in a clinical trial, and establishing suitable archives. In other words the directive may stimulate better quality clinical trials, using all the latest electronic informatics technology in order to obtain better records.

Aspects of the 2001/20/EC directive that does not work well

Unfortunately the directive has not given results matching expectations (Grimes et al., Lancet 2005; 366:172-4). In fact the red tape, the general bureaucratic requirements and the cost of non-profit clinical trials have substantially increased, as documented by recent surveys (Sullivan et al., Eur J Cancer 2007, 43, 8-13), (Hoey, The Lancet 2007, 369, 1777). Depending on the type of study the increase has been estimated at 2-4 times the cost of trials before the application of GCP. The error made in the directive and in national implementations was to require additional work without providing the necessary resources to cope with the new requirements. This has resulted in a reduction in the numbers of independent phase III trials (Hoey) and a consequent increase of industrial trials. In Italy data are available through the Medical Observatory which collects all the clinical trials approved by the local ethical committees. Between 2002 and 2006 independent trials carried out by non-profit organizations decreased by 16% despite the new programme of AIFA.*

Furthermore, international multicenter trials have unexpectedly been made more difficult by the GCP as regulated by the directive. It is very important to avoid so many different rules for the approval of the same trial in the 27 countries. An ad-hoc workshop might help find the best way round this problem. Other negative aspects of the directive are reported in the following points with some suggestions for improvements.

What can be remedied within the present framework

The directive's primary objective is the development of new drugs or new indications in the interest of the EU economy even if this does not necessarily coincide with patients' interests. This seems obvious if one considers that the DG Enterprise still oversees all drug regulation, in evident contrast with the situation in the Member States where drug regulation depends on the Ministry of Health or Social Affairs. The directive therefore fails to recognize the characteristics and the role of academic, non-profit or independent clinical trials. As regards the definition of "non-commercial" trials (a term that should by replaced by "academic trials" as opposed to "industrial trials") the Italian Drug Agency (AIFA) has

*

The need to increase independent trials has been acknowledged by AIFA through a law (Gazzetta Ufficiale della Repubblica Italiana. Capo IV. Accordo Stato-Regioni in materia sanitaria. Art. 48: Tetto di spesa per l'assistenza farmaceutica. 2003; Supplemento Ordinario n.274 (Parte prima, martedi' 25 novembre): 95-98) that establishes a fund using 5% of the pharmaceutical companies' promotional expenses (except salaries). Clinical trials to be supported fall into three groups:

1. orphan drugs for rare diseases;
2. head-to-head comparison of drugs with the same indication;
3. pharmacovigilance.

To date 105 projects have been approved, for a total of 65 M Euro.

developed a set of conditions that allow the designation of an independent trial that may be useful for future amendments to the directive. The promoter (or sponsor) must be an entity with a clear expression of non-profit in its statute; the data obtained in the trial must be owned by the promoter; trial results must be published regardless of the findings; the promoter cannot be the owner of the patent for the drug under investigation; the study should not be intended for industrial development of the drug; the financial participation of the pharmaceutical industry is admitted only if it causes no interference with the various phases of the trial; any conflict of interest must be declared. In addition 13 GCP rules must be followed according to the ministerial decree of 15 July 1997 (see table). Trials that fulfil these specifications are entitled to waive the fees for ethical committees, avoid payment for insurance which is borne by the NHS, and to use reimbursable drugs free of charge; it would be desirable that advantages of this kind to be harmonized throughout all the EU Member States.

The directive's failure to consider academic clinical trials reflects its failure to recognize that academic research is of fundamental importance for public health. The attribution to industry of a sort of monopoly of all the aspects related to production, development, commercialization and monitoring of medicinal products is creating growing areas of orphan medicine. Areas of little interest for industrial research call for a coverage by other organizations, such as non-profit or academic research, to make sure the availability of therapies is not determined solely by commercial interest. To give a few examples: rare diseases that, according to WHO, represent more than 5000 entities affecting different organs and functions of the body, are almost neglected by industry because the development of orphan drugs does not produce profits. Although there is a law to incentivate studies on orphan drugs the results are still disappointing because in about four years only 18 orphan drugs have been made available, and the quality of their documentation has been questioned (Joppi et al. Br J Clin Pharmacol 2006; 61:355-360). Neglected diseases are those typical of developing countries, another area in which the pharmaceutical industry is not particularly interested because though there are millions of patients the resources are miserable.

Academic research is essential for comparative trials: head-to-head comparison of drugs with the same therapeutic indications, comparison of different therapeutic strategies, and pharmacological versus non-pharmacological strategies. In addition, research into "active" pharmacovigilance aimed at detecting serious adverse reactions cannot be left only to the pharmaceutical industry. Finally, academic research is needed to discover markers, to reduce the number of patients who are treated without any advantage. Studies on the ε-variants of apolipoprotein E for statins (Chiodini BD et al.; Eur Heart J 2007; 28: 1977-83) and the mutations (exons 18, 19 and 21) of EGFR for gefitinib (T. Sone et al.; Cancer, 2007, 109, 1836) are examples that may point to which patients are most or least likely to respond.

All these kinds of research, which are usually avoided by the pharmaceutical industry, are essential for NHS in order to establish cost-effective reimbursement of medicinal products. It is reasonable that all

these trials are regulated differently from commercial trials because – with the possible exception of orphan drugs – they usually employ drugs that are already on the market, with approved dosing schedules and known common adverse reactions. Therefore the proposal is to regulate compliance with GCP in relation to the risk patients undergo participating in the different kinds of trials. As an example different rules can be suggested for four classes of drugs:

A. compounds being investigated to obtain approval for marketing for common diseases;
B. compounds being investigated to obtain approval for rare diseases;
C. medicinal products that are already on the market;
D. medicinal products that have already received confirmation after five years on the market.
E. In addition GCP may have different requirements when clinical trials require "minimal interventions" such as for instance the administration of questionnaires or psychological tests or blood withdrawal. Member States have at present different rules for these situations.

Another point that could be improved by modifying the present rules is the question of confidentiality. All the legislation concerning the approval of new drugs is surrounded by "secrecy" with a consequent lack of transparency. According to article 11 of 2001/20/EC directive the European database of clinical trials is only accessible to the authorities of the Member States, the Agency and the Commission. In addition GCP may impose different requirements when clinical trials require "minimal interventions" such as, for instance, the administration of questionnaires or psychological tests or blood sampling. Member States have different rules for these situations at present. It is hard to see why the information exchanged is not available to clinical investigators for information. This would give worthwhile advantage in avoiding duplication of research, or interrupting trials promptly if severe adverse reactions occur. Scientific societies and patient associations should have the right of at least a limited access. After all the data obtained belong to the patients who, without any compensation, have agreed to be the subjects of the trial with all its attendant risk. Access to the database does not damage the pharmaceutical companies' interests and helps create public confidence in clinical research. Similarly, the reports made by the inspectors should be made available, with the reply from the institution inspected.

What should a new legal framework look like?

A new legal framework should make a substantial change by shifting the present emphasis on industrial interests to the central position of the patients. It would make the whole European system on medicinal products more credible if the reference were not the DG Enterprise but the DG SANCO together with the DG Research. It is in fact strange that the DG Enterprise is still responsible today for drawing up the rules for trials by non-profit organizations. Equally strange is the statement in the directive that

"academic trials cannot be used for registration". Today the dossiers for approval of new medicinal products are entirely prepared by the pharmaceutical industry. This does not seem like the ideal way of ensuring objectivity in planning and interpreting clinical trials. There is a clear conflict of interest for instance in selecting the comparator and its doses because, even unconsciously, the aim is to make sure the product will be approved by the regulatory authorities. Therefore not only should academic trials be admitted for registration, but at least one of the two phase III trials necessary for approval should be carried out by an independent non-profit organization accredited by the European authority. This would ensure a better balance of interest, besides serving as a useful control of industrial research. Several studies have indicated that research by industry is more likely to be favourable to new drugs than non-profit trials.

An important introduction in a new legislation could be the concept of "added value". Today the law for approval of a new medicinal product requires three characteristics: quality, efficacy and safety, but without requiring any comparison with available products. In other words products are frequently approved as medicines in a "therapeutic vacuum", meaning that drugs that are less effective or more toxic than those already on the market may be approved. It should therefore be required that each new drug should be proved to offer added value, which might be more efficacy or efficacy for new indications, a different toxicity profile, better compliance or lower cost than the current "gold standard".

Drug approval is severely regulated by GCP while other products can follow gentler paths. In a new legal framework the same set of rules, including GCP, should also be obligatory for diagnostic tools, medical devices, herbal and homeopathic remedies. It is unacceptable in the interest of patients that various categories of health products can reach the market with different set of rules. There should be a single law encompassing all clinical research.

Article 1 of the directive establishes that "GCP is a set of internationally recognized ethical and scientific quality requirements….."compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected…." This set of ethical requirements is, however, not specified in the directive. Although it is evident that ethics are influenced by the "cultures" of the single Member States it may now be time to specify at least some basic principles that introduce partial international harmonisation.

2005/28/EC directive (article 3) mentions the use of placebo. Unfortunately there is still debate on the need for a placebo arm and the tendency to avoid comparators even when they are available. There is also a tendency to design trials that do not look for superiority, i.e. for added value, but for equivalence or non-inferiority. This poses an ethical problem because neither the patients involved in these trials nor future patients will have any benefit, though there will still be the risk of adverse reactions (Garattini&Bertele, Lancet 2007 in press). In fact the only purpose of this type of trials is to obtain marketing authorization, not to improve the therapeutic armamentarium. GCP would require the reasons

for a clinical trial to be clearly explained to participating patients. This is obviously not set out clearly enough in most informed consent forms because very few patients would agree to participate in trials with solely commercial interest. In many cases drugs belonging to the same category have been approved on the basis of a surrogate end-point (e.g. cholesterolemia for statins) even when there were drugs already approved on the basis of hard end-points (morbidity and mortality). It is proposed that a number of ethical requirements should be introduced in the GCP as mandatory for all EU Member States. An *ad hoc* workshop should be convened to draft them.

Table

GDP to be respected by Italian academic trials (decree July 15, 1997)

1. Respect of Helsinki declaration
2. Evaluation of the benefits and risks for individuals and society
3. Interest for patients, their safety and welfare must prevail over scientific interest
4. Available information on the drugs must be adequate to justify the clinical trial
5. Protocols must be clear and detailed
6. Study must follow the protocol approved by an ethics committee
7. All decisions must be taken under a physician's responsibility
8. All personnel involved in the study must have adequate experience
9. Each patient must be free to sign informed consent
10. Information related to clinical trials must be archived in such a way that they can be retrieved whenever necessary
11. Confidentiality must be respected as regards patients' identification
12. GMP must be respected

Procedures must ensure the quality of the trial

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

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Name of Organisation	Country
Medicines for Children Research Network (MCRN)	UK

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1) The Directive per-se is fine in what it says – what has to be changed is the different interpretations of the Directive in each member state.	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1)The various interpretations of the Directive by each member state's legislative body is crippling clinical trials in Europe	1) The Directive per-se is fine in what it says – what has to be changed is the different interpretations of the Directive in each member state.
2) The concept of co-sponsorship across national boundaries needs resolving	2) There needs to be a unified approach (either a single sponsor or a number of co-sponsors) regardless of which country the 'main' sponsor or funder is in
3) Varying requirements regarding clinical trials insurance across national boundaries	3)
4) Definition of what is an IMP is not clearly dealt with in the EU Directive and has led each country to interpret this in their own way	4) The EU Directive could usefully try and define some of the associated issues, such as the appropriate inspection process for manufacture of products such as probiotics or trials of pharmacogenetic tests, for all of Europe rather than relying on each country to do this by themselves and, potentially, reach different conclusions
5) Lack of guidance regarding the approach to monitoring	5) A framework for monitoring which all countries can agree to. The final "modalities of non-commercial studies" is awaited as the draft allowed a risk based approach.
6) Lack of specific guidance about the regulations applying to trials running in non-EU countries where there is an activity in the trial which is in the EU e.g. would approval from the relevant member state competent authority be needed if the trial was not for licensing purposes? 7) Under the Directive consent in an emergency setting requires a legal or personal representative to consent the patient.	7) Amended in the UK regulations but it would be useful for international trials if this could be amended in the Directive.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
2)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

What should a new legal framework look like?	
Comments	**Suggestions**
3)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Please note that the written submissions and the presentation slides from the meeting will be included in appendix to the report of the meeting and be published at the same time as the report.

Name of Organisation	Country
Paediatric-Network Germany (PAED-Net), Coordination Centre for Clinical Trials (KKS) at the University Medical Centre, Mainz	Germany

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1) The overall aim of harmonisation of clinical trials within Member States is highly appreciated.	1) To reach this goal it should be ensured that the implementation in EU-MS is realised in a harmonised way, i.e. strictly according to the directive without MS specific deviations.
2) Harmonisation and clarification of terminology has been well addressed.	2) Some discrepancies in the implementation of the directive between Member States may result from terminology and definitions which are not always used consistently in the directive and the guidance documents.
3) Clear description of sponsor's responsibility	3) See suggestions next pages
4) One approval of ethics committee per Member State	4) See suggestions next pages
5) Requirements concerning clinical trials on minors are considered in the directive	

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) ***Intention of directive*** Directive has been written primarily for harmonisation of commercial trials. However, it has also to be applied to non-commercial trials.	1) As usually the objective of IITs is not the approval of medicinal products there should be a restriction to those requests necessary to ensure protection of study subjects and study quality. Formal requests should in general be restricted to a minimum. A definition of non-commercial trials should be included. Even if not needed from a legal perspective, a lot of practical issues are dependent on this definition. The draft Guidance document on specific modalities for non-commercial trials, however, includes definitions which could lead to a decline in non-commercial trials or make most of them impossible. The definition has to be done very carefully involving those groups who conduct scientific driven trials. Furthermore, the term non-commercial trial might be not the most reasonable one. Another terminology should be considered e. g. academic or scientific driven/guided trial.
2) ***Harmonisation*** Harmonisation in Member States has not been reached yet leading to pronounced difficulties in particular in non-commercial trials.	2) Many difficulties result from different implementations in EU-MS and therefore harmonisation seemed to be not realised well. Competent authorities and representatives of EC`s from all Member States should come to an agreement concerning unique procedures. This is in particular important for paediatric trials and orphan diseases in which many study sites are involved in order to achieve the sample size. **One** application to EC and CA would reduce the burden of administrative processes and the time for submission. **One** approval for the applicant including the opinion of both bodies would remove discrepancies in assessment.
3) ***Written informed consent*** Written informed consent to be obtained for study participation of minors.	3) Informed consent should only be needed from one parent/ legal representative in all Member States. The necessity in some Member States to get informed consent from both parents is a high burden which complicates those trials which are needed urgently.

4) ***Pharmacovigilance***	4) Harmonisation in all EU-MS is highly necessary. Reporting of SUSARs not influencing the benefit-risk-assessment should be restricted. Reporting to ECs, CA and principal investigators should only be needed in an aggregated form twice yearly. This should be valid for all SUSARSs in a trial, not only those from other countries. The directive and ENTR/CT 3 should be amended and be made consistent in this respect. Furthermore, to avoid uncertainity regarding reporting rules, the terminology used should reflect the aim (instead of the term investigator, principal investigator should be used or participating site). There should also be a clarification on how SUSAR reporting should be coordinated in multinational trials. Line listings should be consistent for all EU-MS. We would recommend foreseeing ENTR/CT 3 as a commission directive in 2001/20/EC. Reporting of marketed drugs and non-marketed drugs should not differ.
5) ***IMPD***	5) For all IITs access to IMPD – in particular the pharmaceutical part - should be guaranteed.
6) ***Sponsor in multinational IITs*** For IITs, which do not have a sponsor with legal representatives in the Member States (subsidiaries) and where the university often takes over the sponsorship, it is impossible to take over the sponsor responsibility for other universities in various member states in particular as harmonisation has not been realised yet.	6) Sharing of sponsor responsibility with regard to regulatory issues including all reporting obligations and pharmacovigilance as well as the financing aspects and insurance issues is necessary and should be permitted in academic trials.
7) ***Reporting of changes concerning principal investigator/ investigator***	7) During the course of IITs many changes concerning investigators usually occur. New investigators at already active sites should only be reported to the EC at the end of the trial in aggregated form. Approval of these new investigators should not be required. This would reduce formal workload. Furthermore, there should be no necessity for approval of new sites. For some trials (in particular an issue for paediatric trials which usually involve many study sites) it is very important to be more flexible concerning the inclusion of new sites. Information once yearly to CA and EC would improve conduct of these trials.
8) ***Packaging and Labelling***	8) The restriction in 2005/28/EC to packaging and labelling by university based pharmacy for IMPs which are intended to be used exclusively in their study site should be deleted. It should be possible that all IMPs can be e.g. blistered in one hospital pharmacy and delivered to the other participating study sites, i.e. as many sites do not have a pharmacy in their hospital.

9) ***Fees***	9) Measurable reduction in fees for EC approval would particularly support multicentre IITs in minors as many centres usually have to be involved to achieve the sample size. We would recommend to waive fees for IITs for EC as well as for CA in recital 14 of the directive 2001/20/EC and recital 14 of commission directive 2005/28/EC.
10) ***Clinical Trials on adults not able to give informed consent***	10) A similar consideration as for minors including the acceptance of group benefit appears to be important to realise highly necessary trials in this population to improve morbidity and mortality in dementia, severe psychiatric disorders, stroke and emergent and intensive care diseases. The concept of consecutive consent should be considered for clinical trials in patients in emergency situations where patients are not able to give informed consent and do not have a legal representative. Current practice is different in the Members States which complicates these challenging trials even more.
11) ***Trial Master File***	11) Non-applicability of many topics in IITs should be considered. Minimum requirements should be agreed between MS and subsequently harmonised in the interest of multinational IITs.
12) ***Non-interventional trials***	12) Prospective collection of data for research objectives during clinical care of patients by questionnaires or by measuring research variables e.g. in a blood sample obtained for routine diagnostics without any intervention should be possible within the definition of non-interventional trial.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
1)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

What should a new legal framework look like?	
Comments	**Suggestions**
	A regulation would be preferred.

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Name of Organisation	Country
EMEA Human Scientific Committees Working Party with Patients' and Consumers' Organisation (PCWP)	

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
The Directive has provided for more transparent procedures and greater level of protection of individuals. This greater level of protection is achieved by clear considerations on protection of subjects in the legal text, as well as specific provisions for the establishments and operation of Ethics Committees and the verification of compliance with the standards of Good Clinical Practice. In addition, specific consideration for special protection is given for persons incapable of giving legal consent, and in the case of children.	
Lack of coordination of independent trials and lack of compliance with the good clinical practice principles has lead, in the past, with poor quality research, duplication of conducted trials, less productive outcome. The Directive has also affected the so-called “investigator driven studies” and despite the increased administrative burden it has improved the level of consistency in the conduct of those trials	
The limited time for approval has shortened the time to start a new clinical trial once it has been submitted	

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
According to the Article 11 the database EudraCT is not accessible to the general public. This does not allow the public/patients to consider participation in a clinical trial of interest or to obtain information on the main outcome of trials. It also limits the access to investigators who wish to be informed on phase IV and concept of proof trials.	There is a clear need for transparency on ongoing and terminated clinical trial both for already authorised and new investigational medicines. This should be accompanied with information on the results of the trial performed. The legislation on paediatrics is a good example to be followed.
Non-interventional clinical trials do not currently fall within the scope of the legislation. This can cause a two-standard clinical research, lack of harmonisation in non-observational research amongst different countries and differences in their ethical requirements	
Significant differences are found in "informed consents" across Europe both in terms of quality and quantity of the information provided.	
Composition and qualification of integrants at Ethics Committees (EC) are not detailed. Patients can be or not represented within an EC. Across member states and even within the same country the composition, qualification of members and opinion reached by the various EC are disharmonised offering different level of protection to patients participating in research	.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
	The need for more patient and patient-specific involvement as part of Ethics Committees should be regulated: they can bring either particular expertise as patients for a specific field or disease, or just provide the patients' point of view for general matters.
	There is a need for "informed consent" guidelines aiming for harmonised approach across EU both in terms of content and structure. A readability testing could be proposed. A particular consideration is due for current heterogeneity of "informed consent" for people unable to give consent given the fact that particulars regarding the legal representative can vary across member states.
	There is a need for consistent and continuous provision of information to patients during and after finalisation of the clinical trial.
	At the end of the trial, patients should be offered the opportunity to continue the treatment free of charge

What should a new legal framework look like?	
Comments	**Suggestions**
	The Legislation should give provision to make information on trials entered in EudraCT accessible to public and results must be made available within defined timeline (e.g. one year from completion)
	Even if maximum time is clearly defined for EC review, a minimum time is not provided. This can lead to a rather quick evaluation of the application. The Legislation 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 and no undue expedition is advertised in various countries, regions or clinics
	The Legislation should include non-interventional clinical trials in order to consistently regulate all clinical trials in EU

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

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Name of Organisation	Country
Ministry of Health	**Poland**

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
…	…

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
There is a need to lay down provisions for defining common standards for the Ethics Committee accreditation.	It is necessary to make provision which introduce minimal common standards for the Ethics Committee accreditation at EU level.
There is also a need to define which version of GCP is valid and in force.	There is a necessity to define and underline that the final version of ICH GCP is valid and in force.
Directive 2001/20/EC in the Article 3 imposes provision regarding to insurance or indemnity to cover the liability of the investigator or sponsor. The protection of clinical trial subjects seems to be not sufficient.	There is a necessity to start the discussion about enforcement of "clinical trial subjects" protection. Maybe more precise material or procedural solutions in the insurance matter could be helpful.
	…

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
There is a lack of definition which amendments to the protocol should be understood as substantial and are likely to have impact on the safety of the trail subject.	It is necessary to define it.
…	…

What should a new legal framework look like?	
Comments	**Suggestions**
1)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

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Name of Organisation	Country
Plasma Protein Therapeutics Association (PPTA)	Belgium

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1)	1)
2)	2)
3)	3)
4)	4)
5)	5)

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) The most important difficulties encountered arise from different implementation of the Directive in each Member State: different documentation requirements, timelines; sequential vs parallel submission procedures for ethics committee (incl. leading ethics committee and local ethics committees) and Competent Authority. Some competent authorities only accept submission package shortly before ethics committee approval is to be expected.	1)
2) Constant change of national requirements.	2)
3) The approval procedure takes longer than before as each request results in a prolongation of the 60 day period by 60 days ending up easily at 180 days.	3)
4) Additional players complicate the process, e.g. R&D offices in UK clinics strive for more control of study conductance through additional local requirements even after approval by ethics committee and competent authority.	4)
5) Labelling of clinical trial material with the name of the CRO is mandatory. A change of CRO during the trial is possible, but requires change of label including the necessary control and logistics! This requirement should be removed.	5)
6) The implementation of multi-centre studies is much more complicated in EU as compared to other major markets like USA or Japan because of the various national requirements that have to be considered. This is a clear handicap for performing clinical trials in the EU. A further harmonisation or a centralisation of the regulatory process would help to make the EU more competitive.	6)

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
1)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

What should a new legal framework look like?	
Comments	**Suggestions**
2)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

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Name of Organisation	Country
SIOP Europe (Société Internationale d'Oncologie Pédiatrique – European branch)	International

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1) Setting out general rules for the functioning of clinical trials including certain quality standards, has probably improved the rigour with which academic non-commercial clinical trials are conducted.	1) Regulatory requirements should take account of the level of risk involved in a clinical trial and should recognise that those that involve only "old medicines" with a track record of safety and known side effect profile in a particular patient group are low risk and should require a much lower burden of regulatory oversight than clinical trials involving new drugs or new approaches.
2) The move to create centralised European databases of clinical trials and safety data is welcomed and will be a valuable resource for researchers in the future, once established.	2) Access to the information contained within these databases should be kept simple for the occasional user.
3) For the CTA file initial submission, it is good that the CTA file contents are the same for all countries (study protocol, investigator's brochure, CTA form, EudraCT number). However, at the CTA file assessment stage, each national competent authority has its own assessment rules which mean that the CTA can be modified at each submission according to national requirements.	3) A means to improve harmonisation between competent authorities should be found to reduce this variability, or to allow a single 'European' CTA approval that is then endorsed by each participating national competent authority, without repeating the whole process.
4) Some countries do not require electronic reporting of SUSARs by non-commercial sponsors, which has been very helpful. However, not all countries allow this flexibility.	

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) The bureaucratic workload of trial activation is much too high for rare diseases like many childhood cancers. For the rarer subtypes of childhood cancer such as childhood liver tumours, centres may see between 0-10 recruitable cases during the lifetime of a 5 year phase III trial and even less for a phase II trial. Accordingly, the regulatory burden of activating such a trial with non-commercial (academic) sponsorship is disproportionate to the expected patient recruitment. Specific examples: The SIOPEL consortium has run clinical trials in childhood liver tumours since the early 1990s which have led to dramatic improvements in survival rates. Prior to the EU CTD, the SIOPEL International Collaborative Group ran phase III trials in hepatoblastoma in over 50 centres across Europe. However, the majority of SIOPEL centres have failed to activate two new SIOPEL trials; SIOPEL 4 (phase II single arm trial of intensified treatment for inoperable hepatoblastoma) and SIOPEL 5 (phase II single arm trial for childhood hepato-cellular carcinoma). Most centres would see less than two cases per year of eligible patients for these trials and find the bureaucratic burden too heavy to activate the trial in their centres. However, the same approach to treatment is being used by the majority of SIOPEL centres but without formal trial entry, meaning that valuable clinical outcome data is being lost and preventing progress in these rare diseases with poor outcome. The Langerhan Cell Histiocytosis (LCH) consortium (LCH III) trial has had much slower recruitment than anticipated or seen in previous trials by this consortium following introduction of the EU CTD LCH Salvage 2005:- aimed to improve remission rate (and survival) from 25% to 50% (which is the experience in pilot studies). However, opening	1) The EU CTD should be amended to dramatically simplify regulatory approval procedures for rare childhood diseases where individual tertiary treatment centres may see between zero and a few cases per year. The experience of the several European study groups who have succeeded in launching childhood cancer clinical trials across the EU should be taken into account.

	has been severely delayed in most countries due to the requirements of the EU CTD. In the view of the Chief Investigator, this will have resulted in the death of young children who would have otherwise survived. The Innovative Therapies for Children with Cancer (ITCC) consortium, who design and run multinational clinical trials of novel therapeutic approaches for childhood cancer, have experienced disharmony between the Ethics committee assessments due to cultural differences in ethical review and processes between countries, e.g.: Italy: doesn't implement totally the Directive by the fact that there is one ethics committee approval per hospital. UK: complex system of MREC (Multicentre Research Ethics Committee) submission, hospital ethics committee submission and ARSAC (Administration of Radioactive Substances Advisory Committee) submission if necessary. These multiple levels of submission lead to significant delay in activating each participating centre, even though there is theoretically a centralised submission process. Germany, NL: the obligation is on the academic sponsor to prove that their clinical study is a non profit trial, especially at the ethics committee submission stage.	
2)	It is extremely difficult to find a sponsor for paediatric oncology clinical trials. The need for a single pan-European sponsor is interpreted differently by different national regulatory authorities and has caused severe delays to launch of new protocols by long-established European collaborative groups. Specific examples: Interfant 06, a randomised trial aiming to improve outcome and reduce toxicity in the very rare group of infants (aged less than 12 months) with acute leukaemia has been very slow to open across Europe, as many countries are still struggling with the procedures, in particular sponsorship. This trial is a collaboration between eleven established European groups yet 18 months after the launch of the trial, only six of the EU countries were able to formally open it.	2) The responsibilities of the international sponsor should be clearly defined and limited to those of coordination, as suggested in our previous letter to Dr Santos-Ivo, 18th Dec 2006: • Assuring that the appropriate organisational structure is put in place with national representatives, each of whom confirms that their centre/national group's participation complies with national laws and, • Responsibility for timely communications with all partners of relevant information required by regulatory authorities for safe conduct of the trial. • Also, consideration should be given to providing the necessary support, at a European and/or national level, to allow academic institutions or governmental research bodies to feel more comfortable with taking on the role of European sponsor for non-commercial, investigator-led clinical trials. This is a particular issue

German institutions and the GPOH Liver Group, although willing to join the SIOPEL family of trials, are unable to do so because of the strictness of the German law dealing with sponsorship issues which appears to be extremely difficult to solve at a national level. Innovative Therapies for Children with Cancer (ITCC) consortium: Difficulties in finalising the co-ordinating sponsor – co-sponsor agreements which define the role and responsibilities between both parties has been a prolonged process because of specific requests (for modifications) from each co-sponsor.	for trials involving children, where the perceived risk to the sponsor is felt to be greater than for adult trials by many institutions who are unfamiliar with research on children, thus making them reluctant to accept this role.
3) The requirement for the sponsor to provide free drug is problematic in those countries where treatment within a non-commercial clinical trial is not resourced within their national health care systems.	3) The obligation on the sponsor to ensure that clinical trial participants have access to free drug should be reviewed for academic-led trials without a commercial partner.
4) The variable approach between countries in the definition of what constitutes a clinical trial has led to large and absurd discrepancies in the bureaucracy and resources required to administer a standard arm treatment within a clinical trial. Specific example: The European paediatric soft tissue sarcoma group's clinical trial for the treatment of localised rhabdomyosarcoma includes a single arm treatment recommendation that is considered 'best practice' or standard of care, for ~ 50% of patients enrolled in the current trial and for which there is long established safety and outcome data. Some countries demand that all patients registered with the trial are treated as clinical trial patients, with associated pharmacovigilance, whereas others have permitted separation of this group with reduced reporting requirements.	4) A means should be found to allow consistent application of 'standard of care' treatment guidelines with associated relevant clinical data collection without this being classified as a 'clinical trial'. Guidance should be clear so that the approach is consistent between countries.
5) Liability insurance: there is tremendous national variation in the requirement for this and its cost.	5) There should be no absolute requirement for liability insurance for out of patent medicines used off-label in the paediatric setting, where such use is well established as part of standard practice. The requirement for liability insurance should take account not only of the risk of receiving the treatment but also the risk to the child's life of not receiving potentially curative therapy.
6) The identity of the Competent Authority for academic trials depends on the country, e.g. in the experience of the ITCC consortium for paediatric trials of new drugs which have pre-existing marketing authorisations for adult	6) Need to harmonise the definition of the Competent Authority.

use: in Italy, an academic institution appears to be able to take on the responsibilities of the competent authority for non-commercial trials when the IMP is already registered in the country. The hospital insurance then covers the potential risks due to the trial. In France, UK, NL, Germany, the national health authority assumes some or all of these duties.	
7) Need for identified trial drug supply for off-patent medicines that are manufactured generically by different suppliers in different countries.	7) Where a medicine is off-patent, national regulatory authorities should not demand that the protocol has to specify the drug supplier.
8) The need for labelling of IMPs is variably interpreted by different national regulatory authorities and can be onerous.	8) See above.
9) The requirement for an IMP dossier by every national regulatory authority has led to unnecessary duplication of effort and slowing of the bureaucratic process to approve a trial. Specific example from the ITCC consortium: difficulties in obtaining the investigator's brochure from manufacturers for academic studies and logistic issues in the case where different manufacturer's subsidiaries are involved in the product distribution, have led to long delays in putting together the IMP dossiers. Germany / UK: the competent authority (Bpharm and MHRA) ask for the IMP to be completely similar to the authorised product, which means that it is impossible to provide Germany and the UK with a commercial product registered/packaged in France.	9) A single European submission of an IMP dossier should be sufficient for a drug to be used in a clinical trial run in several Member States and to define what is expected for adverse event reporting. Again, this emphasises the problems caused for paediatric trials of drugs that are called 'IMPs' but which already have a marketing authorisation for adult use and which can be supplied from different routine sources in different countries. Such drugs should be allowed to be supplied from different sources in accordance with each institution's normal suppliers.
10) Pharmacovigilance – there are large differences in national interpretations concerning reporting of SUSARs. This is a particular problem in Germany where expedited reporting is required even for SUSARs occurring in other trials that use the same product if the sponsor is in common and not the holder of the marketing authorisation.	10) National variations in requirements for expedited reporting of SUSARs should be reviewed and harmonised to the minimum standard that is agreed to be compatible with patient safety.
11) There is the unknown negative effect that the EU CTD has had on trials that have never been launched, since academic consortia have been deterred by the cost and erosion of personal time involved in launching a new trial under the current bureaucracy. Some very clever ideas may have been lost as a result and are most likely to affect patient groups with the least common disorders.	

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
1) The key issue is the need for and unlimited responsibilities of the international trial sponsor.	1a) Creation of a pan-European sponsoring body for paediatric non-commercial trials or trials of very rare diseases in other age groups. 1b) Have very clearly defined and limited responsibilities of the international sponsor, confined to coordination and communication duties. 1c) The variation in national interpretations of the need for a single (academic) sponsor per trial and the varying attitudes to the status of national co-sponsors for multi-national trials must be harmonised, to allow certain countries (e.g. Germany) to join such trials.
2) Definition of IMPs There are national variations in whether health insurance systems cover the cost of IMPs. This has led to the ludicrous situation where a child's treatment can be covered by health insurance if they are not enrolled in a clinical trial, yet the same treatment may require funding from the (limited) clinical trial resources if given within the context of a trial.	2a) Off-patent drugs should not be defined as IMPs simply because they are the subject of a randomised comparison. 2b) 'Old' drugs that would be classed as IMPs purely because their marketing authorisation does not include paediatric use but which have a long track record of safe/manageable and effective use in children, should be included under the definition of non-IMPs. 2c) There should be some harmonisation of national attitudes to funding IMPs within national healthcare systems for non-commercial trials, especially when they involve drugs with existing marketing authorisations in adults but which have not yet been fully evaluated in children.
3) Labelling of IMPs	3) The requirement for labelling of IMPs should be modified to allow any reputable, commercially available supply of a drug that is already marketed for adult use, to be used within a paediatric clinical trial across several countries.
4) Definition of a clinical trial and need for pharmacovigilance when the trial question is optimisation of long established use of drugs used off-label in the paediatric age group.	4) Such trials should have greatly reduced regulatory requirements.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
5) Pharmacovigilance: Multiple declaration of the SUSAR's to the national health authorities/competent authorities cause unnecessary duplication of effort and paperwork.	5) Could be replaced by a unique declaration to Eudravigilance.
6) Although there is already in place in the EU CTD the ideal of harmonisation of ethical standards and processes, there remains considerable disharmony in their implementation between countries.	6) We hope that this timely review of problems experienced by the academic, non-commercial clinical trial sector stimulates a review of adherence to the suggested pan-European guidelines for the operation of ethical review processes for clinical research and leads to a simplification of procedures in all countries.

What should a new legal framework look like?	
Comments	**Suggestions**
1) A means should be found to simplify the regulatory approval and registration processes for paediatric non-commercial trials in order to sustain the necessary level of clinical research for progress in therapy of childhood cancers. Although a single pan-European ethical approval body for international trials is viewed as desirable by some groups, this is not felt to be either practical or desirable by others. However, all would support a single ethical standard for clinical trials in children.	1) There should be only one international (European) necessity to register the trial without any further need for national registrations, for uncommon conditions. There should be a review of adherence to the suggested pan-European guidelines for the operation of ethical review processes for clinical research with the aim of simplifying procedures in all countries. In particular, it should be investigated whether countries that appear to have complied with the single ethical opinion for clinical trials have simply replaced the institutional control with another layer of bureaucracy, variably labelled 'Research & Development" approval. Furthermore, there should be no fees charged for non-commercial trials.
2) Rules of sponsorship should be modified and relaxed for paediatric non-commercial international trials since currently they create a significant obstacle for several countries and centres to join. This should be applied especially to rare diseases, where the current administrative burden is so large and disproportionate to expected patient numbers that many centres prefer not to participate in such trials, in order to register one or two patients per year.	2) A pan-Europe body could be created which will take a role of an overall international sponsor for various paediatric trials. Otherwise legislation could be modified and in non-commercial trials the sponsor could bear only scientific and coordinating responsibility, while medical liability should be delegated to the national level or even the level of individual treatment institutions. This would encourage international and national research or academic institutions to accept sponsor's role.
3) Additionally national public research or clinical institutions are reluctant to take the international sponsorship role since it is associated with significant liability and legal responsibility.	3) As stated above the legislation could be modified and in non-commercial trials the sponsor could bear only scientific and coordinating responsibility (including SAEs and SUSARs management), while medical liability should be delegated to the national level or even the level of individual treatment institutions.
4)	4)

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

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Name of Organisation	Country
Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)	Spain

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
The main achievements of Directive 2001/20/CE are: • Setting up common ethical principles and good practices (manufacture and clinical) in order to ensure protection of all CT participants and the quality of the results. • Single opinion by the Ethics Committees is required. • Harmonization of administrative requirements and timeframes for all Member States for the conduction of clinical trials. • Setting up European databases (EudraCT and Eudravigilance-CT) as a mean to enforce cooperation between MS through the exchange of information. • Very good support for MS cooperation on inspections. • Having created a simple system of CT identification (EudraCT No.) and a standard XML file format as a basic tool for updating EudraCT. Public and secure EudraCT are excellent tools, although there is room for improvement. • Discussions of MS experts on CTFG, Commission group on Directive 2001/20/CE development and TIG on EudraCT are being very useful in order to identify problems and progress in harmonization. • Only SUSARs are required for expeditive reporting. • There exist an CT electronic system for SUSARs reporting based on the more experienced Pharmacovigilance SAR reporting one.	

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1. Uniform requirements have been set up for all types of clinical trials (CT) with independence of the involved amount of risk Directive does not differentiate requirements for clinical trials on the basis of the level of risk that the clinical trial involves for the participants, except with respect to minor things e.g. no Investigational Medicinal Product Dossier (IMPD) is needed for CT on medicinal products authorised in the EU and used within the authorised indications. In an attempt to overcome this deficiency within the current legislation, specific modalities have been considered for "non-commercial" clinical trials with the additional purpose of promoting academic research. A draft guidance on these specific modalities has been proposed. However this draft guideline is considered not entirely satisfactory. Reasons follow: First, "Non-commercial" is a characteristic of a clinical trial and not of an sponsor, and from the CT subject perspective having different standards or requirements for CT based on the sponsor type (commercial or non commercial) would not be acceptable nor reasonable. Second, Directive states "Non-commercial clinical trials conducted by researchers without the participation of the pharmaceutical industry may be of great benefit to the patients concerned." However, it is proposed that non-commercial trials can not be used in order to support a marketing authorisation or a new indication dossier, which is inconsistent with highlight the importance of these studies. It would be much useful to interpret that non commercial trials deserving modalities involve those where only EU authorised medicinal products are used or those with a normal clinical practice based approach. Two different levels of requirements could be defined. One, involving most simplification related to clinical trials on authorised medicinal products used within the authorised conditions. The other, for those CT on authorised medicinal products when they are used outside the authorised conditions.	<u>Proposals</u> 1. A rewording of the guideline on non-commercial trials is considered needed with a view on all CT on authorised in the EU medicinal products. Adaptations of requirements could be foreseen depending on use within or outside the authorised conditions and on the level of risk for the CT subjects with respect to the risk assumed on normal clinical practice. 2. For CT on medicinal products authorised in a concerned MS and used under the authorised conditions, the following adaptations could be considered: a. EC opinion and only notification to the CA for information would have been sufficient. b. annual safety reports should have an analysis of all SARs on the subjects' safety report text, but only SUSARs should be included in the listings. A listing referring to all SARs should only be provided on request. c. Adaptation to labelling could be acceptable provided that traceability of the IMP treatment is guaranteed by other means. d. Adaptation on the CT application form. Only core information could be required. e. No insurance would be needed when the Ethics Committee would consider that the participants will be posed to a minimum risk. f. Payment free of charge by the sponsor could be exempted, and the normal way of MP supply could be acceptable for those clinical trials with a normal clinical practice based approach. g. Adaptation on monitoring and CT documentation could be acceptable depending on a clinical based approach in the CT. 3. For clinical trials on medicinal products used outside the authorised conditions, circumstances when some adaptation on labelling, monitoring and CT documentation would be acceptable should be

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
	defined. Cases where the IMP authorisation status differ among the MS participating in the CT should be specifically considered. 4. Modalities acceptable for academic sponsored CT should also apply to commercial trials fulfilling the same conditions when appropriate.
2. Comments on the regulation of clinical trials Common regulation of clinical trials is focused to guarantee the same level of protection to the participants in the CT while assuring the same quality standards. MS should have some flexibility for adapting the way to achieve these objectives to the national circumstances. There is a huge volume of legislation and guidelines, sometimes with rules applicable to a specific topic in different documents. In addition, for international sponsors it could be difficult to access to the national legislations.	<u>All relevant information concerning CT should be made available thorough a single CT web</u> Q&A document elaborated by the CTFG and Commission group on development of Directive 2001/20/EC should be periodically updated. All EU legislation, recommendations, Q&A documents, proposals, useful information coming form the European CT related groups (CTFG, Commission group on developing Directive, etc.) and a summary of national legislations on CT, should be available there. In order to assure that European citizens could have access to any official information in their own language, this web should be multilingual.
3. Need for harmonisation on non-interventional studies The term "non-interventional trial" is an oxymoron in many languages (any trial by definition implies an intervention). Therefore, it is proposed that this term	To replace the term "non-interventional trial" by "observational study"

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
should be replaced by "non-interventional study" or better, by "observational study". The definition of non-interventional trial is a source of important problems of interpretation in most countries. Some studies which have been traditionally considered as purely observational (e.g. a case-control study) are at risk of being wrongly classified as clinical trials, simply because they do not completely fulfil the definition of "non-interventional trial". This concerns mainly with the third part of the definition -"No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data;" This part implies that any procedure required by a research project, for example a case-control study, which is not usually done in clinical practice (e.g. an echocardiogram, a questionnaire, more frequent blood samples, etc) will qualify the study as a clinical trial. Many of these "additional procedures" will have a minimal impact in terms of risk to patients and it would not be reasonable to upgrade the study as a clinical trial only for that. Additionally, even for those procedures posing patients to a risk greater than minimal risk, the best solution would not be to convert the study into a clinical trial but to regulate those epidemiological studies strengthening the ethical and legal requirements. Moreover, this part does not take into account that clinical practice may differ across member states and within a Member State from one region to other or from one health institution to other. Finally, the last sentence of the third part of the definition seems to ignore that the epidemiological methods are also applied to clinical trials.	A possible review of the Directive should delete the third part from the definition of non-interventional study. Meanwhile (and until the Directive could be modified) , we propose to make a more liberal interpretation of which is interpreted as "additional" to clinical practice. The criteria of "minimum risk" would be crucial. Any diagnostic o monitoring procedure not posing to patients more than a minimum risk should be accepted as equivalent to those performed in normal clinical practice. The level of risk should be judged by Ethics Committees. An European guidance for observational studies would be necessary. An observational study should also be submitted to an EC for its evaluation and some requirements for them should be as stringent as in clinical trials if the procedures proposed are invasive.
4. Need for simplification and harmonization of SUSAR reporting Article 17 3. a) may be interpreted as if every CA should receive all SUSARs related to IMPs. This may lead to duplication of reporting.	Art. 17 3.a) should be modified as follows "Each Member State shall see to it that all suspected unexpected serious adverse reactions to an IMP <u>occurred in its territory</u> which are brought to its attention are immediately entered …access." In order to decrease the complexity of SUSAR reporting to Eudravigilance-CT,

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
Normally CA are supposed to assess all received SUSARs and all received annual safety reports. This means huge and overlapping work.	all sponsors should notify all SUSARs there, sending simultaneously those occurred in every MS to the correspondent CA in that MS, when required. This requirement may be waived for academic sponsors provided that the CA could make the reporting on their behalf. To clarify that MS should only assess SUSARs occurred in their territory and who should be responsible for the assessment of SUSARs occurred in third countries. Proposals by the CTFG on this topic would be of interest. To find a way for MS sharing the annual safety report work as it is does for PSURs.
Expeditive SUSAR reporting for EC required by Directive is excessive according to actual EC capabilities.	The EU guideline considering the recording, assessment and reporting of adverse reactions is currently accepted by many MS. This considers that expeditive reporting to the EC should be limited to SUSARs occurred to subjects in the geographical area of the EC. In addition, semestral reports listing SUSARs from other countries should be notified. However, other ways to simplify the EC task could be searched by the CTFG. Standard reports in the Eudravigilance data warehouse could be produced for distribution by CA to the EC.
Complexity and cost of SUSAR reporting to Eudravigilance-CT converts it on inaccessible for many sponsors, specially for academic ones.	Specific training is needed in order to improve the safety monitoring, assessment of AR expectedness, and knowledge of the SUSAR reporting system especially for academic sponsors. Budgetary provisions should be made for this. Eudravigilance-CT training should be free of charge for academic sponsors.
5. Need for harmonization on substantial amendments Substantial amendment definition permits a lot of interpretation which favours disharmony between NCAs, ethics committees and sponsors.	Results of the CTFG work on this topic should be published as soon as possible as they would be very valuable.

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
Criteria with respect to updating the information on EudraCT through substantial amendments are needed. This is very relevant taking into consideration that part of EudraCT information would be made public at least for pediatric CT.	
6. **Need for transparency and IT communication** <u>Compatibility between national databases and EudraCT</u> A centralised database EudraCT has been set up which at the moment does not allows automatic transfer of information from national CT applications. As currently MS are developing their own applications, a bi-directional compatibility requirement for national and EU databases would be essential in order to assure cooperation in future. Lack of compatible databases at present requires duplication of work in MS in order to upload EudraCT. On the other hand, compatibility of the databases in the future will assure 100% update of EudraCT simultaneous to the national CA databases update.	<u>Proposal</u>: Processes allowing automatic transfer of information between national applications and EudraCT should be developed as soon as possible.
<u>Need for improve quality of data by improving automatic validation standard</u> Currently data information on the XML to be loaded in EudraCT is often not adequate.	Appropriate automatic validation functionality should be added before CT information would be made public.
<u>Need for search EudraCT capability and make standard and customised reports</u> Currently the search capability of EudraCT is very much limited.	Content and format of standard reports and added functionality should be agreed.
<u>Need for an European Registry on CT</u> Some MS, such as Spain, are required by law having a public registry on clinical trials. At the same time, major Medical Journal Editors are now requiring registration of CTs on publicly available databases before publishing their results. In addition, the Pediatric Regulation requires publication not only of part of the EudraCT available information on pediatric trials, but also of their results.	

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
Taking into consideration these circumstances it is proposed to create a European CT register that will incorporate part of EudraCT information at least for all CT authorised in any MS.	
Need for clarification on what fields should be updated in EudraCT Criteria with respect to updating the information on EudraCT through substantial amendments are needed. An XML comparison tool would be needed in case the whole initial XML was to be replaced by a new one including the update.	Conclusions of the CTFG analysis on this topic would be very importanrt.
7. Need for better definition of CA responsibilities on CT assessment EC responsibilities are well defined but not those of CA, which results in certain overlapping.	A clarification of the CA responsibilities with respect to the CT assessment would be of interest.
8. **Need for cooperation between CA on multinational CT scientific assessment** All concerned MS evaluating the same information sometimes come to different conclusions. Although local reasons are usually present, there is a need for CA to cooperate in scientific issues in order to share their assessment.	Proposal: CA should cooperate on a voluntary basis, through the CTFG in order to get harmonised scientific assessments of CT, at least for certain CT categories. This Agency supports the proposal made by the AFSSAPS, mainly with respect to share technical analysis and information in an efficient way. However, we are reluctant to set up new regulations on this field.
9. Need for improving article 19 of Directive Investigational Medicinal product (IMP) definition is linked to economic constraints by article 19 ("..., investigational medicinal products, and, as the case may be, the devices used for their administration shall be made available free of	Proposal: article 19th should be modified as follows: "…..medicinal products which are not available in the normal clinical practice for the treatment of patients of similar characteristics to those in the CT, and, as the case may be,

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
charge by the sponsor"). This general link has created difficulties for sponsors, and the need for excluding certain categories of medicinal products essential for the good performance of the CT (i.e background, MP given for measuring primary end-points, provocation agents) of the IMP category. As a consequence, requirements for non-IMP (some of them without a marketing authorisation in the EU) could vary according to MS criteria.	the devices used for their administration shall be made available free of charge by the sponsor. " In addition, it would be important to say that treatments received by the subjects due to their participation on the CT should be available free of charge for them. Or Article 19th should be modified as follows: ".....medicinal products not authorised in the concerned MS or authorised and administered n the CT outside the authorised conditions, and, as the case may be, the devices used for their administration shall be made available free of charge by the sponsor" In addition, it would be important to say that treatments received by the subjects due to their participation on the CT should be freely available for them
10. **A Clock stop is also needed for CA** Article 6 (Ethics Committees) foresees that when the EC ask for some clarifications to the sponsor the assessment period shall be suspended until receipt of supplementary information. However, this clock stop is not foreseen on article 9 for the Competent Authorities.	In case Directive 2001/20/CE is amended this should be remedied.
11. **Need for harmonisation of research sites requirements conducting phase 1 CTs in Europe**	It is necessary to define requirements for sites where phase I CT are conducted with respect to personnel, equipment and procedures aimed to the safety of subjects. The first priority should be definition of criteria for sites where first in man CT should be conducted.
12. **Need for supporting European academic sponsors**	It seems necessary to make available funds in order to enable academics investigators and sponsors to get the resources, specific training and infrastructure necessary to apply the Directive required standards on clinical trials.

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Please note that the written submissions and the presentation slides from the meeting will be included in appendix to the report of the meeting and be published at the same time as the report.

Name of Organisation	Country
Task Force in Europe for Drug Development for the Young (TEDDY) Network of excellence (funded under FP6)	**Network of Excellence involving 19 partners of 11 countries**

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
GENERAL COMMENTS Clinical trials Directive 2001/20/EC is undoubtedly having a considerable effect upon clinical research practice within Member States. On one hand, it provides a good illustration of the powerful impact of the EU-level regulatory measures of harmonisation. On the other, Clinical trial Directive contains some provisions with an ethical dimension, guarantying some human rights, such as rights to physical and mental integrity as well as to privacy. Thus, the ethical dimension appears to be increasingly coming to the fore in the European legislation. Through the incorporation of the ICH Guidance on Good Clinical Practice and its effective adoption as binding law, the Directive can be seen as affording protection to individual research subjects, and especially to vulnerable subjects (e.g. children). It should be noted that Directive 2001/20/EC has devoted, for the first time in the European Legislation contest, a specific article (art. 4) devoted to minors' protection.	In the perspective of the application of EC Paediatric Regulation, it should be particularly important to guarantee the freedom of scientific research and to increase the benefits derived from scientific and technological developments, while providing a universal framework of principles and procedures in accordance with ethical principles and human rights international law to guide EU and States in the formulation of their legislation, policies or other instruments in the field of biomedical research, especially in paediatrics. Furthermore, contents and provisions of the Directive 2001/20/EC should be better released to the European citizens, scientists and regulators. The implementation should be better coordinated.

Aspect of the Directive 2001/20/EC that do not work well

Comments	Suggestions
PROTECTION OF SUBJECTS INVOLVED IN CLINICAL RESEARCH WITH SPECIAL REFERENCE TO MINORS The reference made in the Directive 2001/20/EC to "ethical and scientific requirements" or soft law measures (e.g. good clinical practice, detailed guidance...) aides what may be gradual process of convergence of legal measures towards a set of "EU values" with respect to ethical clinical research in paediatrics. Nevertheless, it seems legitimate to fear that the reference made to "non-binding rules" may be a source of confusion, especially in the case of paediatric research. In the TEDDY "Survey on ethical and legal frameworks existing in Europe for paediatric clinical trials" have been emphasized that, even if all the European countries implemented Directive 2001/20, with respect to clinical research practices in paediatrics, it exists a "regulatory gap" or rather a "regulatory conflict" not only between ethical and legal frameworks at European level but, most of all, between the European ethical/legal frameworks (Directive 2001/20, Oviedo Convention, Additional Protocol on Biomedical research, etc.) and national regulations. In particular, many differences exist in Europe related to the protection of minors involved in clinical trials across Europe due to the directive implementation process as well as to a lack of coordination. Furthermore, the wide range of situations due to a no-coordinate Directive 2001/20 implementation, the great differences in cultural and economic environment, the large number of texts of varying legal force existing in the field of clinical research, with special reference to paediatrics, can cause difficulties in imposing penalties on researches	In application of the principle of equality of treatment, that is an implicit milestone in building a European wide-democratic society based on the respect of fundamental rights, and in order to guarantee the respect of human dignity, autonomy/self determination, beneficence, justice and precaution ethical principles, it shall be important to develop ethical guidelines and/or new legislation, according to European and international ethical/legal requirements, to international human rights law (with special reference to protection of subjects involved in biomedical research) as well as in compliance with ethical/legal national provisions. To this aim, it shall be necessary to make reference to the principles contained in all these international ethical/legal sources: **<u>Ethical sources</u>**: • Declaration of Helsinki (revision 2004); • Clinical investigation of medicinal products in the paediatric population. ICH E11; • CIOMS/WHO International Ethical Guidelines for Biomedical Research Involving Human Subjects (1993, reviewed in 2001); • EC Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (2006). **<u>Legal sources</u>**: • Universal Declaration of Human Rights (UN - 10 December 1948); • Convention on the Rights of the Child (UN-20 November 1989); • Convention for the protection of Human Rights and fundamental Freedoms (COE, 4 November 1950);

that violate human rights of minors in the name of medical research. In addition, **differences existing in Europe could lead some inequality in the protection level of minors involved in multi-centre clinical trials.**	• Convention on Human Rights and Biomedicine (Oviedo Convention , COE, 1997); • Additional Protocol to the Oviedo Convention on Biomedical Research (COE, 2005) ; • Charter of Fundamental Rights of the European Union (2000); • Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997) • Universal Declaration on Bioethics and Human Rights (UNESCO, 2005); • International Declaration on Human Genetic Data (UNESCO, 2003); • Directive 2001/20/EC ; • European Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data. Since it is a matter of fundamental rights, the respect of which constitutes, in value systems recognized in Europe, an indivisible obligation for the public authority to fulfill, the purpose is to ensure that the powers attributed to the Union by the Treaties are clearly limited by respect for the specified rights, and that each person legally implicated on Union territory may rely directly on these rights. That will be more important for vulnerable people (such as minors) involved in biomedical research. The Union's field of competence is not affected: it is a question of ensuring that by its action the Union does not infringe on the enjoyment of fundamental rights, regardless of what they are, most of all because human rights international/European sources could have judicial effect, on the basis of the discretion of the courts (CJCE, CEDH and national ones) to 'refer' to its content.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
1) The key issue when considering carrying out research involving paediatric population is their vulnerability. The vulnerability of children is in large part due to their inability to protect their own interests. Therefore, to protect the rights of children involved in clinical trials and to shield them from undue risk, harm and exploitation, special measures (especially related to selection criteria, informed consent/assent and confidentiality) have to be adopted. ***The purpose is to ensure that each minor involved in a clinical trial in the European Union territory may rely directly on respect for human dignity and for life, as well as for fundamental freedoms, consistent with INTERNATIONAL HUMAN RIGHTS LAW (especially relevant to the protection subjects involved in biomedical research).***	**1) In accordance with art. 1(3) and 21(2) of the Directive 2001/20, principles of good clinical practice and detailed guidelines should be adopted and, if necessary, revised in line with principles of human dignity, safety and well-being as well as consistent with international human rights law.**
2) In accordance with COE-Oviedo convention art.5, art.6 sec.5, art.17 sec.4; COE-Additional protocol on biomedical research, art. 13, 14, 16 (3), 15 (1) and sec.V, and its explanatory report sec.80; UN-Universal declaration on Bioethics and Human Rights, art.6, art.7 (b), EC detailed Guidance, February 2006, **specific measures related to selection criteria** as well as **related to informed consent procedures (that for minors have to be defined as authorization/assent and information procedures)** shall to be integrated.	2) **Selection criteria** A clinical trial on minors may be undertaken only if all the following specific conditions are met: a. the results of the research have the potential to produce real and direct benefit to the health of minors concerned; Exceptionally and under the protective conditions prescribed by European and national law, where the research has not the potential to produce results of direct benefit to the health of the minor concerned, such research may be authorised following additional conditions: a. the research has the aim of contributing, through significant improvement in the scientific understanding of the minor's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the minor concerned or to other children in the same age category or afflicted with the same disease or disorder or

	having the same condition; **<u>Authorisation/assent and information procedures:</u>** A clinical trial on minors may be undertaken only if all the following specific conditions are met: a. legal representatives and the minor (according to his/her maturity degree) undergoing research have been clearly and adequately informed about the trial, the risk and the benefits, as well as of the rights and safeguards prescribed by law for minors protection, and specifically of their right to freely refuse or to withdraw from the trial at any time, for any reason and without being subject to any disadvantage, prejudice, liability and/or to any form of discrimination, in particular regarding minor's right to medical care. This information shall be given according to the minor's capacity of understanding, from a staff with experience with minors, regarding the trial, the risks and benefits. This information shall be documented. The same level of care and information shall be maintained during treatment or investigations. b. the necessary authorisation has been given specifically and in writing by the legal representative or an authority, person or body provided for by law, and after having received the information, taking into account the minor's previously expressed wishes or objections. In particular, the opinion of the minor shall be taken into consideration as an increasingly determining factor in proportion to age and degree of maturity; c. the minor concerned does not object. d.Objection to participation, refusal to give authorisation or the withdrawal of authorisation to participate in research shall not lead to any form of disadvantage, prejudice, liability and/or discrimination against the child concerned, in particular regarding the right to medical care.
3) In accordance with Additional Protocol art. 25,26,27; Universal Declaration on Bioethics and Human Rights –Art. 9; Oviedo	3)**<u>Confidentiality:</u>** Any information of a personal nature collected during biomedical research

Convention art.12, International declaration on Human Genetic data; Charter of Fundamental rights UE art.8, **specific measures related to confidentiality issues and right to information** shall be integrated.	shall be considered as confidential and treated according to the rules relating to the protection of private life. Such information shall not be used or disclosed for purposes other than those for which it was collected or consented to. **Right to information** Minor participant in research shall be entitled to know any information collected on his/her health. Other personal information collected for a research project will be accessible to him/her in conformity with the national law on the protection of individuals with regard to processing of personal data. If research gives rise to information of relevance to the current or future health or quality of life of research participants, this information must be offered to them. That shall be done within a framework of health care or specific counselling, most of all in the case of predictive genetic tests. In communication of such information, due care must be taken in order to protect confidentiality and to respect any wish of the minor (and/or his/her legal representative) participant not to receive such information, in accordance with national law.
4) **Specific measures related to paediatric expertise** shall be introduced.	4) **Paediatric expertise** The Ethics Committee opinion on the protocol has to contain in addition of the reasons of its conclusion a description of the way to respect the condition of the paediatric expertise in the decision process.
5) In accordance with art. 21 of Oviedo Convention and art. 12 of its Additional Protocol on biomedical research, **specific measures related to the interdiction of undue influence of a financial nature** shall be integrated.	5) **Undue influence** No undue influence, including that of a financial nature, will be exerted on child or his/her legal representative to participate in research.
6) In accordance with art.24 of Additional protocol on biomedical research, **specific measures related to new developments** shall be integrated.	6) **New developments** The research project shall be re-examined if this is justified in the light of scientific developments or events arising in the course of the research. The purpose of the re-examination is to be established whether: i. the research needs to be discontinued or if changes to the research project are necessary for the research to continue;

	ii. research participants (minor), and their representatives, need to be informed of the developments or events; iii. additional authorisation and assent for participation is required. iv. any new information relevant to their participation shall be conveyed to the research participants (minor), and to their representatives, in a timely manner. v. The competent body and Ethics Committees shall be informed of the reasons for any premature termination of a research project.
7) In accordance with art.31 of the Additional protocol on biomedical research, **specific measures related to damage compensation shall be integrated**. Furthermore, it seems important to propose an analysis of the differences related to insurance conditions and procedures of compensation for damage existing in the European Member States, in order **to create a common and specific regime to guarantee safety of minors, in the light of consideration that the minor is a person whose body is in development.**	**7) <u>Damage compensation</u>** The minor who has suffered damage as a result of participation in research shall be entitled to fair compensation according to the conditions and procedures prescribed by law. In this respect, specific and more protecting guarantees have to be provided for minors.
8) In accordance with art.21 of Additional protocol on biomedical research, **specific measures related to minimisation of risk and burden** shall be integrated. Furthermore, it shall be important to create a **European register, regularly updated, of the investigators and team having the necessary qualification and experience in paediatric research in general, and, in particular, in the field of the applied project, as well as of the safe and adequate infrastructures, to be consulted by the ethics committees**. That should be particularly useful in the multicentre studies, in order to guarantee the safety and quality of paediatric clinical research.	**<u>8)Minimisation of risk and burden</u>** All reasonable measures shall be taken to ensure and to minimize risk and burden for the minors participant in a clinical trial. Clinical trials may only be carried out under the supervision of a clinical professional who possesses the necessary qualifications and experience in paediatrics.
9) According to Convention on Human Rights and Biomedicine Additional Protocol on Biomedical research (art.11, 13 and its appendix) and some national legislation, given that important differences existing across Europe concerning consent procedures (authorization/assent, information procedures for minors), the following integrations are proposed.	**<u>9)Informed authorisation/assent sheets</u>** The following documents have to be submitted to ethics committees for examination: -Loyal, comprehensive, understandable Informed authorisation and Information sheets for legal representatives, <u>in accordance with</u>

These measures respond to the necessity of avoiding distortions in the legal frame at European level in the current situations related to clinical trials. Related to documents to be provided to ethics committees for examination, the following integrations shall be adopted.	national law, even in the international multicentre studies. -Loyal, understandable, age specific Informed assent and Information sheets for children, in accordance with national law, even in international multicentre studies.
10) In accordance with the appendix of the additional protocol on biomedical research, **information of the following items (related to authorisation/assent, information procedures) shall be provided to the ethics committee.**	**10)Content of protocol and authorisation/assent sheets related to information to give to minors and legal representatives to be submitted to ethics committees** Protocol and informed authorisation/assent sheets to be submitted to the ethics committee for examination shall contain the following items: a. justification for involving minors in the research project; b. criteria for inclusion or exclusion of the categories of minors for participation in the research project and how these minors are to be selected and recruited; c. a description of the nature and degree of foreseeable risks that may be incurred through participating in research; d. nature, extent and duration of the interventions to be carried out on the research participants, and details of any burden imposed by the research project; e. arrangements to monitor, evaluate and react to contingencies that may have consequences for the present or future health of research participants; f. timing and details of information for legal representatives and minors who would participate in the research project and the means proposed for provision of this information; g. loyal, comprehensive and understandable documentation intended to be used to seek authorisation of legal representatives and assent of minor for participation in the research project, in accordance with national law even in multicentre studies; h. arrangements to ensure respect of the private life of these minors who would participate in research and ensure the confidentiality of personal

	data; i. arrangements foreseen for information which may be generated and be relevant to the present or future health of minors who would participate in research and their family members; j. details of any foreseen potential further uses, including commercial uses, of the research results, data or biological materials; k. details of any insurance or indemnity to cover damage arising in the context of the research project.

What should a new legal framework look like?	
Comments	**Suggestions**
1)In the light of all the above mentioned considerations, the new legal framework for paediatric research will be focused on minors. It means, for example, that consent procedures have to be defined as authorization (for legal representative) and assent (for minors) procedures. With reference to **criteria selection, authorisation/assent and information procedures**, in accordance with principles contained in the COE-Oviedo convention art.5, art.6 sec.5, art.17 sec.4; COE-Additional protocol on biomedical research, art. 13, 14, 16 (3), 15 (1) and sec.V, and its explanatory report sec.80; UN-Universal declaration on Bioethics and Human Rights, art.6, art.7 (b), EC detailed Guidance, February 2006, the new legal framework shall be as indicated in the suggestions part.	**Clinical trials on minors:** **ART.1 Protection of persons not able to consent to research (minors):** In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if all the following specific conditions are met: a. the results of the research have the potential to produce real and direct benefit to the health of minors concerned; b. legal representatives and the minor (according to his/her maturity degree) undergoing research have been clearly and adequately informed in accordance with provisions of article 3; c. the necessary authorisation has been given specifically and in writing by the legal representatives or an authority, person or body provided for by law, and after having received the information, taking into account the minor's previously expressed wishes or objections. In particular, the opinion of the minor shall be taken into consideration as an increasingly determining factor in proportion to age and degree of maturity; d. the minor concerned once informed does not object. 2. Exceptionally and under the protective conditions prescribed by European and national law, where the research has not the potential to produce results of direct benefit to the health of the minor concerned, such research may be authorised subject to the above mentioned conditions (points b, c and d) as well as to the following additional conditions: a. the research has the aim of contributing, through significant improvement in the scientific understanding of the minor's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the minor concerned or to other minors in the

	same age category or afflicted with the same disease or disorder or having the same condition; b.the research entails only minimal risk and minimal burden for the minor concerned; and any consideration of additional potential benefits of the research shall not be used to justify an increased level of risk or burden. 3. Objection to participation, refusal to give authorisation or the withdrawal of authorisation to participate in research shall not lead to any form of disadvantage, prejudice, liability and/or discrimination against the minor concerned, in particular regarding the right to medical care. 4. The interests of the minor always prevail over those of science and society. **ART.2 Authorisation of legal representative and assent of minor** **1.** No research on a minor may be carried out, subject to the provisions of art.1, without the necessary authorisation given specifically and in writing by legal representatives or an authority, person or body provided for by law, and after having received the information, taking into account the minor's previously expressed wishes or objections. In particular, the opinion of the minor shall be taken into consideration as an increasingly determining factor in proportion to age and degree of maturity; **2.** Such authorisation and assent may be freely withdrawn at any time and for any reason, in the best interest of minor. Refusal to give authorization or assent or withdrawal from the trial shall not lead to any disadvantage, prejudice, liability and/or to any form of discrimination, in particular regarding minor's right to medical care. **3.** The plan for taking care of a statement that the minor's decision not to participate or to withdraw from a trial will be respected, even if authorisation is given by the legal representative, shall be outlined in the protocol.

	ART. 3 – Information prior to authorisation Before being asked to authorise (for legal representative) or to assent (for minors) to participate in a research project, the legal representative and the minor concerned shall be given specific and adequate information in a comprehensible form, according to the nature and purpose of the research: i. on the purpose, the overall plan and the possible risks and benefits of the research project; ii. on the nature, extent and duration of the procedures involved, in particular, details of any burden imposed by the research project; iii. on available preventive, diagnostic and therapeutic procedures; iv. on the arrangements for responding to adverse events or the concerns of research participants; v. on arrangements to ensure respect for private life and ensure the confidentiality of personal data; vi. on arrangements for access to information relevant to the participant arising from the research and to its overall results; vii. on the arrangements for fair compensation in the case of damage; viii. on any foreseen potential further uses, including commercial uses, of the research results, data or biological materials; ix. on the source of funding of the research project; x. on the opinion of the ethics committee; xi. on the rights and safeguards prescribed by law for minors protection, and specifically of their right to freely refuse or to withdraw from the trial at any time, for any reason and without being subject to any disadvantage, prejudice, liability and/or to any form of discrimination, in particular regarding minor's right to medical care. This information shall be given according to the minor's capacity of understanding, from staff with experience with minors, regarding the trial, the risks and benefits. This information shall be documented. The same level of care and information shall be maintained during treatment or investigations.

	ART. 4 – Research with minimal risk and minimal burden 1. Clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored. 2.For the purposes of the minor protection it is deemed that the research bears a minimal risk if, having regard to the nature and scale of the intervention, it is to be expected that it will result, at the most, in a very slight and temporary negative impact on the health of the person concerned. 3. It is deemed that it bears a minimal burden if it is to be expected that the discomfort will be, at the most, temporary and very slight for the minor concerned. In assessing the burden for an individual, a person enjoying the special confidence of the person concerned shall assess the burden where appropriate.
2) Related to **confidentiality issues** and in accordance with Additional Protocol art. 25,26,27; Universal Declaration on Bioethics and Human Rights –Art. 9. The new legal framework shall be as indicated in the suggestions part.	**2) Confidentiality:** Any information of a personal nature collected during biomedical research shall be considered as confidential and treated according to the rules relating to the protection of private life. Such information shall not be used or disclosed for purposes other than those for which it was collected or consented to.
3) Related to the **right to information** and in accordance with Additional Protocol art. 25,26,27; Oviedo Convention art.12, International declaration on Human Genetic data; Charter of Fundamental rights UE art.8; Universal Declaration on Bioethics and Human Rights –Art. 9-, the new legal framework shall be as indicated in the suggestions part.	**7) Right to information** Minor participant in research shall be entitled to know any information collected on his/her health. Other personal information collected for a research project will be accessible to him/her in conformity with the national law on the protection of individuals with regard to processing of personal data.

	If research gives rise to information of relevance to the current or future health or quality of life of research participants, this information must be offered to them. That shall be done within a framework of health care or specific counselling, most of all in the case of predictive genetic tests. In communication of such information, due care must be taken in order to protect confidentiality and to respect any wish of the minor (and/or his/her legal representatives) participant not to receive such information, in accordance with national law.
4) Related to **interdiction of incentives or financial inducements**, according to Convention on Human Rights and Biomedicine (art.21 related to Prohibition of financial gain) and its Additional Protocol on Biomedical research (art.12 related to undue influence), the new legal framework shall be as indicated in the suggestions part.	**1) <u>No indue influence</u>** No undue influence, including that of a financial nature, will be exerted on child or his/her legal representative to participate in research.
5) Related to **new developments**, according with art.24 of Additional protocol for research, the new legal framework shall be as indicated in the suggestions part.	**5) <u>New developments</u>** The research project shall be re-examined if this is justified in the light of scientific developments or events arising in the course of the research. The purpose of the re-examination is to be established whether: vi. the research needs to be discontinued or if changes to the research project are necessary for the research to continue; vii. research participants (minor) and their representatives need to be informed of the developments or events; viii. additional authorisation and assent for participation is required. ix. any new information relevant to their participation shall be conveyed to the research participants (minor) and to their representatives, in a timely manner. x. The competent body and Ethics Committees shall be informed of the reasons for any premature termination of a research project.
6) Related to **compensation for damage**, in accordance with art.31 of the Additional protocol on biomedical research, the new legal framework shall be as indicated in the suggestions part. Furthermore, it seems important to propose an analysis of the differences	**<u>6) Compensation for damage</u>** The minor who has suffered damage as a result of participation in research shall be entitled to fair compensation according to the conditions and

related to insurance conditions and procedures of compensation for damage existing in the European Member States in order **to create a common and specific regime to guarantee safety of minors, in the light of the consideration that minor is a person whose body is in development.**	procedures prescribed by law. In this respect, **specific and more protecting guarantees have to be provided for minors.**
7) Related to **minimisation of risk and burden**, in accordance with art.21 of Additional protocol on biomedical research, the new legal framework shall be as indicated in the suggestions part. Furthermore, it shall be important to create a **European register, regularly updated, of the investigators and team having the necessary qualification and experience in paediatric research in general, and, in particular, in the field of the applied project, as well as of the safe and adequate infrastructures, to be consulted by the ethics committees**. That should be particularly useful in multicentre studies, in order to guarantee the safety and quality of paediatric clinical research.	**7) Minimisation of risk and burden** 1. All reasonable measures shall be taken to ensure and to minimize risk and burden for the minors participant in a clinical trial. 2. Clinical trials may only be carried out under the supervision of a clinical professional who possesses the necessary qualifications and experience in paediatrics.

Spontaneous written submissions

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Please note that the written submissions and the presentation slides from the meeting will be included in appendix to the report of the meeting and be published at the same time as the report.

Name of Organisation	Country
CNCP Conference National of committees of protection of persons (REC)	FRANCE

Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
1)	1)
2)	2)
3)	3)
4)	4)
5)	5)
…	…

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1)ARTICLE 6	1) We propose to delete "a single" request because it creates problems when the sponsor does not answer exactly and completely.
2)ARTICLE 10	2)The definition of "substantial" is not clear and sometimes with differences of interpretations. We propose to delete it.
	3)
	4)
	5)
…	…

SUITE	
Comments	**Suggestions**
3) ARTICLE 17 Notification of serious adverse reactions In France EC receive only SUSAR which happen in France and a semestrial report of other ADR. But it would be better to receive all information in case of change in the benefit -risk evaluation of an ongoing trial	1)
	2)
	3)
	4)
	5)
…	…

What should a new legal framework look like?	
Comments	**Suggestions**
1) It would be necessary to consider other health products clinical trials in a large CTD (like in France)	1)
	2)
2)	3)
4)	4)
5)	5)
…	…

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Please note that the written submissions and the presentation slides from the meeting will be included in appendix to the report of the meeting and be published at the same time as the report.

Name of Organisation	Country
Directive and Research Governance in Europe	

Aspects of the Directive 2001/20/EC that work well Session 2	
Comments	**Suggestions**
1) Scope of legislation	1)
2) Definitions	2)
3) Clinical Trial Authorisation and IMP Dossier • To Ethics committee • To Competent Authority	3)
4) IMP related issues (definitions, labelling, GMP etc)	4)
5) Ethics committee structures and processes	5)
6) Competent authority processes	6)
7) Roles of ECs and NCAs	7)
8) Trials conducted in third countries, including developing countries	8)
9) Other (specify)	9)
10) Other (specify)	10)

Aspect of the Directive 2001/20/EC that do not work well Session 2	
Comments	**Suggestions**
1) Scope of legislation	1) The 2001 CT Directive allows 'specific modalities' for non-commercial clinical trials of investigational medical products within their market authorisation. The 2005 GCP Directive allows specific modalities in CTIMP of medicinal products for new indications or patients with different characteristics outside the market authorisation. I do not think that it is desirable to have two Directives on the same subject-matter dealing exclusively with different forms of CTIMP. The 2001 Directive should be extended to cover non-authorised CTIMP in the interests of uniformity. The 2005 Directive should be amended likewise. This situation may have contributed to delay in the production of UK MRC/DH Joint Project guidance on specific modalities, in that R&D leads may have thought that specific modalities should only be afforded to CTIMP with market authorisation. A UK joint response to the EC draft guidance on specific modalities in 2006 made the point that the EC guidance did not deal with non-authorised CTIMP. What was the justification for excluding non-authorised CTIMP from the special status provisions for non-commercial research in Recital 14 of the 2001 Directive?
2) Definitions	2) There is a discrepancy between the 2001 CT and 2005 GCP Directives as to the status of ICH GCP as an international standard. Article 1 CT Directive states that GCP must be observed in designing, recording, conducting, and reporting clinical trials. It states that the principles of good clinical practice and detailed guidelines in line with those principles shall be adopted and, if necessary, revised to take account of technical and scientific progress in accordance with the procedure referred to in Article 21(2).

	Compare this statement with Recitals 8 and 9 of GCP Directive which state that the ICH 1995 agreement is a consensus paper which needs only 'to be taken into account'. It is described as a set of scientific guidelines only. This discrepancy may already have generated, and will in future generate, confusion among researchers as to whether ICH GCP is a set of standards which are mandatory or merely directive. This confusion may stifle creativity and flexibility in the application of clinical research methods and standards at national level. This is relevant to the application of specific modalities for non-commercial CTIMP. ICH GCP Topic 6 states that on-site data monitoring for pharmacovigilance is the normal standard but can be replaced by centralised monitoring in exceptional cases if the circumstances justify it. MRC/DH Joint Project final guidance on data monitoring is only now being produced and interim guidance acknowledges that centralised monitoring is acceptable subject to a risk assessment in non-commercial CTIMP. To what extent has the discrepancy in the Directives as to the status of ICH GCP contributed to this delay? 3) There is an inconsistency in the 2001 CT Directive as to the core ethical principles to be applied to clinical trials involving incapacitated persons, now referred to in the UK as 'adults lacking capacity'. The CT Directive affirms that the accepted basis for the conduct of clinical trials are the fundamental rights and dignity of the human being as reflected, *for instance*, in the 1996 Helsinki Declaration (my emphasis).The CT Directive Recitals 3 and 4 apply to CTIMP and require a likelihood of direct benefit to the patient under treatment, where that patient is incapacitated by disease, as a requirement for recruitment and for the conduct of the trial. More relaxed criteria apply to the enrolment of a child in view of the importance of developing paediatric medicines for the child population as a whole. The revised Helsinki Declaration contains no such requirement for direct benefit to the patient in a trial, but instead requires a likelihood of direct benefit to the patient population to which the incapacitated person belongs, see Articles 19 and 24 Helsinki Declaration (Edinburgh 2000 revised version). This Declaration does not distinguish in its application between CTIMP and

	non-CTIMP. The Oviedo Declaration on Human Rights and Bio-Medicine seems to adopt a more stringent standard than the Helsinki Declaration in that it does not require a likelihood of direct benefit to the patient under treatment but rather in exceptional cases it may suffice to show a potential for future benefit to the patient or the patient population to which the participant belongs and where there is minimal risk and minimal burden to the participant, see Articles 16 and 17. The Oviedo Declaration applies also to CTIMP and non-CTIMP. The 2001 CT Directive therefore requires clarification as to the core values to which it adheres in respect of incapacitated research participants in CTIMP. 4) The Clinical Trials Directive 2001 and 2005 Directive need to facilitate the strategic plan for the European Research Area as set out in Lisbon 2000 and FP6 and FP7. The Directives cannot be examined in isolation from this. As such, they need to deal with the relationship between researchers and clinicians in EU member states and research participants in EU neighbour states and research participants and patients in Developing World countries. Those tasked with the redrafting of the Directives must have regard to the current debate in the research community between the proponents of the Helsinki Declaration and the proponents of the supposed 'International Consensus'. The latter object to the requirement in Article 29 of the HD for clinical trials to be conducted with a comparison to the best current prophylactic diagnostic and therapeutic methods. They say this requirement in HD compromises effective research amongst Developing World participants because they are thereby denied access to sub-optimal treatments that would otherwise constitute an improvement upon those currently available to the participants in their host countries. There is a real question as to whether it is ethical to deprive such participants of the benefit of trials with sub-optimal treatments but with a proven safety standard or whether it constitutes an abuse of a disadvantaged population that might in turn result in further abuse. I cannot provide an answer to that problem but I want to see it addressed. This problem will require debate and a new consensus on the ethics of research in Developing World states or even within states that are not subject to the Directive for some other reason. The Helsinki Declaration might require revision, but what would be of greater use is a specific statement in a guidance document, and which is expressly referenced within primary legislation as an amendment or supplement to the Directives, dealing with the required standard for comparative treatment in clinical trials run in non-

	member states.
3) Clinical Trial Authorisation and IMP Dossier • To Ethics committee • To Competent Authority	5) See Session 2 Comment 5 below
4) IMP related issues (definitions, labelling, GMP etc)	
5) Ethics committee structures and processes	6) See the terms of reference and provisional recommendations of the UK Medicines and HealthCare Products Regulatory Agency (MHRA) consultation on the amendment of the UK Clinical Trial Regulations 2004, in document MLX 340: the relevant recommendations propose that: • *the definition of expert REC member be widened to include experts with qualifications in wider clinical research* • *new procedures to enable a final decision to be made by a sub-group of members* • *the power to give favourable opinions subject to conditions* • *procedures for co-option and appointment of deputy members* It is significant that the UK guidance in GAFREC 2001 and the MHRA Consultation does not place any emphasis upon the appointment of trained lawyers to deal with the regulatory and legal aspects of ethical approvals. This is a real deficiency. Ethics boards should be able to deal with matters relating to the EU Data Directive, EU Tissue and Cells Directive, insurance and indemnity, and other legal matters such as Intellectual Property Rights in research material and products for donors and sponsors. The 2001 Directive Article 2(k) should be amended to require the appointment of legally qualified members to ethics boards according to arrangements to be determined by member states. Such members might be attached to one ethics board or circulated amongst several ethics boards according to cost and need.

6) Competent authority processes	6)
7) Roles of ECs and NCAs	7) The 2001 Directive Article 6 should be amended to make it clear beyond doubt that data protection issues under the EU Data Directive are matters that the ethics boards are specifically required to consider. There is an unjustifiable debate and confusion amongst certain UK research ethics committees as to whether they should give an opinion on data protection rights of research participants as engaged by the research proposal. The Governance Arrangements for UK Research Ethics Committees (2001) states that ethics committees are not required to give a legal opinion but should take into account applicable laws and regulations. This guidance is logically inconsistent in this respect and an amendment to the 2001 Directive to include an obligation to deal with data protection and/or other legal issues would resolve the problem.
8) Trials conducted in third countries, including developing countries	8) see comment 4 above
9) Other (specify)	9)
10) Other (specify)	10)

What can be remedied within the present legal framework (by modification of guidelines or clarifications)? Session 2	
Comments	**Suggestions**
1) Scope of legislation	1) See comment above on specific modalities for non-commercial CTIMPS. Amend 2001 CT Directive and 2005 GCP Directive to apply to authorised and non-authorised non-commercial CTIMPS.
2) Definitions	2) Clarify the status of ICH GCP as a scientific guideline for all CTIMPS and for all non-commercial CTIMPS in particular. Is it merely directive and not mandatory? Is it a legal requirement or an operational guidance? This will require amendment to Art.1 CT Directive 2001 and restatement in 2005 CGP Directive. Clarify the right of health providers in the national state to adopt their own working within the parameters of an overarching standard made up of core ethical values and core clinical standards. 3) Article 1 CT Directive 2001 must be amended to clarify which core values are to be followed in respect of the rights of incapacitated persons involved in research by CTIMP. There is an inconsistency between HD, OD and the 2001 Directive on the need for direct benefit to the patient as a condition of enrolment. Clinical and legal consensus will be needed before the amendment can take place. Modification to the chief guidelines and to the reference in Recitals 2, 3 and 4 of the 2001 CT Directive would therefore be required. 4) In order to resolve the current debate as to whether research with Developing World participants using less than the best available treatments is ethical, amendment to the Helsinki Declaration might be required. But it would be of greater benefit to have clarification through a legislative amendment or supplement to the 2001 and 2005 Directives as to the required standard for comparative treatment in clinical trials conducted in non-member states.

3) Clinical Trial Authorisation and IMP Dossier • To Ethics committee • To Competent Authority	5) See the terms of reference and provisional recommendations of the UK Medicines and HealthCare Products Regulatory Agency (MHRA) consultation on the amendment of the UK Clinical Trial Regulations 2004, in document MLX 340: Paragraph 39: reduction in the number of documents to be sent to an ethics committee. The MHRA propose to remove from the list of documents to be submitted to an ethics committee, on the grounds that they are unnecessary, the following: • *Details of competent authorities in other member states to which requests for authorisation have been made. It is stated that there is no requirement for this in the 2001 Directive, the Commission Guidance or ICH GCP. It is stated that it is a matter for the licensing authority.* • *Details of any person responsible for the importation or manufacture of the IMP and details of any Art.13 authorisation held by him. It is stated that there is no requirement for this in the 2001 Directive, the Commission Guidance or ICH GCP. It is stated that it is a matter for the licensing authority.* • *The address of the premises on which the IMP has been or is to be checked and the statement of the manufacture method in the case of IMP imported from outside EEA. It is stated that there is no requirement for this in the 2001 Directive, the Commission Guidance or ICH GCP. It is stated that it is a matter for the licensing authority.* • *A description of the proposed clinical trial on the reasoning that the applicant must in any event supply the ethics committee with a summary of the trial and a copy of the protocol.*

	At the present time such documents are not relevant to the deliberation of an ethics committee. However, in a future harmonised European Research Ethics system operating as part of the European Research Area, it might be very necessary to know the details of any other ethics board to which a request for ethical approval had been made in any other member state. This information would be necessary to the implementation of a 'European research passport' allowing ethical approval to be migrated amongst other ethics boards in other member states. If such information were to be deleted from the application requirements now, then researchers would have to be re-educated to include such information at a later time, if such recommendations were carried into operation. Primary legislation would very probably be required to implement a research passport system involving ethical approvals, given the requirement in Article 7 of the 2001 Directive that a single ethical opinion be given in each member state in which a multi-centre clinical trial is to be carried on.
4) IMP related issues (definitions, labelling, GMP etc)	4)
5) Ethics committee structures and processes	6) The 2001 Directive Article 2(k) should be amended to require the appointment of legally qualified members to ethics boards according to arrangements to be determined by member states. Such members might be attached to one ethics board or circulated amongst several ethics boards according to cost and need. See above.
6) Competent authority processes	
7) Roles of ECs and NCAs	7) The 2001 Directive Article 6 should be amended to make it clear beyond doubt that data protection issues under the EU Data Directive are matters that the ethics boards are specifically required to consider. There is an unjustifiable debate and confusion amongst certain UK research ethics committees as to whether they should give an opinion on data protection rights of research

	participants as engaged by the research proposal. As stated above. The Governance Arrangements for UK Research Ethics Committees (2001) states that ethics committees are not required to give a legal opinion but should take into account applicable laws and regulations. This guidance is logically inconsistent in this respect and an amendment to the 2001 Directive to include an obligation to deal with data protection and/or other legal issues would resolve the problem.
8) Trials conducted in third countries, including developing countries	8)
9) Other (specify)	9)
10) Other (specify)	10)

What should a new legal framework look like? Session 2	
Comments	**Suggestions**
1) Scope of legislation	1) The 2001 and 2005 Directives need to be examined anew within the strategic framework of the Lisbon Summit 2000 and FP6 and FP7 as to the implementation of the European Research Area (ERA). The Directives cannot be examined in isolation as legal or ethical statements. Research can be stimulated within ERA by the implementation of a research passport system whereby authorisation and ethical approval could be applied across national boundaries in every member stated in which the research project was to be carried on. This might require the abolition of the requirement for a single ethical opinion in a member state in which multi-national CTIMP is to be carried on, as currently required under Article 7 of the 2001 Directive. A new regulatory system based on harmonised approvals would have to be adopted through amendment to the 2001 Directives or by new Directives. 2) In implementing the ERA strategy there is a difficulty in that the 2001 Directive chiefly applies to CTIMP and does not deal with other forms of research in the Life Sciences and Bio-Technology for Health, and these are Thematic Priorities within FP6 and FP7. New regulation will be needed to facilitate Thematic Priority research in the ERA by means of research passport approvals or specialist ethics boards and competent authorities with special responsibility for Thematic Priority research. The current EMEA consultation does not address these issues and is therefore compromised in its design and scope.
2) Definitions	2)
3) Clinical Trial Authorisation and IMP Dossier • To Ethics committee	3)

• To Competent Authority	
4) IMP related issues (definitions, labelling, GMP etc)	4)
5) Ethics committee structures and processes	5) see comment 7 below
6) Competent authority processes	6)
7) Roles of ECs and NCAs	7) In order to ensure harmonisation and the maintenance of proper standards of research within the European Research Area and beyond it may well be necessary to invest ethics boards with additional powers consistent with a regulatory function and a function of oversight and ongoing scrutiny. Research ethics committees in the UK lose control over a research project after an ethical approval has been given. They are entitled to raw data submissions for SAR and SUSAR in the context of pharmacovigilance/Eudravigilance reporting, but the Directives do not make requirement for any other types of data monitoring or trial monitoring to be supplied to an ethics board in the course of the clinical trial. It may therefore be necessary to invest ethics boards with the power to withdraw an ethical approval in the event of adverse incidents or complaints outside the definition of SAR or SUSAR but which are referent to the welfare and ethical treatment of the participants. It may therefore also be necessary to invest ethics boards with the power to monitor the progress of research with periodic assessment reports dealing with matters referent to the welfare of the research participants and the ethical basis of the research.
8) Trials conducted in third countries, including developing countries	8) It should be noted that the lack of harmonisation between ethics boards in member states and non-member states means that it is difficult for ethics boards in a member state to be assured of ethical practice in that third state. This problem is compounded by UK guidance in Standard Operating Procedures that states that ethics committees should not consider ethical issues that could be left to the ethics board in the host state to resolve. Primary legislation could be enacted to make it a condition of ethical approval in the case of multinational clinical research taking place in third states and non member countries that Service Level Agreements be put in place between the

	sponsors and the participating authorities of the third state which guarantee the protection of the research subject according to core values approved by the Directives. Ethics boards in member states should be permitted to require ongoing monitoring reports concerning compliance with the service level agreement. This might signal the need for ethics boards to have an ongoing supervisory role in research which does not end with the ethical approval. This may require ethics boards to have the right to withdraw an ethical opinion and approval after it has been made and upon receipt of evidence of failings by the sponsor or its agents.
9) Other (specify)	
10) Other (specify)	10)

Aspects of the Directive 2001/20/EC that work well Session 3	
Comments	**Suggestions**
1) Dossier maintenance including substantial amendments	1)
2) Safety information, collection, reporting and review of safety information • Expedited reports • Annual safety reports	2)
3) Databases: • EudraCT • EudraVigilance	3)
4) Inspection (GCP, GMP)	4)
5) Other (specify)	5)
6) Other (specify)	6)

Aspect of the Directive 2001/20/EC that do not work well Session 3	
Comments	**Suggestions**
1) Dossier maintenance including substantial amendments	1)
2) Safety information, collection, reporting and review of safety information • Expedited reports • Annual safety reports	2)
3) Databases: • EudraCT • EudraVigilance	3)
4) Inspection (GCP, GMP)	4)
5) Other (specify)	5)
6) Other (specify)	6)

What can be remedied within the present legal framework (by modification of guidelines or clarifications)? Session 3	
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1) Dossier maintenance including substantial amendments	1)
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4) Inspection (GCP, GMP)	4)
5) Other (specify)	5)
6) Other (specify)	6)

What should a new legal framework look like? Session 3	
Comments	**Suggestions**
1) Dossier maintenance including substantial amendments	1)
2) Safety information, collection, reporting and review of safety information • Expedited reports • Annual safety reports	2)
3) Databases: • EudraCT • EudraVigilance	3)
4) Inspection (GCP, GMP)	4)
5) Other (specify)	5)
6) Other (specify)	6)

Comments on the Clinical Trials Directive 2001/20 EC

European Cancer Patient Coalition (ECPC)

30 September 2007

Clinical trials are helping patients in their fight against cancer and are one of the key steps in the long process of cancer drug development before a medicine receives a marketing authorisation.

Cancer is still all too often a life-threatening disease. Regularly, cancer patients have only very limited treatment options.. Therefore cancer patients often search for the most effective treatment available, or in the absence of such approved treatments, need to consider to use investigational drugs just to stay alive. Participating in clinical trials gives some patients the opportunity to access new, promising therapies before they are commercially available.
Of course, all investigational drugs do have risks, more or less severe, and patients should be able to discuss these with their physicians prior to joining a clinical trial.

ECPC calls for the availability of information, informed consent, and accessibility of clinical trials

ECPC calls for more transparency and improvement of "informed consent"

For safety reasons the Clinical Trials Directive (CTD) requires informed consent documents to be signed by the patient. But daily practice has shown that there are significant differences in all EU Member States concerning the extent and the quality of information. Hence, ECPC Calls for harmonised conditions of "informed consent" in all Member States.

Access to information and transparency about ongoing, completed and published clinical trials is essential for informed decision-making and public trust in clinical research. Researchers, research funders, policy makers, medical professionals, patients and the general public need such information, to help guide research or to make treatment decisions.

ECPC therefore suggests that a revision of the CTD should include the transparency policy developed by the World Health Organisation (WHO) and the International Committee of Medical Journal Editors (ICMJE). Hence, ECPC suggests the directive should require that

- all clinical trials be *publicly* registered with all of WHO's 20 data sets at inception of the clinical trial, and
- all results must be made *publicly* available within a year of completion of the clinical trial.

Following the example of the Paediatrics Regulation which requires clinical trial information to be made publicly available on the EMEA database, ECPC urges that EudraCT is opened for public access.

In future we would urge that the EMEA website also includes the notice of up-coming clinical trials. The trial can be formulated to include the type of cancer addressed but company proprietary information can be omitted. The website should include a feature that enables cancer patients to register for a clinical trial.

ECPC requests that patient groups have a seat in Ethics Committes

ECPC is not convinced that patients' rights protection in non-commercial clinical trials or clinical trials sponsored by pharmaceutical companies have improved significantly. Patient groups were not sufficiently consulted and involved when the CTD was drawn up and adopted.Even now patients are rarely consulted when new cancer trials are being set up.

In ECPC's view participation of patient groups in the design process of clinical trials can improve consent, recruitment and outcome of clinical trials. Involvmentent of patient groups at the beginning of the Trial design would allow patients to contribute their ideas and requirements, and would avoid unnecessary or misleading research work.

Therefore, ECPC proposes that a revised CTD requires to give patient representatives the right for a seat in Ethic Committees in all Member States.

Cancer research needs to be facilitated, not hindered

Driven by the ambition to increase patient safety, the CTD has significantly increased the work load, bureaucracy and legal risk of investigator driven trials. Hence, setting up new cancer trials have become more complicated, require more documentation and require more expensive insurance.

There are clear signs that the last revision of the CTD has severely hindered cancer research in Europe, and has already reduced the number of newly established cancer clinical trials significantly. As a result, it seems that leading research has started to move out of the European Union. In addition, academic research which represented around a quater of all clinical trials before implementation of the CTD now represents less than one fifth of newly started trials (FECS Press Release 28 Sept 07)

IAs a consequence, we fear that this will not only have impact on Europe's research and jobs for highly qualified researchers sts , but will also cost lives, as cancer patients will not any longer have the possibility to participate in investigative clinical trials which are potentially life-saving.

Hence, ECPC calls for a revision of the CTD to reduce the unnecessary administrative burden and risk of litigation for investigators.

ECPC calls for continuation of beneficial treatments on conclusion of clinical trials

Article 30 of the Declaration of Helsinki requires that "at the conclusion of a clinical trial, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study".

However, the declaration left open issues on continuation of beneficial experimental drugs where despite positive results for some patients, investigators were not willing to continue their efforts for approval. In this case, cancer patients had to stop beneficial therapies.

ECPC is convinced that those patients that have had a clinical benefit from the investigative drugs within a clinical trial should be able to continue with the experimental treatment as long as they need it, independent of whether the investigator or company decides to continue towards the approval of the drug for this indication.

ECPC suggests an agreement should be included in study protocols that in case of a measurable benefit, cancer patients should have the right to continue to receive the investigative treatment after the conclusion of the clinical trial.

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cc: Mr. Thomas Lönngren, EMEA

Date: 26 September 2007

Dear Mr. Santos Ivo,

The GCP-RMA* notes with interest the forthcoming meeting entitled "European Commission-EMEA Conference on the Operation of the Clinical Trials Directive and Perspectives for the Future" to be held in London on 3 October 2007 at which you are participating.

In the program announcement, the Commission indicates its concern specifically with obstacles related to "administrative burden and differences in implementation".

In respect to these obstacles, and as professionals entrusted with managing active and archived clinical trial records, we would like to call your attention to inconsistencies in the current definition in Directive 2003/63/EC of retention periods for these essential records.

The GCP-RMA has welcomed the changes introduced by the relevant Directives over the last few years particularly as they pertain to the controlled management of trial records in order to demonstrate investigator and sponsor compliance with GCP and other applicable regulatory requirements.

However, Clinical Trial Directive 2003/63/EC (unlike Directive 2005/28/EC on Good Clinical Practice) is ambiguous with respect to document retention, thereby contributing to the administrative burden on investigators, ethics committees, sponsors, CROs and other key stakeholders in clinical trials.

Article 17 of Directive 2005/28/EC states the minimum retention requirement as five years following completion of a clinical trial ("the sponsor and the investigator shall retain the essential documents relating to a clinical trial for at least five years after its completion"). This five-year retention period is unambiguous (and is consistent with comparable U.S. legislation).

In contrast, the detailed guidance given in Directive 2003/63/EC, Annex 1, 5.2 (c) to which 2005/28/EC refers is resulting in inconsistent interpretation and application across industry and across member states. (Please see attached table that highlights current inconsistencies between both Directives as well as a variety of retention periods assigned in a number of member states).

Whereas the first part of section (c) stipulates specific retention periods depending on whether the trial is discontinued, progresses to marketing authorisation or clinical development of the NCE is discontinued, the subsequent paragraph states that "all other documentation pertaining to the trial" shall be retained "as long as the product is authorised".

If indeed *all* documentation is to be retained *for as long as the product is authorised*, it cannot therefore be clear *to which documents the initial five-year retention requirements* apply. It could easily be understood to mean that *only "all other" documents are retained*, while the first group of documents – which are by definition *key, essential documents* - do *not* require retention for the longer period.

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It is also unclear whether the requirements stated in each paragraph apply only to the investigator essential records, or to the sponsor essential records - or to both.

We therefore feel that a *single defined minimum retention period*, assigned pragmatically, would be consistent with the goals of the Commission and the EMEA "to reduce administrative burden", as well as being consistent with protecting patient safety as judged by clinical investigators.

Specifically, we ask the Commission to consider implementing a formal minimum retention period of five years following trial completion/discontinuation. Again we call the Commission's attention to the fact that this five-year retention (after trial completion) is already enshrined in Directive 2005/28/EC, relating to essential trial documents. We are simply suggesting that the five-year minimum extend to all trial documents held by the sponsor and the investigator.

Should it be the Commission's intention to require a longer period of retention of trial documentation, we nevertheless urge the Commission to set an *unambiguous minimum* time period for all documentation.

In conclusion, we believe that a single, unambiguous and consistent minimum period (such as "five years post trial completion") for retention of trial records will greatly reduce both the administrative burden and differences in implementation which this Conference seeks to address. We welcome the Commission's call for suggestions for improvements and hope the Commission will consider implementing our proposal in a formal, binding document.

Yours sincerely,

on behalf of the GCP-RMA
Susan Vaillant, President
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Annex. Health care related records retention times (as specified in National Legislation of EU Member States, EEA countries and other European countries.)

***About the GCP Records Managers Association**
The GCP-RMA was formed in 2001 by members of the former Records Management & Archiving Working Party of the European Forum for Good Clinical Practice (EFGCP). The GCP-RMA currently represents over 15 companies and organisations including pharmaceutical companies, contract research organisations, clinical trial units and independent consultants. The member companies have records management responsibilities across the whole European region. The Association has published articles in professional journals such as Clinical Researcher, Applied Clinical Trials and the GCP Journal and has contributed to the development of European Directives and Guidelines.

GCP - Records Managers Association

GCP-RMA

Health care related records retention times

(as specified in the EU Directives and national legislation of a representative sample of EU Member states, EEA countries and other European Countries)

DEFAULT GUIDANCE

Unless an exception is specified in the country-specific guidance below then the default guidance would be the International Conference on Harmonisation (ICH) E6 Good Clinical Practice: Consolidated Guidance (April 1996). For those Member States of the EU which have not specified anything different then the EU Directives (as transposed into National Legislation) and Regulatory Guidance should be followed.

The obligation for retention of trial-related records is divided between the sponsor, investigator and/or hospital or institution, and ethics committee, depending on the nature of the records. The sponsor **must not**, however, under any circumstances retain patient records.

ICH

The Sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required, by the applicable regulatory requirement(s) or if needed by the Sponsor (CPMP/ICH/135/95 E6 Good Clinical Practice: Consolidated Guidance (April 1996) : Sections 4.9.4, 4.9.5, 5.5.7, 5.5.8, 5.5.11). NB Chapter 8 of CPMP/ICH/135/95 E6 identifies records considered to be “essential trial records”.

European Union

European Union		
Record Type	**Retention Time**	**Source (i.e. Law)**
TMF (Sponsor)	"All other documentation" (excl. Investigator files like patient identification codes, patient files and other source data) as long as the product is authorized Final report five years after the medicinal product is no longer authorized MA Holders must arrange for essential clinical trial documents (including CRF's), other than subjects' medical files, to be kept by the owners of the data: - for at least 15 years after completion or discontinuation of the trial, - or at least 2 years after granting the last MA in EC with no pending or contemplated MA's in EC, - or at least two years after formal discontinuation of clinical development of the investigational product For trials conducted within EC, the MA holder shall make any additional arrangements for archiving of documentation in accordance with the provisions of Directive 2001/20/EC and implementing detailed guidelines {see Rules Governing Clinical Trials Vol 10] The final report shall be retained by the sponsor or subsequent owner for 5 years after the medicinal product is no longer authorised. continued…	DIR_2001_83_EN - Part 4 B 2. (c) DIR_2001_83_EN - Part 4 B 2. (d) 2003/63/EC Annex 1: Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use [5.2c]

Record Type	Retention Time	Source (i.e. Law)
	…from previous page The sponsor or other owner of the data shall retain all other documentation pertaining to the trial as long as the product is authorised. This documentation shall include: the protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product, the reference medicinal product and/or the placebo used; standard operating procedures, all written opinions on the protocol and procedures, the investigator's brochure, case report forms on each trial subject, final report, audit certificate(s) (if available). The sponsor and investigator shall in every case retain the essential documents relating to a clinical trial for at least 5 years after its completion. They shall retain the documents for a longer period, where required by other applicable regulatory requirements or by an agreement between the sponsor and the investigator.	2005/28/EC: Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products: Article 17
Investigator Site File (ISF) (Investigator)	Patient identification codes for at least 15 years after the completion or discontinuation. The sponsor and investigator shall in every case retain the essential documents relating to a clinical trial for at least 5 years after its completion. They shall retain the documents for a longer period, where required by other applicable regulatory requirements or by an agreement between the sponsor and the investigator.	DIR_2001_83_EN - Part 4 B 2. (a) 2005/28/EC: Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products: Article 17

Record Type	Retention Time	Source (i.e. Law)
Patient records at Government (state) hospitals	Patient records should be retained for the maximum period of time permitted by the hospital, institution or private practice. Subjects' medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The documents can be retained for a longer period of time, however, if required by the applicable regulatory requirements or by agreement with the sponsor. The trial subjects' medical files should be retained in accordance with the maximum period of time permitted by the hospital, institution or private practice	DIR_2001_83_EN - Part 4 B 2. (b) 2003/63/EC Annex 1: Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use [5.2c] 2005/28/EC: Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products: Article 17

Country-Specific Exceptions to Retention of Record Types

Belgium		
Record Type	**Retention Time**	**Source (i.e. Law)**
TMF (Sponsor)	The sponsor and investigator should retain the essential documents relating to the clinical trial for at least 20 years after its completion. These documents should be retained for a longer period if required by other applicable regulations.	Belgish Staatsblad, #169, 26-May-06: !8-May-06: Amendments to the Royal Order of 30-Jun-04 on Implementing Measures of the Law of 07-May-04 on Experiments on Human Beings regarding clinical trials with medicinal products for human use: Article 24.
Investigator Site File (ISF)	As above	As above
Patient records at Government (state) hospitals	As above	As above

Czech Republic		
Record Type	**Retention Time**	**Source (i.e. Law)**
TMF (Sponsor)	The sponsor is obliged to ensure that the documents on the clinical trial laid down by the decree are kept for a period of 15 years	Act # 472/2000, amended 301/2003: Good Clinical Practice and Conditions for Clinical Evaluation of Medicinal Products: Part 2, Section 3.
Investigator Site File (ISF)	As above	As above
Patient records at Government (state) hospitals	As above	As above

France		
Record Type	**Retention Time**	**Source (i.e. Law)**
Clinical Trials: Documents and data relative to a biomedical research project on a drug intended for human use, archived by the sponsor and the investigator. The dossier includes as a minimum document and data listed by AFSSAPS [French medicines safety agency] for good clinical practice in biomedical research using drugs intended for human use.	**Summary:** - 15 years minimum; - longer if agreed. Sponsor and Investigator will retain their documents and data relative to the research project for at least fifteen years after study termination or study interruption, without prejudice to applicable laws and regulations. These documents may be retained for longer if agreed to between sponsor and investigator.	http://www.admi.net/jo/20061122/SANP0624618A.html *Arrêté du 8 novembre 2006 fixant la durée de conservation par le promoteur et l'investigateur des documents et données relatifs à une recherche biomédicale portant sur un médicament à usage humain* *Public health code article R 1123-61*
Marketing dossier: Marketing authorization requestors or holders will take measures necessary to retaining documents from all trials on the drug. The data owners will retain essential clinical trial documents (notably the CRFs) other than the subjects' medical dossiers	**Summary:** - Either 15 years or relative to marketing authorization (cf Directive) - Longer if sponsor agrees - All other documents relative to trial as long as drug is authorized - Five years post-marketing authorization termination for Final Report - And in accordance with 2001/20/CE - Sponsor/Investigator/Third Parties must make data available at any time to authorities For at least 15 years after the termination of a trial; For at least two years after the most recent EU marketing authorization delivered, where no further authorization requests are envisaged.	http://www.admi.net/jo/20040520/SANP0421445A.html http://www.legifrance.gouv.fr/WAspad/UnTexteDeJorf?numjo=SANP0421445A

Germany		
Record Type	**Retention Time**	**Source (i.e. Law)**
Essential documents (includes CRFs)	Retained by the Sponsor for 10 years after completion or discontinuation of the trial.	GCP decree (Verordnung) - § 13 (10)
Patient files	Retained by investigator, depending on Federal States law, in general 10 years after treatment	Professional code of conduct (Berufsordnung)

Latvia		
Record Type	**Retention Time**	**Source (i.e. Law)**
TMF (Sponsor)	The sponsor and the investigator shall retain the essential documents relating to a clinical trial for at least 5 years after its completion. The sponsor shall retain the protocol, SOPs, IB, CRFs of each subject, clinical trial report, written opinions on the protocol and the procedures of the clinical trial for at least 5 years after authorisation of the test product.	Cabinet Regulation # 172 – 2006: Regulations on conducting clinical trials and non-interventional studies (abbreviated): Chapter XII: paragraphs 90,91 and 92.
Investigator Site File (ISF)	As paragraph 1 above. The investigator shall retain the list of subject identification codes for at least 15 years, (and other source data for at least 10 years after the completion of the clinical trial[1]).	Cabinet Regulation # 172 – 2006: Regulations on conducting clinical trials and non-interventional studies (abbreviated): Chapter XII: paragraphs 90,91 and 92. [1] Cabinet regulation #312 – 2000 (replaced with regulation # 172)
Patient records at Government (state) hospitals		

Portugal		
Record Type	**Retention Time**	**Source (i.e. Law)**
TMF (Sponsor)	The Trial Master File and Essential Documents must be retained at the disposal of the competent authority for a period of 10 years.	Law 46/2004: Approval of the regulation applicable to Clinical Trials with medicinal products for human use: Art. 31.2
Investigator Site File (ISF)	As above	As above
Patient records at Government (state) hospitals		

Sweden		
Record Type	**Retention Time**	**Source (i.e. Law)**
TMF (Sponsor)	Comprehensive guidelines on archiving can be found in the Archives Act (Arkivlagen 1990:782) and the Archives Ordnance (Arkivforordningen 1991:446). The Swedish National Archive has issued provisions in conjunction with this legislation. The archiving period must be adapted to regulations in force and should not be shorter than ten years after the termination of the trial and the presentation of the final report.	LVFS 2003:6 MPA Provisions and Guidelines: Clinical Trial of Medicinal Products for Human Use, 26-Jun-2003: Ch. 8; Section 3.
Investigator Site File (ISF)	As above	As above
Patient records at Government (state) hospitals		

Switzerland		
Record Type	**Retention Time**	**Source (i.e. Law)**
TMF (Sponsor)	The sponsor is required to retain all information relating to the clinical trial until the expiry date of the last delivered batch of the products tested or the last manufactured medical device, but at least 10 years starting from the completion or termination of the clinical trial.	Ordinance of 17-Oct-2001: Clinical Trials with Therapeutic Products: Article 25
Investigator Site File (ISF)	As above	As above
Patient records at Government (state) hospitals		

The Netherlands		
Record Type	**Retention Time**	**Source (i.e. Law)**
TMF (Sponsor)	ICH E6 4.9.5***	CPMP/ICH/135/95 (Clinical Directive 2001/20/EC)
Investigator Site File (ISF)	15 years after completion of the study	Artikel 55 van het Besluit Bereiding en Aflevering van farmaceutische producten (BBA) bij de wet op de Geneesmiddelenvoorziening (WOG).
Patient records at Government (state) hospitals	Reduce after 10 years to basic data. Destruction of the records after 115 years	Dutch Archive law (1995)

The United Kingdom		
Record Type	**Retention Time**	**Source (i.e. Law)**
Health records of participants that are the source data for the trial	For the UK, the records management requirements are stipulated in the NHS Code of Practice, 2006 which is based on current UK legal requirements. The Code of Practice includes a detailed retention schedule for all record types generated within an NHS environment. However, it also includes a specific retention requirement for source data from clinical trial patients: **For trials to be included in regulatory submissions:** At least 2 years after the last approval of a marketing application in the EU. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by agreement with the Sponsor. It is the responsibility of the Sponsor/someone on behalf of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained **For trials which are not to be to be used in regulatory submissions:** At least 5 years after completion of the trial. These documents should be retained for a longer period if required by the applicable regulatory requirement(s), the Sponsor or the funder of the trial. In either case, if the period appropriate to the specialty is greater, this is the minimum retention period. NB The Master File shall at all times contain the essential documents relating to that clinical trial. The essential documents relating to a clinical trial are those which: (a) enable both the conduct of the clinical trial and the quality of the data produced to be evaluated; and (b) show whether the trial is, or has been, conducted in accordance with the applicable requirements of Directive 2001/83/EC, the Directive, the GCP Directive and Commission Directive 2003/94/EC.	European Directive 2005/28/EC of 8-Apr-2005 Statutory Instrument 2006 #1928: The Medicines for Human Use (clinical Trials) Amendment Regulations 2006: 31A 2-4.

Notes:
Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and United Kingdom are Members of the European Union (EU).

Iceland, Liechtenstein and Norway are Members of the European Economic Area (EEA), but are not members of the European Union (EU).
Switzerland is not a Member of the EEA or EU, but has Treaty Agreements with both.

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Name of contributor
EMEA/CHMP Working Group with Healthcare Professionals' Organisations (HCP WG)

Aspects of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
1) The necessity for denoting as "study drug" those medicines which are being used within a study in accordance to their licensed indication is onerous and increases pharmacy, monitoring, pharmacovigilance and data process related costs. An example would be a pharmacokinetic study where the patient is not given an unlicensed agent.	1) An approach could be to discriminate among types of trials depending on the level of risk of the intervention being tested. If it is an already authorised medicine used within its authorised conditions of use, the requirements could be reduced while for a new, biotech product they should be tighter.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
1) There is a need to invest in European infrastructures to conduct Directive compliant trials. The European Commission has initiated programmes such as ECRIN but further initiatives are necessary.	1) The EU should consider funding large management focused trials. This would create opportunities to further improve implementation of the CT Directive.
2) A specialised office could help potential investigators streamline their trials. This would be of benefit to both academia and SMEs.	2) Establish a CT office in relation to a European agency/body (the EMEA's establishment of an SME office could be used as a model).
3) There is a need to find resources to continuously fund training at different levels.	…

What should a new legal framework look like?	
Comments	**Suggestions**
1) The decentralisation of the process of authorisation of clinical trials makes the process redundant and slow.	1) A kind of mutual recognition procedure could be considered at least for the regulatory approval. The ethical approval could still be done at national level but there is a need for substantial training of members of ethical committees.

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Please note that the written submissions and the presentation slides from the meeting will be included in appendix to the report of the meeting will be published at the same time as the report.

Name of Organisation	Country
Novartis Pharma AG (sponsor) Novartis Pharma Services AG (legal representative)	Switzerland Germany

Summary

The ***text*** of the directive and accompanying guidance provides for a quite clear and consistent regulatory framework and led to a number of improvements in the clinical trial process in Europe.
However, unfortunately, although the directive aims for harmonisation of the requirements and processes concerning clinical research, the ***implementation*** of that framework led to even greater disharmony across the EU. This has very negative impact on the overall value of the directive.

In particular, there are different national interpretations of the legal framework with the following aspects:

- Requirements for applications for clinical trial authorisations and amendments of approved clinical trials
- Ethical review
- GMP and quality related issues
- Safety reporting

In order to improve the disharmonised situation quickly, we propose as **short-term measure**:
The Commission, Heads of Medicinal Agencies and all other relevant authorities in Europe shall strongly endorse and support the objective of directive 2001/20/EC for harmonisation of requirements for clinical trial applications and their assessment. All available legal tools to strengthen the harmonised implementation of the Clinical Trials Directive and associated framework should be exhausted.

As **long-term measures** we propose to:
Have a ***regulation***, which establishes a new parallel approach for a centralised and a decentralised system for the application and assessment of clinical trials in Europe. Reasons for selecting one or the other pathway may be the conduct of single centre or multi-national trials or the nature of the product in investigation (such as orphan designated products or biotech products). Consequently, we would have a centralised and decentralised system with a European body in charge, similar to the system for Marketing Authorisation Applications.

List of acronyms

ASR	Annual Safety Report
CA	Competent Authority
CoA	Certificate of Analysis
CoC	Certificate of Compliance
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Application
CTD	Common Technical Document
EC	Ethics Committee
GMP	Good Manufacturing Practice
HA	Health Authority
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug (Application)
MS	Member State
NHS	National Health Service
NIMP	Non Investigational Medicinal Product
QP	Qualified Person
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction

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Aspects of the Directive 2001/20/EC that work well	
Comments	**Suggestions**
The **text** of the directive and accompanying guidance provides for a quite clear and consistent regulatory framework and led to a number of improvements in the clinical trial process in Europe. However, unfortunately, although the directive aims for harmonisation of the requirements and processes concerning clinical research, the **implementation** of that framework led to even greater disharmony across the EU. This has very negative impact on the overall value of the directive.	
• The Clinical Trials Directive provides for a consistent regulatory framework for all those who conduct clinical research in Europe with standardized processes, timelines, roles and responsibilities of Ethics Committees (ECs), Competent Authorities (CAs) as well as sponsors for the compilation, submission and assessment of clinical trials applications (CTA)	Please refer to "Aspect of the Directive 2001/20/EC that do not work well" and "What can be remedied within the present legal framework (by modification of guidelines or clarifications)?
• Harmonised application form for clinical trial applications to Competent Authorities and Ethics Committees is helpful	
• Implementation of EudraCT increases transparency	
IMPD • Acceptance of simplified IMPD for IMPs known to the concerned CAs due to previous applications is beneficial. • IMPD is structured according to CTD (Common Technical Document) and summary information to be provided is considered positive.	Simplified IMPD should as well be accepted in Poland.
Ethical Review • ECs have a statuary role now, which should make them independent form the institutions • Review by ECs has been improved; in principle ECs provide a single opinion per MS now	• A more consistent implementation should be achieved now in terms of a single opinion per country.

• Generally the 60 day time line and the process of the ethics review works well and is adhered to. The 60 day clock is suspended when the responses come back to the applicant requesting further information. Certain ECs have made more than 1 request for information or clarification on the response given but this is rare and does not delay the study by too much	Please refer to "Aspect of the Directive 2001/20/EC that do not work well" and "What can be remedied within the present legal framework (by modification of guidelines or clarifications)?
• Majority of MS allow for parallel review of application by EC and CA in line with the directive	Please refer to "Aspect of the Directive 2001/20/EC that do not work well" and "What can be remedied within the present legal framework (by modification of guidelines or clarifications)?
• ASRs and acceptance of compound specific approach (rather than trial specific) is appreciated.	A harmonisation of safety reporting between EU and US could be considered.

Aspect of the Directive 2001/20/EC that do not work well	
Comments	**Suggestions**
Aspects that do not work well are results of the text of the Directive and associated Guidelines or (in most cases) a result of the different implementation of them into national legislation of the MSs **For more detailed suggestions please refer to the proposals under "What can be remedied within the present legal framework (by modification of guidelines or clarifications)?"**	
Definitions • Definition of 'Sponsor' does not consider all organisational scenarios within clinical research, e.g. in case of co-development ***(text issue)*** • EU guidance allows too much flexibility for MSs' interpretation of certain definitions, such as IMP, NIMP, amendment etc. This has consequences for the release of the study medication by the Qualified Person (QP) and SUSAR reporting. ***(implementation issue)***	• Introduce concept of co-sponsorship and its definition, which may resolve as well issues linked to investigator initiated trials • Strengthen definitions for IMP, NIMP and endorse uniform implementation of IMP definition across Europe (consequently, national legislation to be adjusted and changed); e.g standard of care or challenge agents should not be an IMP.
Biologic IMP • Handling of studies with biologics differs between MSs, e.g. Finland does not accept any extrapolation of stability data for allocation of shelf life, i.e. a clinical trial can only be placed in these countries if there are stability studies running on batch(es) sufficiently older than the clinical batch(es) ***(text and implementation issue)***	• Available legislation and guidelines (CPMP?QWP/2934/99, CPMP/BWP/328/99 incl Annex, etc) should be updated and consolidated to reflect current clinical research practice and to be in line with Directive 2001/20/EC.
Amendments/updates of Clinical Trial Applications • Risk of over-notification of minor changes as CA and EC feel uncomfortable with non-reporting or yearly update reporting of minor changes only. Later sponsor decisions/classifications of minor non-substantial amendments are challenged during inspections for instance. This leads in particular with multinational trials to divergent information provided to the CAs and ECs within one MS and/or across MSs.	• An Annex to the Directive could provide information to distinguish between different classifications of amendments or provide a definition of non-substantial amendments in order to achieve simplification and less workload for ECs, CAs and sponsors.

(text issue) • Amendments to the Clinical Trial Application are differently interpreted between the MSs, e.g. Slovakia does not accept a shelf-life extension on the basis of an approved protocol/scheme without a substantial amendment ***(implementation issue)*** • 35 day timeline is generally adhered to for amendments and the directive states that we may proceed with the amendment once EC is favourable and the CA of the MSs have raised no grounds for non-acceptance. However, in the UK the NHS Care organization still needs to be notified of the changes and checked as to whether it affects their approval – another step which delays studies. ***(implementation issue)***	• MSs should implement the principle of one single EC opinion per country (Art 7 of Directive 2001/20/EC).
Requirements for clinical trial applications • At the moment each MS is diverging further apart in terms of requirements and process based on their local interpretation and legal requirements for the contents and format of a Clinical Trial Application as specified in attachment 1 of guidance ENTR/F2/BLD CT1; rev. Oct 2005. Some MSs, however, have even additional requirements which are not mentioned in that guideline. ***(implementation issue)*** • E.g. some MS require case report forms (CRFs) or draft CRFs, summaries in national languages, labels in national languages, import license in addition to import authorisation, legalisation of documents, fill-in of application form in national language, contracts with investigators, etc. ***(implementation issue)***	• There should be agreement on ***<u>one set of requirements</u>*** in the EU (delete attachment 1 of guidance ENTR/F2/BLD CT1, rev Oct 2005)
Timelines • A few MSs do not follow the maximum assessment time of 60 days (e.g. Poland). • Some MSs assess and approve healthy volunteer (HV) studies and single centre studies in very short time, e.g. 14 days, others need longer. • Handling of clinical trials with biologics differs between MSs. ***(All: implementation issues)***	• Maximum assessment time of 60 days for CTA should be followed by all MSs (CA and ECs). • Reconsideration of timelines for review and approval in MSs with maximum approval timelines applying as the rule for studies where no concern was identified.
Ethical Review	

• Inconsistent implementation of ECs responsibilities according to article 6.3 /6.4 (patient's insurance) and 7 (timelines for assessment, single opinion) • High level of diversity regarding implementation of article 7: In some MSs (e.g. Germany) Site Specific Assessment is requested, i.e. local/regional (hospital) ECs insist on reviewing the clinical trial application, although an approval by the national EC is already granted, this leads to delays • Some MS do not have dual review of applications by EC plus CA, some MS do not allow parallel review by EC and CA. ***(All: implementation issues)***	• Harmonize process across the community through guideline • In contrast to provisions of Art 6.4, opinion on 6.3 (h, i, j) (insurance for trial subjects) should always be given by the EC. • Ensure that ***<u>one EC approval</u>*** per country is sufficient for the start of all involved clinical trial centres of that country. • A dual review shall be obligatory and parallel review of CA and EC shall be accepted in all MS.
Pharmacovigilance/safety reporting • The Directive clearly specifies the time frame for reporting of SUSARs to ECs and CAs, but is less clear about Investigator Notifications: The ENTR/3 Guidance states that the sponsor shall inform all investigators as soon as possible of relevant information about SUSARs that could adversely affect the safety of subjects which is not clarified by the Directive provision ***(text and implementation issue)*** • Complex expedited SUSAR reporting requirements to CAs and ECs due to inconsistent implementation in each MS (e.g. reporting of all SUSARs of the clinical trial or reporting of local SUSARs or unblinded SUSARs only, reporting on paper or in electronic format) leading to resources being used to satisfy a variety of burdensome administrative variations at a country level which is not in the spirit of the Directive ***(text and implementation issue)*** • Potential for double reporting of SUSARs in case a CA reports SUSARs directly into the EudraVigilance database by electronic transmission without informing the sponsor; and the sponsor reports the same cases; as well as potential underreporting as some MSs do almost no reporting into EudraVigilance database ***(implementation issue)*** • Some ECs request fees to cover the cost of managing the SUSAR reports ***(implementation issue)*** • Inconsistent application of ASR requirements across MSs with lack of clarity of the requirements of line listings and summary tabulations. ***(text and implementation issue)***	• Provision in Directive of what safety information should be provided to investigators and when information should be reported; this provision should be in line with the ENTR/CT3 guidance. • Clear definition of the time frame for reporting Investigators Notifications (it could be the same as the one for SUSARs). • Stronger provisions in Directive (or have a Regulation requirement ?) and Guidance (cited opposite) of requirements for single case reporting and periodic line listing reporting to EC and CAs which should be acceptable in all MSs and harmonised accordingly but do not create unnecessary burdensome administration • Elaborate an SOP for MSs on how, what and when to report into the Clinical Trial module of the Eudravigilance database. • No fees should be charged to sponsors for the administration of SUSAR reports to ECs • Clearer provision in Guidance required to clarify listing requirements for ASRs • Guidance on how sponsors should create/merge/produce ASRs on a

• The number of combination compounds grows, it is going to become more and more complex to compile ASRs for these types of products. ***(implementation issue)***	compound basis if there are combination products
Good manufacturing practice/quality issues • Significant differences exist amongst member states regarding the requirements for IMP release by the QP, acceptance of extrapolation of stability data for re-test dates, for retention of clinical samples in the country, and for import licenses in addition to import authorisation ***(implementation issue)***	• Member states should accept general requirements listed in the directive and respective guidelines whilst not insisting on national specific additional requirements as identified in attachment 1.
• Some countries require the provision of supporting GMP documentation for 3rd country manufacturers, such as a GMP certificate, and authority inspection reports if available (either from 3rd country or EU) at the time of CTA submission. ***(implementation issue)***	• The responsibility of the QP to confirm that the manufacturing is performed to a standard equivalent to EU GMPs should also be accepted.
• Reanalysis for medication used in the clinical trial as comparator is needed in some country, if the product is imported from countries outside the EU without mutual recognition agreement (MRA) ***(implementation issue)***	
• The text of the directive enables to avoid expiration date labelling if there are suitable controls in place such as interactive voice recognition system (IVRS, electronic phone system for patient randomisation), in practice the MSs do not accept this in many cases. ***(implementation issue)***	• Some clearer guidance is needed for labelling issues of study medication.
• In order to minimise waste and contain costs, it would be desirable to prepare and hold supplies of study medication within a central warehouse/depot at the study programme level and not at the study/protocol level, this requires being able to label at the programme level and being able to ship directly to study centres, however, this is not allowed by some MSs ***(implementation issue)***	
• Some MSs (such as France) interpret that commercial products (such as a pack of blisters) used in a clinical study must have an auxiliary label with the sponsors name on the immediate packaging (blister card/strip) and on the outer packaging (the carton itself). ***(interpretation issue)***	• Clarification and consistency on labelling of immediate as wells as outer packaging for clinical supplies – also in connection with the definition and interpretation of IMP (see above) - is needed.
• The GMP framework of the Directive 2001/20 and Annex 13 does only	• Adaptation of the legal framework needed, e.g. Advanced Therapy Regulation (…) and Cell and Tissue Directive need to reference to

apply to pharmaceutical products but is not compatible with cell, gene or tissue based products or products obtained from genetically modified animals. ***(text issue)***	each other and should be in line with Directive 2001/20/EC.

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?	
Comments	**Suggestions**
In order to improve the disharmonised situation quickly, we propose as **short-term measure**: **<u>Commission, Heads of Medicinal Agencies and all other relevant authorities in Europe shall strongly endorse and support the objective of directive 2001/20/EC for harmonisation of requirements for clinical trial applications and their assessment.</u>** Exhaust all available legal tools to strengthen the harmonised implementation of the Clinical Trials Directive and associated framework.	
Requirements for the application of clinical trials	Consensus building between the Clinical Trial Facilitation Group, the Commission ad hoc group and the Heads of Medicinal Agencies and their strong endorsement of the harmonisation of the before mentioned requirements and processes by the MSs. MS should accept requirements for IMPDs and amendments, GMP, review by ECs, which are listed in the Directive 2001/20/EC and respective guidelines. Agee on **<u>one set of clear and complete requirements</u>** for the application and assessment of clinical trials which - should be followed by all EU/EEA Competent Authorities - Contain clear and complete provisions for safety reporting requirements, - Have clear and complete provisions for GMP/quality requirements There should be no need for any additional national and/or local requirements. Therefore, we propose to delete attachment 1 of guideline ENTR/F2/BLD CT1; rev. Oct 2005.
Biological IMPs • Handling of clinical trials with biologics differs between MSs.	Update available framework and bring it in line with the Directive 2001/20/EC.
Definitions needed, e.g. for - IMP, NIMP - Amendments	Provide clearer definitions, such as: - The existing definitions of **IMP** and **NIMP**s need additional clarifications, e.g. comparators used under the terms of its licence and without any modification or repackaging are no IMPs,

- Sponsor	the same is valid for standard of care medication or any challenge agents. - An Annex to the Directive could provide information to distinguish between different classifications of amendments or provide a definition of non-substantial amendments in order to achieve simplification and less workload for ECs, CAs and sponsors. - Add to the existing definition for **'Sponsor'** the following**:** co-sponsorship is possible and must be covered by a contractual agreement which specifies the roles and responsibilities of each co-sponsor.
Pharmacovigilance, safety reporting, ASR	• Consistent SUSAR reporting across all MSs should be ensured. Allow periodic line listing reporting to ECs and investigators. • Stronger provisions in Directive (or better a Regulation ?) and guidance of requirements for single case reporting and periodic line listing reporting to ECs and HAs which should be acceptable in all MSs and harmonised accordingly but do not create unnecessary burdensome administration • Clearer provision in Directive of what safety information should be provided to investigators and when information should be reported • Clearer provision in guidance required to clarify listing requirements for ASRs
Eudravigilance database	The European database of SUSARs (Eudravigilance) is currently only accessible by CA but not by sponsors. It would be surely useful to grant filtered (maintaining confidentiality) access to sponsors (e.g. to see aggregated reported SAEs for the same class of drugs, in the same indications, etc.), to improve safety planning/monitoring in clinical studies and risk management.
There appears to be a lack of communication between competent authorities and ethics committees in some member states	A **guidance** document could help to clarify and encourage appropriate dialogue between EC and CA including at European level.

What should a new legal framework look like?	
Comments	**Suggestions**
As **long-term measures** we propose to: Establish a new parallel approach for a central system for application and assessment of clinical trials, which can be chosen by clinical trial sponsors. Reasons for selecting one or the other pathway may be the conduct of single centre or multi-national trials or the fact that an increasing number of products receive marketing authorisations through a centralized procedure via EMEA. Consequently, we would have a centralised and decentralised system for the application and assessment of clinical trials in Europe, similar to the system for Marketing Authorisation Applications.	
Have a **Regulation**, which provides for **two parallel application systems** for clinical trials	Introduce an additional central system for application and assessment of clinical trial via a **new regulation**, which • Provides for ***one single CTA dossier*** (incl IMPD) • Uses ***Eudract Database*** as an application and assessment tool • Establishes a ***European competent authority (Clinical Trials Facilitation Group or EMEA***?), which is responsible for the central assessment of clinical trials • Allows the application of the subsidiarity principle to allow individual MS to opt out in case the product applied is not acceptable for ethical reasons (see 65/65/EC) for a defined category of ethical reasons.
Ethical aspects remain a national competence and are difficult to be regulated on a European level.	**Widen the scope of directive 2005/28/EC** by including the process of assessment and approval of clinical trials by ethics committees. (transfer the relevant paragraphs from directive 2001/20/EC to 2005/28/EC.
Work on EU/US harmonisation for safety reporting	**Short-term**: Alignment of birthdates of US annual IND report and EU ASRs **Mid/long-term:** Replacement of EU ASR and US annual report and acceptance of a global development safety annual report as suggested by CIOMS Working Group VII (The Development Safety Report (DSUR): Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials . This includes harmonization of format and content for periodic safety updates during clinical trials