HOPE answers to the public consultation paper
on the assessment of the functioning of the "Clinical Trials Directive" 2001/20/EC

HOPE is the acronym of the European Hospital and Healthcare Federation, an international non-profit organisation, created in 1966. HOPE, the European Hospital and Healthcare Federation, is made up of national organizations representing public and/or private hospitals. It covers more or less 80% of hospital activities in the European Union.

KEY ISSUE N°1 TO BE ADDRESSED: MULTIPLE AND DIVERGENT ASSESSMENTS OF CLINICAL TRIALS

The Consultation paper presents an accurate description of the situation concerning multiple and divergent assessments of clinical trials.

Consultation item n°4: options

Assessment by NCAs

HOPE recognizes the need to establish an EU-wide streamlined approach to clinical trials. Any mechanism to improve clinical trials processes should enable faster approval of clinical trials and avoid being open to different interpretation by the national competent authorities in different member states.

Considering the limitations of the voluntary cooperation of NCAs, HOPE supports the option of a community-wide streamlining of NCA-authorisation with a fully harmonised system. But this procedures should only being applied in a limited way, applying only to multinational trials or to specific categories of trials.

Assessment by Ethics Committees

HOPE supports a one-shop-stop approach as regards the submission of the request for authorisation of a clinical trial to the NCA and Ethics Committee. This would reduce the administrative burden of multiple submission of information to separate actors, and would speed up the approval process.

HOPE supports stronger cooperation between ethics committees in Member States and further legal clarity of the respective scope of assessment by NCAs and Ethics Committees.

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

Consultation item n°6 and n°7

The Consultation paper presents an accurate description of the situation concerning the inconsistent implementation of the Clinical Trials Directive.

Example n°1: Substantial amendments:

With regards substantial amendments there is a need for clarification of the definition and management of substantial amendments. This would provide consistency across member states and should reduce the burden of reporting, given that some sponsors are over-classifying amendments as substantial.

Example n°2: reporting of SUSARs

Reporting of serious adverse reactions (SUSARs) has increased since the implementation of the current Clinical Trials Directive. This has been a disincentive to engage in clinical trials.

Clarifying the procedures and modalities of reporting SUSARs to the Community database would restrict the scope for variations in interpretation of the law and it would improve the current situation.

An additional issue raised concerns the identification of SUSARs and the definition of what adverse events may be expected during a given trial. Many investigators do not realise the importance of such information in ensuring that SUSARs are truly unexpected events rather than those which may reasonably occur, especially in trials where individuals are not in good health when enrolled. This is a point of education at national and regional level. The reporting of SUSARs may be avoided where appropriate information has been provided prior to the trial taking place.

Assessment of seriousness

The actual definition of seriousness given in the Directive is the following: *Article 2 (o) "serious adverse event or serious adverse reaction': any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect."* The definition of seriousness in the directive is incomplete and inconsistent with the CIOMS VI group, Volume 9A, the ICH E2A and the FDA. HOPE suggests adding the 6th seriousness criterion: "*important medical event with a clear definition*."

Assessment of expectedness

The actual definition of expectedness given in the Directive is the following: *Article 2 (p) "Unexpected adverse reaction: an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product)."*

Although general guidance is provided, the correct reference document and the version to use for assessing expectedness of a serious reaction are not very clear and can finally impact on the risk benefit balance of clinical trials.

HOPE suggests to have the possibility to use the Summary of Product Characteristics for authorised product which is being used outside the terms and conditions of the marketing authorisation (this is mainly the case for non commercial sponsors); and to change the version of the reference document only once a year (at the date of the first authorisation of the concerned clinical trial by a competent authority) or to keep the same version of the reference document during the entire trial course to better assess the risk associated with clinical trials (a SUSAR will stay a SUSAR during all the study).

SUSAR reporting

Concerning SUSAR reporting in the future HOPE recommends that reporting would be made to:

- National Competent Authority: local SUSARs which occur within the concerned trial; foreign SUSARs which occur within the concerned trial; SUSARs which occur outside the concerned clinical trial;
- Eudravigilance: local SUSARs which occur within the concerned trial; foreign SUSARs which occur within the concerned trial; SUSARs which occur outside the concerned clinical trial;
- Ethics Committees (*In several Member States, the single opinion from Ethics Committee (article 7) is not implemented. Reporting SUSARs appears difficult to comply with the different requests from Ethics Committees (different kind of SUSAR, different means of reporting, different timelines):* local SUSARs only which occur within the concerned trial; grant a read-only access to Eudravigilance Database; not to report 6-month line listings.

Annual Safety Report (or Development Safety Update Report (DSUR) to be implemented soon)

The annual safety report has to be reported to National Competent Authority and to Ethics Committees

The actual definition of the annual safety report given in the Directive is the following: *Article 17 "(2) Once a year throughout the clinical trial, the sponsor shall provide the Member States in whose territory the clinical trial is being conducted and the Ethics Committee with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety*." HOPE recommends reporting all serious adverse events and all serious adverse reactions that occurred during the trial not only during the one-year period covered by the report to have a global safety overview of the trial.

HOPE also recommends when the DSUR will be implemented to keep the possibility to do: an annual safety report for one trial which tested several Investigational Medicinal Products (mainly the case in non-commercial clinical trials; or an annual safety report for several clinical trials conducted with the same Investigational Medicinal Product.

Interventional and non-interventional trials

HOPE agrees there is a need to find a common interpretation between EU countries in defining what is an interventional trial and what is a non-interventional trial. Non-interventional trials should not be included within the scope of the Directive as this approach would result in more and unnecessary bureaucracy.

HOPE supports clarification to reduce the scope for differences in interpretation and implementation across the Member States any related costs and additional bureaucracy must be kept to a minimum. Patient Safety must be at the core of any review.

KEY ISSUE N°3 TO BE ADDRESSED: REGULATORY FRAMEWORK NOT ALWAYS ADAPTED TO THE PRACTICAL REQUIREMENTS

The problems identified in the consultation paper are accurately described.

Risk-based approach

With regards to safety reporting and insurance requirements, the same requirements apply to all trials, with little or no flexibility for variation depending on the level of risk involved. Applying the same approach to trials with varying risk levels is a barrier to research and a disincentive to engage in clinical trials. HOPE supports a review of the existing implementation guidelines which proposed a more risk-based approach to the Directive

Requirement for a single sponsor

The existing Directive is based on the principle that there should be a single sponsor per clinical trial. This creates problems in practice for multinational trials, as it is difficult for a sponsor, particularly those from non-commercial and academic sectors, to take responsibility for trials in other countries. The increased amount of work and costs associated with doing this acts as a powerful disincentive to academic and non-commercial led trials, and limits their ability to participate. As a result some studies are simply not carried out. The requirement for a single sponsor can also be difficult for a national competent authority where they may be required to take action against a sponsor based in another country.

HOPE supports changing the requirements with regards a single sponsor and reviewing insurance in line with risk should be a priority when reviewing the Directive.

Excluding academia

HOPE does not support the exclusion of clinical trials carried out by academic sponsors from the scope of the Clinical Trials Directive. Exclusion would lead to each member state setting its own rules for clinical trials carried out by academic sponsors. This would cause confusion, and make multinational academic-sponsored trials more difficult to carry out, with classification difficult for some studies, for example commercially-funded studies managed as academic trials. In addition an exclusion of academia from the scope of the Directive would prevent the results of academic-sponsored trials from being used to support a marketing authorisation application. The methodology and risk-assessment behind a research proposal should determine which guidelines a clinical trial should adhere to, rather than the type of sponsor.

Options to address these issues

HOPE supports a review of the Clinical Trials Directive, particularly with regards safety reporting, reviewing insurance in line with risk and the requirement for a single sponsor.

KEY ISSUE N°4 TO BE ADDRESSED: ADAPTATION TO PECULIARITIES IN TRIAL PARTICIPANTS AND TRIAL DESIGN

HOPE supports proposals to adapt the Clinical Trials Directive to facilitate and promote special types of clinical trials. It is appropriate to establish requirements to ensure the interests of special patient groups, such as children and patients in emergency care, are taken into consideration in the design and conduct of trials. There may be value in a common EU system to clarify how specific categories of trials should be carried out. Any future mechanisms should not however, create further approvals and documentation, and a proportionate approach to risk and ethical soundness must be central to the process.

KEY ISSUE N°5 TO BE ADDRESSED: ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

HOPE shares the concern that clinical trials carried out in third countries may not always meet with good clinical practice standards, for example with regards participant safety issues and data quality.

HOPE supports an EMEA mandate to ensure that good clinical practices are enforced in third country trials, and for greater scrutiny by European regulators of clinical trial results submitted to them, for example as part of a CTA or marketing authorisation application.

Alternatively third countries could have the option of becoming part of a good clinical practice approved group following an EMEA inspection.

Finally the European Commission should have a responsibility to investigate the practices of clinical trials receiving financial support from EU funding programmes.

Attempts to raise the standards of clinical trials in third countries should consider specific challenges individual countries may be facing. Reasons may include lack of interest, lack of time, lack of resource, lack of understanding, all of which would require different solutions. Ultimately there should be support for assistance to third countries where the regulation of clinical trials is currently weak. This would lead to strengthened international cooperation in good clinical practice inspection activities and mutual recognition of GCP rules.