CTFG's objectives include supporting the efforts of the European medicines network with regard to public health by fostering a harmonised regulatory environment for clinical trials conducted in the EEA. CTFG is working to establish and improve communication channels within the European medicines network, and to develop and promote harmonised processes and procedures relating to clinical trials within the scope of the duties of the NCAs. It acts as a forum for discussion and agreement on common principles and processes to be applied throughout the network, and operates to improve harmonisation of the administrative procedures and assessment decisions for clinical trials across the NCAs. This work includes sharing of scientific assessment, harmonisation of processes and decisions, participation in the development of information systems, communication and cooperation with other working groups, including the Commission's Ad hoc working group, telematics implementation groups and the scientific working parties of the Community.

The EMEA works with the CTFG and with other technical groups on the management of two databases: the clinical trials database (EudraCT) and the EudraVigilance Clinical Trial Module (EVCTM — a specific module for the electronic reporting of suspected unexpected serious adverse reactions (SUSARs) by sponsors during clinical trials). The EMEA also convenes and chairs the Good Clinical Practice and Good Manufacturing and Distribution Practice Inspectors Working Groups, which contribute towards preparing implementing guidance for the Directives on good manufacturing practice (GMP), good distribution practice (GDP) and good clinical practice (GCP) inspections.

The Committee for Medicinal Products for Human Use (CHMP), through its Quality Working Party, developed a guideline on the 'Requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004)' in order to harmonise the requirements. The CHMP, through its Safety and Efficacy Working Parties and in collaboration with clinical trials experts representing the CTFG, has recently developed a scientific guidance document, 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07)', which is important to the conduct of first-in-human clinical trials in the EU.

The conference held on 3 October 2007 was a stocktaking exercise, involving all major interested parties, with a view to evaluating whether further work on the implementation of the regulatory framework could resolve existing problems or whether a revision of the current legislation is necessary.

Representatives of commercial sponsors, non-commercial sponsors, ethics committees, national competent authorities, patients and investigators were invited to provide their views on the practical implementation of the regulatory framework, and to identify practical difficulties.

The conference was attended by 267 delegates representing national competent authorities, ethics committees, commercial and non-commercial sponsors, contract research organisations, patients' organisations, the European Commission and the EMEA. Six journalists were also present. (Attendees are listed in Annex B.)

A programme committee was established to prepare the conference, to identify topics and to identify representatives of the various interested parties who would present their respective positions. Each organisation invited to nominate delegates was also invited to prepare a written submission. These are available on the EMEA website. (See Annex C.)

Interested parties were requested to reflect upon and focus their presentations on four key questions:

- What aspects of the current legislative framework work well?
- What does not work well?
- What can be remedied within the current legal framework?
- What should a new legal framework look like?

A further topic in the programme related to clinical trials in third countries.

Sections of the report

This report is divided into sections on key issues arising from the conference presentations:

- Scope of the legislation and definitions
- Clinical-trial application and review process
- IMP and GMP issues
- Ethics committees
- Safety reporting in clinical trials
- Transparency
- Inspections
- Patients' perspective
- Clinical trials in developing countries

At the end of each of these sections, the recommendations are summarised as bullet points. Section 3.10 contains the summary of perspectives for the future as seen by the stakeholder groups. Section 3.11 contains the closing comments from the European Commission's DG Enterprise.

These are the key recommendations made by one or more of the stakeholder groups during the meeting. In some cases, they may be contradictory or may not represent the views of all present, since the purpose of the meeting was to listen to all positions, not to establish consensus at this point in time.

The slides of all presentations given during the conference, plus other documents relating to the conference, are available through the 'Conferences & Events' section of the EMEA website:

http://www.emea.europa.eu/meetings/conference.htm

Summary of the conference programme

Session 1

Opening statement, objectives, and background.

Session 2

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 ethics committees and NCAs.

Trials conducted in third countries, including developing countries.

Session 3

Dossier maintenance, including substantial amendments.

Safety information, collection, reporting and review of safety information:

- expedited reports
- annual safety reports.

Databases:

- EudraCT
- EudraVigilance.

Inspections (GCP, GMP).

Session 4

Potential solutions and recommendations for the future, including views from patients, healthcare professionals and investigators:

- implementation within the current framework
- implementation requiring changes to guidelines
- solutions requiring changes to the legislation.

Session 5

Final views of stakeholders, with general discussion and conclusions.

Session 6

European Commission — Perspectives for the future.

3. KEY ISSUES ARISING FROM THE CONFERENCE PRESENTATIONS

The conference opened with a presentation of figures illustrating the current situation with regard to the numbers of patients involved in clinical trials in the EU, the US and other regions, and to financial investment in pharmaceutical research and development in the EU, Japan and the US.

Based on data from EudraCT, 80% of clinical trials conducted in the EU since 2004 have been by commercial sponsors and 20% by non-commercial sponsors.

Most of the trials are performed in multiple sites and multiple countries. A major question is how to ensure a favourable environment for clinical research in the EU, taking into account the complexity of the EU network.

The challenge in Europe is therefore to optimise our regulatory environment to:

- ensure protection of subjects participating in clinical trials (EU and third countries)
- ensure a framework for high-quality research in the EU and its acceptability worldwide (product development, product authorisation)
- promote a favourable research environment (clear, efficient and effective administrative and scientific procedures).

3.1. Scope of the legislation and definitions

Directives 2001/20/EC and 2005/28/EC have introduced a number of beneficial elements into the EU legislation, which were welcomed.

These establish a common legal framework for:

- interventional clinical trials of medicinal products in the EU
- compliance with good clinical practice (GCP) and good manufacturing practice (GMP)
- definitions of tasks, responsibilities and legal entities
- timelines and administrative processes
- improvements in the quality of research and the protection of patients.

However, the presentations and discussions revealed calls for a number of clarifications or changes to the legislation.

3.1.1. Scope of the legislation

The Directives have set out a legal basis for GCP compliance in the conduct of clinical trials. This has had the welcome result that in some Member States, there has been increased investment in the development of clinical-research infrastructure and the promotion of training programmes on clinical trials. As a result, increased awareness of the requirements for the conduct of clinical trials, including GCP, has led to improvements in the available infrastructure for clinical-trial management and improved GCP compliance.

The ethics committee speaker noted an increased implementation of GCP requirements in non-commercial clinical trials. The patients' representative reinforced this point, adding that the Directive promotes a more rational conduct of clinical trials and provides a greater level of patient protection in commercial and non-commercial trials.

Nonetheless, the lack of transparency and harmony in the application of GCP standards among Member States was raised as a concern. The GCP Inspectors Working Group recommended that there be a harmonised reference to ICH GCP as the EU standard in the EU legislation.

Sponsors' representatives considered that there should be an adaptation or interpretation of GCP standards (perhaps through specific annexes to the GCP guidance) according to the type of trial (purpose, characteristics), or in relation to the risk of the products for subjects (e.g. novel products, orphan products, marketed products or products used for minimal intervention). This approach would greatly facilitate the application of the requirements in these different situations. The particular needs of very large-scale clinical trials, involving many hundreds of sites and thousands of patients, were emphasised in this context.

Non-commercial sponsors noted that, whilst requirements for clinical trials of medicinal products are well regulated and relatively well harmonised, requirements for other biomedical research on human subjects are poorly regulated and lack harmonisation, leading to major discrepancies in the protection afforded to subjects and difficulties in setting up such trials. They called for the scope of the legislation to be widened to include all categories of biomedical research in human subjects (with or without health products, whether interventional or observational), and not only interventional clinical trials of medicinal products. It was recommended that both the GCP standards and harmonised administrative requirements should apply not only to clinical trials with investigational medicinal products but also to other types of trials, including those for in vitro diagnostics, medicinal devices, herbal medicinal products and homeopathic remedies, among others.

Further investment in the development of the clinical-research infrastructure and in the provision of training to all stakeholder communities in the EU will increase trial quality, improve GCP compliance of clinical trials and help to provide a strong stimulus for research in the EU.

3.1.2. Definitions

Commercial and non-commercial trials and sponsors

There was a clear consensus that there should be one set of GCP standards for all trials, and not different standards for commercial trials and for non-commercial trials. Non-commercial sponsors warned that the suggestion (in the draft guidance on specific modalities for non-commercial trials) that non-commercial trials might not always be acceptable in marketing-authorisation applications can be damaging to non-commercial research, and to investment in it. Trials conducted by non-commercial sponsors should be admissible for marketing authorisation application purposes. There are many examples of where such trials have been very important to the development of medicinal products and their marketing authorisation, and to the development of the use of medicines in practice.

Rather than a distinction between commercial and non-commercial trials, the idea of a differential application of the legislation, using a risk-based approach, was proposed. This approach should be based on the risk involved in the trial and on the extent of knowledge of the product (e.g. novel product, marketed product, marketed product used within its

summary of product characteristics (SmPC), etc.), thus avoiding the development of double standards in terms of GCP compliance and the quality and credibility of data (refer also to the paragraphs on GCP in section 3.1.1.). This approach would prevent the perception of there being two levels of quality in the present legislation and in its implementation, as seen in the current 'Draft guidance on specific modalities for non-commercial trials'. It would lead to a general improvement in the quality and cost-effectiveness of trials (e.g. better prioritisation of monitoring and of other quality-control activities).

The non-commercial sponsors expressed serious concerns about the cost to them of implementing various aspects of the legislation and its administrative procedures. They consider that this cost has reduced the number of independent trials. Non-commercial sponsors should benefit from waiving of fees for applications to ethics committees and NCAs, waiving of the obligation of the sponsor to supply the IMP free of charge when it has a marketing authorisation, support in SUSAR reporting, harmonisation of insurance requirements, and insurance coverage by the public health systems. An EU regulatory affairs helpdesk, aimed at supporting non-commercial sponsors, was also proposed.

Proposals to improve the cost-effectiveness of non-commercial trials without reducing GCP compliance included adapting record-keeping and monitoring requirements (e.g. by web-based trial master files/investigator site files, and by developing models of monitoring and audit adapted to the structures or their organisations and the risk of the trials).

Non-commercial sponsors explained that the European Science Foundation – European Medical Research Councils (ESF-EMRC) is initiating a 'Forward Look' activity entitled 'Investigator Driven Clinical Trials' during 2007/2008 to develop key recommendations on better coordination of the various national and European initiatives in this domain and on strengthening investigator-driven clinical trials in Europe in an international perspective.

Other issues raised included the potential role of non-commercial sponsors in providing independent research on topics such as safety and combination therapies, and suggestions that one of the pivotal pre-authorisation studies should be performed by an independent non-commercial sponsor.

Interventional and non-interventional trials

Sponsors' representatives pointed out that there are divergent interpretations at Member State level of the definition of interventional and non-interventional studies, and that, as a consequence, the same post-marketing study may be regarded as an interventional clinical trial in one Member State and as a non-interventional study in another. These differences mainly relate to the interpretation of what constitutes 'intervention' in terms of blood samples, questionnaires or other measurements. A proposal was made for the creation of an intermediate category of trials between interventional and non-interventional — perhaps to be called 'minimally interventional' — with only low-risk intervention and without clinical-trial authorisation by national competent authorities, but with a favourable opinion of the ethics committee required.

The lack of a precise non-IMP definition (see 'Investigational medicinal product', below) leads to disharmony between NCAs with respect to the classification of trials as (non-)interventional, since the diagnostic and/or monitoring procedures are not classified in the same way across the Member States.

The NCAs share the sponsors' concern over the difficulty in interpreting this aspect of the legislation.

Substantial and non-substantial amendments

There was a consensus among stakeholders (sponsors, NCAs and ethics committees) on the need for further guidance to ensure consistency across Member States in the classification of substantial and non-substantial amendments. In addition, guidance is needed on whether NCA and/or ethics committee approval is required. Speakers for the CTFG highlighted the current work of this group on the preparation of a proposal for further guidance or Q&A text, to include different examples.

Investigational medicinal product (IMP)

All stakeholders expressed concern about the difficulties in interpreting the definition of IMP. It is not clear to what extent these can be remedied in the context of the existing definition and to what extent the definition itself may need some revision. It was pointed out that there is divergence among Member States, with the result that, in a multistate trial, a treatment might be considered to be an IMP by some NCAs and not by others. In addition, it was considered that the concepts applying to other medicinal products used in clinical trials and referred to as 'non-investigational medicinal products' (NIMPs) have no clear legal basis. Particular difficulties arise in relation to: the obligation of the sponsor to provide the IMP free of charge; the labelling requirements; and the SUSAR reporting requirements, all of which can add a large financial and organisational burden if a product is classified as an IMP. The CTFG pointed to the availability of the 'Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials', published recently by the Commission in EudraLex Volume 10. It was not clear whether this would be an adequate solution to the problems encountered, partly because the guidance had only been published recently.

Off-label use of products is often the standard of care in routine clinical practice in many paediatric and oncological settings. It is a cause of particular concern to sponsors (to non-commercial paediatric and oncology research groups and to commercial sponsors) that these products may be classified by some NCAs as IMPs when they are neither the test nor comparator per se. They would be considered background treatments based solely on the trial design but become IMPs due to the off-label nature of their use.

There are differences in interpretation of marketing-authorisation status (pre- versus post-authorisation), with some NCAs recognising a marketing authorisation anywhere in the EU whereas others consider only the national marketing-authorisation status in their territory.

Sponsor

Confusion around the concept of 'single sponsor' for a trial was an issue of major concern throughout the EU, raised mainly by non-commercial sponsors. The problems they encounter represent a major obstacle to the initiation of multinational, collaborative clinical research by academic institutions. Academic institutions typically lack the legal and infrastructural capacity to fulfil, within a single organisation, the sponsor's tasks in multinational trials. Sponsors said there is a need, therefore, to allow multiple sponsorship of both multinational and national trials, whereby the roles, responsibilities and liabilities in the various Member States are shared on a contractual basis between the organisations/institutions/persons involved (including third-country non-commercial sponsors).

Legal representative of the sponsor

Contract research organisations (CROs), in particular, raised concerns about the concept of 'legal representative' and its implications. They reported that it is very difficult to get

clear advice on the real role and liability of a legal representative. It was proposed to replace the concept with that of an 'authorised representative' or 'agent of the sponsor' instead, with civil and criminal liability being retained by the sponsor. In addition, clear guidance on the roles and responsibilities of the sponsor and this authorised representative should be provided.

Non-commercial sponsors also have trouble with the concept of legal representative, where third-country non-commercial sponsors have difficulties establishing a legal representation in the EU.

Research contracts with investigators/institutions

CROs also stated that it would greatly improve the efficiency of research and the setting-up of trials in the EU if investigator/institution contracts could be based on a standard template established in each Member State.

3.1.3. Summary of recommendations in relation to the scope of the legislation and its definitions

Proposed measures within the current legal framework:

- Provide harmonised and clear guidance, and ensure pan-EU agreement on the interpretation of IMP/non-IMP.
- Provide harmonised guidance and ensure pan-EU agreement for consistency across Member States regarding substantial and non-substantial amendments, the process for notification of substantial and non-substantial amendments to the NCA and the ethics committee, and clarification on whether NCA and/or ethics committee approval is required.
- Improve communication on harmonised GCP standards, with mechanisms in place for input from stakeholders on issues of divergence among Member States.
- Apply GCP standards in an adapted manner to different categories of product, based on the risk and extent of knowledge available (e.g. novel products, products with a marketing authorisation, products with a marketing authorisation used according to the SmPC) and avoiding the introduction of double standards for the quality of commercial and non-commercial research.
- Guidance on the role and responsibilities (and liabilities) of the legal representative, and on how the entity should be established.
- Development of standard templates for contracts between the sponsor/CRO and the investigator/institution at Member State level.
- Explore the possibility of multiple sponsorship of a single clinical trial within the present legal framework.
- Ensure that research by non-commercial sponsors is admissible for marketing-authorisation purposes.
- There should be no double standards for the quality of commercial and non-commercial research. However, non-commercial sponsors should be given support, due to their limited financial and infrastructural resources, through:

  waiver of fees for applications to ethics committees and NCAs

waiver of the obligation to supply the IMP free of charge when it has a marketing authorisation

support for SUSAR reporting

harmonisation of insurance requirements and insurance coverage by the public health system

establishment of an EU regulatory affairs helpdesk for clinical trials

cost-effective models for trial master files/investigator site files, monitoring and auditing, with reduction of GCP compliance or data quality.

- Investment in the development of clinical-research infrastructures and in the training of all stakeholder communities, in particular for the benefit of non-commercial organisations and for investigators and their support staff.

Proposed measures in the context of a new/revised legal framework:

- A single legislative framework for all biomedical research on human beings, with or without health products, interventional or observational; preferably in the form of a regulation rather than a directive.
- Adapt the legislation in different ways according to the risk involved in the trial and the extent of knowledge of the product:

  define categories of research and products, based on risk involved

  develop a regulatory requirement based on the risk associated with each category

  organise workshops to reach agreement on categories.
- Revise the definition of interventional and non-interventional trials to introduce the concept of 'minimally interventional trials', in order to facilitate post-authorisation studies.
- Remove the concept of commercial and non-commercial trials, to remove any perception of, or actual, dual standards of GCP compliance and data quality.
- Include a clearer framework for the CPMP/ICH/135/95 GCP guideline in the Directives and their implementing texts.
- Establish a basis for multiple sponsorship of a single trial, with sharing of responsibilities. (Also consider the possibility of this within the present legal framework.)
- Establish a concept of authorised representative instead of legal representative, with civil and criminal liability retained by the sponsor.
- Revise the definition of IMP and reduce the scope of products that fall within this definition in a clinical-trial setting.
- Clarify the non-IMP concept, especially when authorised medicinal products are used as standard therapy in ways different to those foreseen in the SmPC.

3.2. Clinical-trial application and review process

Improvement of the application process for clinical trials was considered to be one of the benefits of Directive 2001/20/EC. The application process was considered more predictable, clearer, and more consistent and standardised, resulting in reduced timelines for the review of applications and substantial amendments by NCAs and ethics committees in most Member States. The NCA and ethics committee review processes run in parallel in most countries.

Advantages cited included:

- the unique identifier for a clinical trial in the EU (the EudraCT number)
- the common (EudraCT) clinical-trial application form accepted in most Member States
- the common IMP dossier (IMPD) accepted in most Member States
- guidance documents with details on the content of the CTA and IMPD
- clear timelines in most Member States.

European CROs have had positive experiences with the acceptance of a common IMP dossier by most NCAs. Thorough completion of the IMPD results in the generation of robust and reliable data.

The legislation has also improved the ethics committee review process, and interaction between the NCAs and ethics committees has become more harmonised. The CTFG representatives also highlighted the importance for the clinical-trial application (CTA) review process of sharing information through EudraCT and its alert system, so that NCAs are aware of the decisions and activities of other NCAs. This promotes harmonisation of the scientific assessment process, and the sharing of experience and interpretations, thus promoting harmonisation and improving the safety of research participants. The different cultural and ethical requirements across and within Member States remain an issue that is difficult to solve through legislation.

Despite the gains achieved through the implementation of the legislation, there were many concerns that the promises of the Directive had not been fulfilled, particularly with respect to the insufficient harmonisation of administrative processes. There remain differences between Member States in the IMPD requirements (some countries have specific national requirements, some do not accept the common CTA form) and a lack of transparency about the Member State requirements. There are also differences in timelines between Member States, including validation periods and clock-stops added to the 60 days provided for in the Directive. Sponsor representatives consider that greater efficiencies need to be achieved. In particular, there is a need to reduce the administrative burden associated with applying for the same clinical trial across multiple Member States, which results from having to be aware of, and comply with, multiple differences in the detail of the processes.

It is important to note that where differences in requirements or timelines arise, even between a minority of Member States, this still causes a significant increase in the burden on applicants/sponsors.

It was noted that although the CTA form is harmonised for most NCAs, there has not been the same progress for ethics committee submissions, where there are additional differences in documentation requirements.

Commercial and non-commercial sponsors highlighted a number of specific issues, with the latter finding it especially difficult to maintain an oversight of the particularities of each Member State's requirements. This difficulty is also encountered by small and medium-sized enterprises (SMEs), and by those third-country sponsors who do not have a major presence in the EU. Commercial sponsors, on the other hand, generally have dedicated regulatory affairs departments with the necessary resources to track the national differences.

3.2.1. Availability and transparency of information

In the short term, and awaiting further harmonisation, detailed information on all national requirements should be available in English and at a single point (website). The CTFG representatives clarified that its CTA subgroup is collecting national CTA requirements for the purposes of harmonisation.

Sponsors requested a one-stop shop (pan-EU office/helpdesk) to provide advice and support to applicants, and to monitor and provide rapid resolution of issues where difficulties in implementation and/or disharmonies are identified.

3.2.2. Clinical-trial application

The burden of paperwork should be reduced by rationalising the application forms and the content of dossiers and by reducing the number of times the same or nearly the same information has to be submitted to different NCAs and ethics committees. The EudraCT form should be improved to make it more user-friendly.

A clear definition of an IMP (see also 3.1.2 above) would assist in clarifying the data required to support applications for different types of IMP and non-IMP.

The overall aim should be for Member States to comply with a single common CTA form with harmonised data requirements for all NCAs and ethics committees, and to have a single electronic submission point through the EudraCT portal. This single submission point should be for both the CTA form and the supporting IMPD and study documentation.

3.2.3. Review procedure

Recommendations were made that the review process be streamlined further, in particular for multistate clinical trials. Recommendations covered the following range, all based on a need for a single harmonised dossier and review procedure:

- shared assessment by the concerned Member States with an agreed outcome
- mutual recognition or decentralised procedure
- centralised procedure.

Such an approach would avoid duplication of assessments, saving time and human resources, would reduce the administrative burden and the perception of difficulty in conducting clinical trials in the EU, and would ensure that a common CTA and IMPD were maintained throughout. Moreover, it would provide greater predictability of the review outcome for marketing-authorisation applications at a later stage.

NCA representatives did not support the concept of a centralised procedure for authorisation of clinical trials, since the national particularities should be taken into account as well.

The CROs indicated that ideally 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. Non-commercial sponsors also considered that a regulation would be preferable.

Regarding the single ethics committee opinion, different views were expressed during the conference from the different stakeholders, but it was generally recognised that a single national-ethics-committee opinion is preferred. This should nonetheless be based on a common dossier and application form.

3.2.4. Assessment process

There were calls for more-harmonised and coordinated assessments by ethics committees and NCAs. Pan-EU training for NCA assessors and ethics committee members was recommended, to facilitate scientific consistency and information requirements and to improve patient protection.

There should be a clear identification of the roles and responsibilities of ethics committees and NCAs in order to avoid duplication of work between the two bodies (i.e. NCA assessing the medical and scientific merit of the trial, whereas the ethics committee would determine whether the protocol meets the ethical standards, is in line with the medical practice of a given country, preserves the rights and integrity of trial subjects, and assess the suitability of the site concerned). This clarification of the roles and responsibilities of the ethics committees and NCAs should include more guidance on the interactions between them.

One major issue is the lack of harmony in the assessment of substantial/non-substantial amendments as well as in the definition of these (see 3.1.2 above) by both NCAs and ethics committees.

The CTFG recognised the need for further communication on, and harmonisation of, scientific assessments and related processes, and considered this achievable within the current CTFG framework.

3.2.5. CTFG

There was a call for strengthening of the role of the CTFG by giving it legal status and a clear mandate to coordinate the CTA application and review process, including the possibility of arbitration between Member States, and for the establishment of processes for sponsors to appeal decisions.

Greater transparency regarding the objectives and workplan of the CTFG and a systematic involvement of the stakeholders were also called for.

3.2.6. Timelines

The sponsor and CRO groups asked for compliance with the legal timelines for review set out in the Directive, without additional pre-submission and clock-stop mechanisms.

Concerning amendments, the CROs recommended the introduction at EU level of:

a maximum time for review of substantial amendments by the NCAs (as has been done in the legislation of some Member States), in order to avoid delays in approvals

an expedited process for review and implementation of 'efficacy' amendments by NCAs and ethics committees (e.g. to permit rapid closure of a trial arm that is not proving effective).

3.2.7. Summary of recommendations concerning the clinical-trial application and review process

Proposed measures within the current legal framework:

- Ensure national requirements are readily available in English, and through a single source (website).
- One-stop shop (pan-EU office/helpdesk) to provide advice and support to applicants (to ethics committees and NCAs), and to monitor and provide rapid resolution of issues where difficulties in implementation and/or disharmonies are identified.
- Single and unique CTA form and dossier (also for substantial amendments), with harmonised data requirements for all NCAs and ethics committees.
- Guidance that defines the relative roles and responsibilities of ethics committees and NCAs.
- Guidance on interaction between ethics committees and NCAs.
- Harmonised assessment methodologies for ethics committees and NCAs.
- Provide pan-EU training for assessors and ethics committee members, to facilitate consistency in approach.
- Strengthen the role of the CTFG for the harmonisation of the CT application and assessment process.

Proposed measures in the context of a new/revised legal framework:

- Single point of entry for submission of CTA applications (form and dossier), e.g. single submission point through EudraCT portal.
- Enforce legal timelines for review and add a maximum timeline for the review of substantial amendments by the NCAs.
- Streamlined review processes: shared assessment, mutual-recognition/decentralised procedure or centralised approval system with provision for a single assessment by one competent authority, valid for multistate trials.
- Specialisation of NCAs in particular types of health product in the context of a streamlined application and authorisation procedure.
- Provide legal status for the CTFG.

3.3. IMP and GMP issues

The establishment of common GMP requirements for IMPs, the role of the QP (qualified person) responsible for batch release and the acceptance of the IMPD were all welcomed. The problems raised result mainly from differences between Member States in the interpretation of these requirements, and from the absence of guidance in some specific areas. Transparency in the area of country-specific conditions for an IMP dossier would also be welcomed, although fulfilment of these requirements can be complicated for some sponsors and CROs, and harmonisation is much preferred.

The experience of the non-commercial and the commercial sponsor representatives as well as the speakers for NCAs to date shows that amendment of the IMP definition (see 3.1.2) and harmonisation of GMP requirements are key areas that need to be addressed urgently.

3.3.1. GMP

It emerged that the various additional requirements of the individual NCAs for the scope of the IMP manufacturing licence and labelling requests have been introduced, and these must be followed by the pharmaceutical industry regardless of the requirements of the Clinical Trials Directive.

The commercial sponsors proposed involvement of the GMDP Inspectors Working Group in addressing a number of issues, including:

- varying levels of acceptance by NCAs of the QP declaration of GMP compliance of a third-country manufacturer
- definition of the content of the QP declaration (the absence of a definition has led to the generation of apparently non-compliant documents)
- classification of what is a manufacturing process, e.g. the reconstitution of an IMP in water immediately before its use, or administration of a precursor of a radionuclide with an extremely short half-life
- distinction between the responsibilities of the QP and the sponsor's legal representative in case of quality defects.

The CROs and commercial sponsors also called for harmonisation of requirements for the importation of an IMP, and for elimination of the separate submission of the importation certificate after trial approval. They struggle to comply with the country-specific requirements for IMP labelling, stability testing and testing of comparators originating from third countries.

The NCAs welcomed the concept of a common IMP dossier submission and expressed a positive experience overall. They are concerned about differences in the areas of QP activities and documentation required, IMP labelling, and GMP-compliance documentation. The NCAs consider that a dedicated meeting of the CTFG, GMDP IWG and European Commission would be beneficial in resolving a number of the current problems.

3.3.2. Summary of recommendations in relation to IMPs and GMP

Proposed measures within the current legal framework:

- Modify labelling requirements for IMPs to allow any commercially available medicinal product marketed for adult use to be used as IMP in paediatric clinical trials in multiple Member States.
- Clarification and guidance regarding the roles and responsibilities of QP and legal representative (e.g. in the context of quality defects).
- Elimination of the separate submission for import licence by including importation authorisation within the NCA's approval of the clinical trial application.
- Simplify and harmonise requirements for the testing of comparators originating from third countries (may also require some modification of the legislation).
- Improve acceptance of the QP declaration of GMP compliance of a third-country manufacturer.
- Define the content of QP declarations and batch-release certificates.
- Eliminate national differences in IMP-labelling requirements.
- Clarify and harmonise stability-testing requirements.
- Improve classification of what activities (e.g. reconstitution) fall under GMP and require GMP authorisation, and what activities do not.
- Involve the CTFG, GMDP IWG and European Commission in discussions/workshop to find solutions to labelling, QP role and documentation, and GMP-related issues.
- Develop mechanisms to ensure that the assessment of trial methodology by ethics committees and NCAs is of high quality and can contribute to reducing the risk of trial design errors (both random and systematic errors).

Proposed measures in the context of a new/revised legal framework:

- Revise labelling requirements.
- Revise the definition of IMP (see 3.1.2).
- Develop uniform GMP requirements for all IMPs, including advanced therapies, gene and cell therapies, and radiotherapy products (suggested by non-commercial sponsors and CROs).

3.4. Ethics committees

The Directives have established clear requirements for the role of ethics committees in the protection of participants in clinical trials. They have set up the requirement for a single opinion on ethics per Member State for multi-centre trials. In order to achieve this single opinion many Member States have put in place appropriate procedures and established provisions for the functioning of the ethics committees based on common guidelines. The creation of a single ethics committee in the few Member States where legal regulation did not previously exist was also received very positively. During the conference, these

requirements were welcomed, and this approach was considered adequate in the context of national differences of culture and ethics.

Although some sponsors asked for further centralisation of ethical review at EU level, there was much support for the system of a single opinion per Member State. It was considered that the legal framework should reflect the need to respect national, cultural and therefore ethical differences across the EU, though ethical principles should be universal. There should be standard requirements for administrative processes, forms and dossiers. There might be a role for a European body to develop consensus guidance on specific ethical issues, such as use of placebo or clinical trials in the context of emergency care.

The large majority of attendees, in particular patients' representatives, considered that the implementation of the Directives has resulted, overall, in better protection of human subjects in clinical trials. A key benefit of the legislation is the single ethics opinion per Member State, which is a real improvement and has generally resulted in shorter times for provision of ethics-committee opinions within the EU.

Ethics committee representatives stressed there is "no ethic without methodology or methodology without ethic". Ethical review should be independent.

During the discussion, ethics committee representatives stressed the importance of maintaining the current public trust in ethics committees.

Concerns remain in a number of areas, including:

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

There was a widespread view among speakers and attendees that national implementation of the legislation and guidance on ethics committees has been heterogeneous.

Non-commercial sponsors proposed an EU coordination role for the development of common standards, tools and procedures for ethics committees. It was suggested that a conference to develop this topic should be organised.

3.4.1. Applications to ethics committees

Sponsors requested further standardisation of ethics committees' requirements for data and application formats (paper or electronic). The diversity of these requirements and the complexity of national processes add to the burden on researchers (and on the ethics committee structures), especially where local ethics committees are involved in reaching the single opinion. In this context, ethics committee representatives also commented on the need for a correct balance between central opinion and local knowledge.

Sponsors would also like those requirements to be more transparent — for example through the existence of a one-stop shop — and would like it to be possible to submit the same dossier to a single point in the Community for both ethics committees and NCAs (EudraCT portal) (see 3.1.2).

Another problem, raised by sponsors, concerns the operation in some Member States of a process of sequential review by the NCA and ethic committee — a process that extends timelines.

The individual responsibilities and interactions between the NCA and ethics committee should be clarified (e.g. for the assessment of SUSARs).

3.4.2. Structure and procedures

In most Member States, multiple ethics-committee structures exist. Their interaction often induces complex procedures, extends the timelines required for the adoption of the single opinion, and creates the potential for duplication of work.

The Directive and its implementation have not changed the status quo as far as the constitution of the membership of ethics committees is concerned. There are no specifications in the Directive on this point, despite it being addressed in the GCP guideline. There are some legal and institutional requirements at national or committee level, but it is not always easy for ethics committees to find the appropriate balance of members or experts, e.g. a mix of medical and lay members, lawyers or philosophers familiar with the fields of clinical trials and of ethics.

Patients' representatives also expressed the wish to have more systematic participation in ethics-committee activities. They pointed out that patients may have a different perception, compared to medical experts or other parties, of the risks and discomforts they are prepared to tolerate in particular situations.

There is a need to provide ethics-committee members and experts with more training on the law, the methodology and the ethics of clinical trials.

The GCP Inspectors Working Group noted the need to include in the Directive a set of provisions (or a reference to those provisions) that ensure that the requirements set out in the GCP guidelines are applicable to ethics committees in the context of the EU legislation.

3.4.3. Guidance on issues of common ethical concern

Commentators indicated that it would be very helpful for individual ethics committees, and for consistency of ethical review, to have universal guidelines on ethics defined at EU level (e.g. in relation to: use of placebo; clinical-trial designs, such as those where dose interruptions are foreseen; and informed consent, especially of vulnerable subjects).

3.4.4. Access to information

Ethics committees asked for direct access to EudraCT and EudraVigilance in order to optimise their oversight of clinical trials. This would help ethics committees to ascertain promptly the status of, and updated information on, a clinical trial. They also requested better information on, or involvement in, inspections (see sections 3.7.1 and 3.7.2).

3.4.5. Infrastructure

In many cases, ethics committees have very limited resources. Members are generally voluntary and perform their committee duties in addition to their principal activities. The financing of ethics committees is an issue that has been addressed differently in different Member States. In some cases, this has involved the establishment of a fee for application to the ethics committee. When it is requested, there is usually the possibility of a waiver for non-commercial sponsors.

Ethics committees consider that their available resources are often absorbed in the management of paperwork resulting from large numbers of dossiers, substantial amendments, safety reports, etc., and in the maintenance and archiving of records of applications, meeting minutes and deliberations of the committees, and of their procedures. There is a need to reduce unnecessary submission of information or duplication of activities (e.g. between ethics committee and NCA), and steps should be taken to ensure that ethics committees have adequate support staff, members and resources (e.g. space for files and records).

3.4.6. Safety reporting to ethics committees, including SUSAR reporting

The large number of individual suspected unexpected serious adverse reaction reports (SUSARs) received by ethics committees places an enormous burden on them. This excessive and unnecessary amount of information cannot be effectively reviewed. Furthermore, it does not provide concise safety data that would better protect trial subjects.

The SUSARs are usually provided without any additional information or analysis to put them in the overall context of the clinical trial(s), IMP-safety profile and patient population. The same reports are submitted to NCAs and to other ethics committees. The considerable effort involved in processing the paperwork is not matched by adequate structures for review of the information, and the resource could be put to better use.

Annual safety reports are lengthy documents and are provided to multiple ethics committees. Within one Member State, more than one ethics committee may have reviewed the clinical trials addressed in a single annual safety report. Again, better processes are needed to ensure that these are adequately reviewed by, or on behalf of, the ethics committees, and by people with the necessary expertise, role and resources.

The topic of safety reporting, including to ethics committees, is addressed in more detail in section 3.5.

3.4.7. Informed consent of subjects

Patient representatives asked for further harmonisation on the presentation of 'informed consent' across the EU, in terms of both the quality and quantity of the information provided.

Delegates noted concern about trends in some cases to provide exhaustive and excessive amounts of information to patients, such as long lists of potential adverse reactions, which contribute little towards truly informing the patient and which are intended rather to address liability concerns of the sponsors.

They also noted that the legislation does not regulate what happens at the end of a trial, in terms of continuation of the treatment or publication of the trial.

The requirements for informed consent as currently set out hamper research in situations of medical emergency. Some Member States have consequently instituted national rules, which can be particularly problematic for performing multi-centre trials in several Member States. In other Member States, trials in situations of medical emergency may be difficult or impossible to conduct.

Another concern expressed by patients' organisations is the difficulty they have experienced in designing studies that comply strictly with ethical requirements in the field of rare diseases, where the usual requirements for confidentiality may not be practicable.

3.4.8. Summary of recommendations in relation to ethics committees

Proposed measures within the current legal framework:

- Member States should establish a single, national ethics-committee review and opinion, by clarifying, where necessary, the responsibilities of central and local ethics committees, and by rationalising the procedures to be followed by committees and applicants.
- The composition of ethics committees should be further defined, consistent with ICH GCP requirements, and appropriate involvement of medical and other experts and laypersons, including patients, should be established.
- Further education and training for ethics-committee members and their support staff should be established to reinforce capacity for scientific and ethical review.
- Quality assurance systems should be put in place to ensure consistency of ethics committees with requirements such as GCP principles. This might include systems for accreditation of ethics committees, self-evaluation, etc.
- Establish an EU coordination role for the development of common standards, tools and procedures for ethics committees.
- Organise a conference to further support the development of these common items.
- The GCP IWG proposed that ethics committees should be subject to GCP inspection.
- Establish a common application form and dossier for all ethics committees.
- Provide common EU guidance on the process for waivers to informed consent in emergency settings.
- Establish guidelines on ethics at EU level (e.g. in relation to: use of placebo; clinical-trial designs, such as those where dose interruptions are foreseen; informed consent, especially of vulnerable subjects; etc.).
- The separate roles and responsibilities of ethics committees and NCAs should be clarified, following the principle that the NCAs should focus on the product and ethics committees on the person.
- Necessary resources for the ethics committees — in terms of finance, training and administrative support — should be ensured at national level and, where applicable, at EU level (e.g. aspects of training, coordination and communication/information sharing, development of common standards, IT infrastructure, etc.).

Proposed measures within the context of a new/revised legal framework:

- To enforce or make mandatory some or all of the above-mentioned recommendations, e.g. composition of ethics committee, where appropriate.
- Amend the legislation to ensure a workable process for consent in clinical trials in emergency settings, including, where necessary, waiver of consent.
- To give ethics committees direct access to EudraCT and EudraVigilance databases.
- To reinforce the role of ethics committees, e.g. by entitling them to suspend a clinical trial temporarily, for example whilst awaiting clarification on a safety or inspection issue.
- Establish provisions to ensure the applicability of ICH GCP requirements to ethics committees.
- Reinforce the obligations to ensure the necessary infrastructure and resources are available to ethics committees.

3.5. Safety reporting in clinical trials

The topic of safety reporting in clinical trials was one of the most intensely discussed of the day, by all stakeholders. This issue was referred to in almost all presentations and was extensively debated during the discussions.

Directive 2001/20/EC has brought a welcome and potentially coherent set of definitions and requirements, and has opened the way to electronic reporting of SUSARs. Beneficial elements include:

definitions of adverse reactions and of SUSARs

annual safety reports

use of EudraVigilance

use of international birth date for annual safety reports once the product has received a marketing authorisation somewhere in the world

common EU guidelines on adverse reaction reporting (expedited and annual).

The provisions for reporting timelines, electronic reporting and the EudraVigilance database were regarded as positive contributions of the Directive, although the lack of harmonised implementation of these rules across the Member States remains a major problem. Although the Directive defines the responsibilities regarding transmission of safety information to the NCAs, ethics committees and investigators, there are still too many different interpretations made by Member States of some safety definitions and reporting requirements.

Non-commercial sponsors stated that the current system of safety-information collection, reporting and review is unnecessarily complex, especially for multinational trials, and this results in a great administrative and bureaucratic burden for both the sender and the receiver, without a commensurate contribution to improving study-subject safety.

Commercial sponsors considered the safety guidelines on reporting to investigators involved in the clinical trials ineffective, as these are applied differently by Member States and vary at national level from the expedited submission of all safety reports to generation of country-specific periodic listings of selected cases. The situation is similar across the