No compensation for injured trial participants in USA?

Unlike in Europe where Directive 2001/20/EC requires trial sponsors to provide adequate insurance for investigators and participants in clinical trials, no such provision is required in the USA. Nevertheless, many US sponsors do provide insurance and there have been recent calls for a national requirement. Read more on page 2.

FDA to modernise clinical trial regulation and bioresearch monitoring

The FDA has released a series of new policy and regulatory publications to strengthen the oversight and protection of patients in clinical trials and the integrity of the resulting data. The Human Subject Protection and Bioresarch Monitoring (HSP/BIMO) Initiative, announced on 26 June 2006, is being introduced under the auspices of the Critical Path Initiative. It is part of a programme by the Department of Health and Human Services to use recent advances in basic science – including genomics and molecular analysis – to bring about the more effective development and review of therapies, and to enable increasingly targeted and individualised care for patients. More details on page 3.

Sixth TGN1412 volunteer leaves hospital

The last of the volunteers who suffered serious adverse reactions in the Phase I study of TeGenero’s monoclonal antibody TGN1412 has now left hospital. Some of the medical team treating the volunteer are amazed that he survived the ordeal. Despite leaving hospital, the volunteer has suffered permanent damage and will return to hospital for surgery to remove several toes and parts of his fingers.

Russian GCP now in force

The National Standard of the Russian Federation relating to GCP has now entered into force. The Russian GCP guidelines were prepared by the Association of International Pharmaceutical Manufacturers, the International Conference of Consumer Associations and the Russian Academy of Medical Sciences. The guidelines, which were approved by Order No. 232 of the Federal Agency of Technical Regulation and Metrology on 27 September 2005, were implemented on 1 April 2006 and are identical to the ICH Consolidated Guideline for Good Clinical Practice (ICH E6).

Impact of EU Directive 2001/20/EC in Central and Eastern Europe

Transposition of EU Directive 2001/20/EC in the Central and Eastern Europe (CEE) accession countries began long before they joined the EU, and also before Detailed Guidance documents were available to clarify what was required. The new CEE Member States have now implemented the key principles of the Directive, but harmonisation of provisions has not yet been achieved across the region. Full story on page 4.

Pharmacovigilance regulatory obligations and inspections in Europe

A draft guideline released by the European Commission for consultation, covering the monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections, is summarised in this issue. See page 5.

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No compensation for injured research subjects in the USA?

In Europe, Directive 2001/20/EC requires trial sponsors to provide adequate insurance for investigators and research participants. However, no such provision is required in the USA.

Sponsors of trials in the USA are not required to provide either free medical care or compensation to participants in clinical trials, although some actually do. The subject has recently been debated by Dr Robert Steinbrook in the New England Journal of Medicine.

Whilst participation in clinical trials always carries some risk, injuries may result from the research procedure, from the medication or device being tested, or from an investigator’s failure to follow the protocol or to perform the procedures correctly.

Dr Steinbrook states, “One view is that sponsors and institutions are obligated to compensate injured subjects, particularly in trials with commercial sponsors and regardless of who may be to blame or whether the participants were paid. The contrary view is that routine compensation is not required because subjects are made aware of the risks through the informed-consent process, understand them, and voluntarily agree to participate”.

He claims that “it may be difficult to determine whether a medical problem is related to participation in a clinical trial, particularly if it develops months or years later or if a subject has other risk factors. The costs of providing compensation include the need to adjudicate claims and resolve disagreements. Plans with broad coverage are more costly and difficult to administer than those that are limited to covering direct medical costs”.

The US Department of Health and Human Services (DHHS) requires potential subjects to be told whether any compensation or medical treatments are available if injury occurs. Dr Steinbrook claims that a recent study commissioned by the DHHS found that most research institutions do not have policies that provide free care or compensation to injured participants. The authors of the study reviewed 129 policies at 102 academic medical centers and found that there was no institution or sponsor offering to compensate for lost wages or pain and suffering, that only 21 policies (16.3 percent) involved providing free care or treatment, and that health insurance serves as the primary vehicle for compensation of such injuries in the United States. The extent of coverage for research injuries may vary among health insurance policies.

A number of institutions in the USA, eg. the Institute of Medicine, have called for organisations conducting research to compensate subjects who are injured as a direct result of participating in research, regardless of fault. Surprising as it may seem, in the USA there is no national policy relating to compensation for research subjects who are injured in trials. In the wake of recent problems involving injury to trial subjects, further consideration of this matter may be required.


New arrangements for the ethics committee review of device studies

Following consultation between representatives of the device industry and the UK’s Medicines and Healthcare products Regulatory Agency, new arrangements have been introduced for the ethical review of medical device research in the UK. The COREC Central Allocation System (<www.corec.org.uk>) now recommends allocation to one of 11 National Health Service research ethics committees that have been identified as having relevant experience in reviewing device research. These arrangements apply to clinical investigations of devices, performance evaluation of in vitro diagnostic devices and all other research into medical devices.
New FDA initiative aims to modernise clinical trial regulation and bioresearch monitoring

The FDA has released a series of new policy and regulatory publications to strengthen the oversight and protection of patients in clinical trials and the integrity of the resulting data.

The Human Subject Protection and Bioresearch Monitoring (HSP/BIMO) Initiative, announced on 26 June 2006, is being introduced under the auspices of the Critical Path Initiative. It is part of a programme by the Department of Health and Human Services to use recent advances in basic science – including genomics and molecular analysis – to bring about the more effective development and review of therapies, and to enable increasingly targeted and individualised care for patients.

Since the FDA first began inspecting trials in 1977, the agency has progressively established a bioresearch monitoring programme that includes compliance programmes to provide guidance for inspections of investigators, sponsors, contract research organisations, institutional review boards (IRBs) and other facilities. As clinical trials become larger, and with the increasing use of electronic record-keeping and the greater participation of vulnerable subjects, the role of the compliance programmes must expand and evolve. The HSP/BIMO Initiative aims to address this need.

Launch issues

Over the past 18 months, the FDA has carefully assessed its programmes and identified specific issues with which to launch the HSP/BIMO Initiative. As the initiative proceeds, the FDA – with input from stakeholders, including the pharmaceutical industry – will identify more issues, conduct workshops and create other opportunities for public input. Highlights of the projects completed to date include

• Draft Guidance; Process for Handling Referrals to FDA under 21 CFR 50.54; Additional Safeguards for Children in Clinical Investigations, published May 2006
• Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, published March 2006
• Information Sheet Guidances for IRBs, Clinical Investigators, and Sponsors, published January 2006.

Ongoing projects include

• modernising adverse event reporting to IRBs to accommodate the major trend towards multicentre trials
• developing a proposed rule on the registration requirements for IRBs
• finalising a rule for foreign clinical studies not conducted under an investigational new drug (IND) application.

Source: <www.fda.gov/bbs/topics/NEWS/2006/NEW01396.html>

Special announcement

Factors affecting clinical trials in Europe

Next quarterly update seminar:
28 September 2006

• Application for ethics committee opinion in the UK: new processes and procedures, and how to avoid deferral (Hugh Davies, Training & Ethics Advisor, COREC, Patient Safety Agency, UK)
• Update on new developments and requirements in Europe
• Ways to enhance subject recruitment – interactive session
• The Good, Bad and the Ugly – the management and quality of clinical trials in CEE countries and India (Lillian Natoff, Nigel Dent)

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Impact of EU Directive 2001/20/EC in Central and Eastern Europe

EU Directive 2001/20/EC has been implemented by national legislation in almost all EU Member States. An informative article in Applied Clinical Trials explores the impact of the Directive on clinical research in the countries of Central and Eastern Europe (CEE) that joined the EU on 1 May 2004.

In the article, Dr Iwona Capala-Szczurko MD PhD explains that transposition of EU Directive 2001/20/EC in the CEE accession countries began long before they joined the EU, and also before Detailed Guidance documents were available to clarify what was required. As a result, some regulations had to be revised ahead of the 1 May 2004 deadline. Today, all the new CEE Member States have implemented the key principles of the Directive. However, harmonisation of provisions has not yet been achieved across the region.

Review process
The new Member States – plus the non-EU member countries Romania, Croatia and Russia – have procedures and the legal framework in place for accepting a single ethics committee (IEC) opinion for all sites in a multicentre study. However, in some countries this single opinion has been added to the opinions previously required of local IECs.

Having parallel review by the competent authority (CA) and IEC(s), as well as timelines imposed by law, has made the 60-day review timeline realistic in all new CEE Member States, although in Hungary – where the CA acts as a go-between for the sponsor and central IEC – the submission is made to the CA only.

Differences still exist in the regulatory process for trial authorisation, not only with respect to the application process and the attachments required but also – more importantly – in the CA's view of its own role, responsibilities and power. Some CAs focus on a scientific review of the study concept, while others concentrate on the investigational medicinal product (IMP). Nevertheless, the majority of CAs perceive their role as purely administrative, which results in either a smooth, predictable CA review process (in most cases) or a lengthy, unpredictable one. In Poland, the CA has now introduced an additional layer of bureaucracy that adds little to subject safety, requesting originals or notarised copies of certain documents.

There is no common understanding and approach across CEE to terms in the Directive such as substantial amendment or implicit approval. In Poland – where implicit CA authorisation is legally binding (in line with the Directive) – the CA considers that even a minor question during the review process (not in itself a reason for refusal, according to the Directive) transforms the application into an exceptionally complex case, and that such cases require explicit written authorisation even if 60 days have passed after valid submission.

In many CEE countries, implicit approval is not allowed at all.

The results of a survey in the first 10 months following accession revealed that most major sponsors had an optimistic view of approval times in post-Directive CEE: in most countries ethical review took far less than 60 days and CA review 30–60 days. However, in Poland CA approval timelines went from approximately 40 days pre-Directive to approximately 75 days post-Directive.

IMPs
In most CEE EU Member States, an IMP import permit is issued following CA approval of a specific study. The article describes how the procedure for obtaining the import permit and its definition differ across the region. The EU Directive regulates who should be in charge of IMPs in a Member State and requires that this body holds an authorisation for...
IMP manufacture or importation. Legal frameworks and procedures for obtaining authorisation have been implemented in most new CEE Member States, but requirements differ from country to country.

**Insurance**
Clinical trial insurance is mandatory in all CEE countries but country-specific requirements exist, eg. who is insured, the type of insurance policy, policy terms and the place of issue.

**Safety reporting**
In most new CEE EU Member States and in Romania, Bulgaria and Croatia, there is a legal obligation for expedited reporting of suspected unexpected serious adverse drug reactions. However, this is the only uniform safety reporting rule across the region: differences exist regarding the scope and timing of reporting and the recipients of safety reports.

In some CEE countries, the law does not specify sponsor or investigator obligations related to reporting adverse events/reactions to the CA/IEC. Elsewhere, regulations are very detailed and describe several reporting scenarios.

CAs have, or should have, an institutional base for processing safety information derived from clinical trials. At the same time, many IECs are overwhelmed by the number, volume and complexity of reports and it may be that reporting requirements are failing to add to subject protection.

**Conclusions**
Implementation of EU Directive 2001/20/EC has so far resulted in only a limited harmonisation of procedures across CEE. In practice, it has increased administrative requirements, with some CAs adopting a more cautious attitude in the post-Directive era. Harmonising and simplifying administrative procedures could be achieved by implementing a single CA approval process across the EU. This might also eliminate some of the repetitive paperwork that risks obscuring the patient in the clinical trial process.

Dr Capala-Szczurko believes that the transition difficulties have not detracted from the merits of conducting research in the CEE region, ie. high-quality data and rapid patient recruitment. Moreover, regulators, IECs, legislators, sponsors and investigators have been involved in lengthy discussion of GCP principles, leading to improved understanding and the potential for better subject protection.

Source: <www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=310809&pageID=1&sk=&date=>

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**Pharmacovigilance obligations in Europe**

A European Commission draft guideline sets out a framework for monitoring compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections.

The guideline sets out a revised framework for monitoring compliance in the context of current pharmaceutical legislation. It describes the information that needs to be provided in a marketing authorisation (MA) application, with respect to the system that the MA Holder (MAH) has in place to ensure its pharmacovigilance obligations are met. Proof that the MAH has access to a qualified person (QP) responsible for pharmacovigilance and is able to notify the relevant bodies about adverse reactions is also required. The guideline applies to any medicinal product, although the inspection process described focuses on centrally authorised products.

**Pharmacovigilance system**
The elements to be included in the description of the pharmacovigilance system are described, most notably the QP responsible for pharmacovigilance.
and the organisations within which pharmacovigilance activities are undertaken. Information is also needed about:

- documented procedures and policies, and locations of pharmacovigilance source documents
- databases used for pharmacovigilance
- links with other organisations, e.g. as a result of co-marketing or outsourcing
- training and quality management systems.

**Monitoring of compliance**

The sections in the guideline on the monitoring of compliance outline the activities of competent authorities with respect to compliance monitoring, including exchange of information in cases of non-compliance. The guideline also covers:

- the activities of QPs responsible for pharmacovigilance
- the availability and accessibility of pharmacovigilance data
- changes in the evaluation of the risk/benefit balance of a product and the implications of failure to notify such changes
- expedited adverse reaction reporting, including procedures that might follow submission of reports judged to be of poor quality
- periodic safety update reports
- requests for information from competent authorities
- submission of safety variations
- agency commitments in respect of centrally authorised products
- post-authorisation safety studies.

**Pharmacovigilance inspections**

The results of pharmacovigilance inspections will be provided to the inspected MAH, who will also be given the opportunity to comment on any findings. Results will be used to help MAHs improve compliance and may form the basis for enforcement action. The new guideline outlines:

- the difference between routine and targeted inspections and the reasons why targeted inspections may arise
- the timing of inspections
- pharmacovigilance system and product-specific inspections
- requesting and reporting of inspections
- inspections of other parties involved in pharmacovigilance on behalf of or in conjunction with the MAH
- inspections in third countries
- inspection fees
- procedures for pharmacovigilance inspection, including coordination for centrally authorised products
- unannounced inspection
- inspection reports, sharing of information and follow-up of inspection findings.

**Regulatory action**

Action to be taken by competent authorities in the event of non-compliance with pharmacovigilance obligations will be judged on a case-by-case basis, but may include:

- education and facilitation, such as advice on how non-compliance can be remedied
- the inspection of non-compliant MAHs to determine the extent of the problem and re-inspection to ensure compliance is achieved
- the issue of a formal warning reminding MAHs of their obligations
- public release of a list of MAHs found to be seriously or persistently non-compliant
- urgent safety restrictions
- variation, suspension or revocation of the marketing authorisation.


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Uptake of electronic patient-reported outcomes: challenges ahead

As reported recently in the newsletter, the FDA has released draft guidance on patient-reported outcomes that applies both to paper and electronic diaries (eDiaries). eDiary vendors now expect to see a rapid transition from paper to eDiaries, with eDiaries accounting for 25–40% of patient diaries in clinical trials in the next year, according to CenterWatch.

In the past 5 years, more than 280,000 subjects have used eDiaries in 500 trials at more than 20,000 sites worldwide. Over the past 2 years, eDiary vendors have seen a shift from scepticism about the technology to an acceptance that eDiaries provide benefits not seen in paper projects. A growing number of studies have found that eDiaries help to make self-reported patient data more reliable, with higher compliance rates and lower error rates than their paper counterparts. Other changes to the market environment include

- the growing use of eDiaries in studies where patient diaries would not previously have been used
- increased willingness on the part of contract research organisations to work with niche electronic providers
- the approval by the FDA of four drugs where clinical trials were conducted using eDiaries
- the creation by eDiary companies of partnerships with electronic data capture vendors, in order to offer sponsors more complete electronic services
- technological improvements in handheld eDiaries alongside the development of devices with longer battery life and larger screens, making eDiaries easier to use
- the development of new features allowing handheld eDiaries to record information that paper diaries cannot capture (e.g. how a drug affects a subject by testing reaction time).

As the pharmaceutical industry scales up its eDiary use, vendors face a number of challenges, such as demonstrating that they can maintain the desired level of performance despite being in a rapidly growing business environment. Similarly, like all those involved in study start-up, eDiary vendors will have to cope with pressure from the industry to reduce the time needed to get a study up and running. Finally, regulators will demand that clinical study assessments – such as patient questionnaires – are optimised and validated for the electronic platform.

Source: CenterWatch, March 2006, Vol 3, No 3, p 1, 10–15

Consultation on the implementation of UK REC changes

In the UK, the consultation on the implementation plan for the recommendations of the Report of the Ad Hoc Advisory Group on the Operation of NHS Research Ethics Committees concluded on 21 April 2006. The National Patient Safety Agency’s (NPSA) Central Office for Research Ethics Committees (COREC) announced on 19 June that they ‘have reviewed the comments received and the subsequently revised plan was discussed and agreed by the NPSA’s Change Advisory Group and the NPSA Board. The implementation plan has now been formally submitted to the Department of Health (DH). Once comments are received from the DH, the agreed implementation plan will be disseminated and will also be available online on this website [www.corec.org.uk/recs/index.htm]. The timescale for this is not yet available.

Dr Hugh Davies will be speaking about the changes to the UK ethics system at Brookwood International Academy’s quarterly update seminar on 28 September. For more information, visit www.brookwoodacademy.org.

Corautus gene therapy trial placed on clinical hold

Clinical Trials Advisor (15 June 2006) has reported that ‘the FDA has placed a rare clinical hold on a trial of gene therapy products after the sponsor, Atlanta-based Corautus Genetics, reported three serious adverse events within 10 days’. It went on to report that, ‘Corautus Genetics announced that it hopes to be able to continue trials. The sponsor believes that the events are not related to therapy. It has filed a response to the FDA and went on to report that, “Corautus Genetics announced that it hopes to be able to continue trials. The sponsor believes that the events are not related to therapy. It has filed a response to the FDA and

Task force on ‘higher risk’ research

In the wake of the adverse events of the Phase I TGN1412 study, a joint taskforce has been set up by the BioIndustry Association (BIA) and the Association of the British Pharmaceutical Industry (ABPI). Its aim is to provide industry input to the expert working group set up to learn from the incident. The BIA/ABPI industry taskforce – co-chaired by Dr David Chiswell and Sir Colin Dollery – comprises bioscience and pharmaceutical industry experts in fields such as immunology, biopharmaceutical development and clinical trials.
The ABPI states that the taskforce will offer input in the areas to be considered by Professor Gordon Duff’s expert group, which is reviewing early-stage clinical trial design with specific reference to:

- biological medicines with novel molecules of action
- new agents with a highly species-specific action
- new drugs directed towards immune-system targets.

Dr Richard Barker, Director General of the ABPI, comments: “Safety is at the forefront of all that we do, and it is imperative to examine carefully every aspect of the clinical development of ground-breaking medicines that work in a novel way related to that at the centre of this incident. We must do everything possible to prevent such an event ever again occurring without unnecessarily complicating a well-established procedure for testing the broad range of new medicines.”

Aisling Burnand, Chief Executive of the BIA, states: “As a responsible industry, we have brought together this group of world-class individuals with significant experience in the clinical development of innovative medicines. We look forward to sharing this expertise with Professor Duff and his group to ensure the highest possible standards of patient and volunteer safety.”

**Phase I trials under precautionary measures**

The UK Medicines and Healthcare products Regulatory Agency (MHRA) has announced that, as an interim measure, it will take a precautionary approach for all further clinical trial applications involving first-in-man trials of any monoclonal antibody (regardless of intended target) or other novel molecules targeting the immune system, acting via a novel mechanism. Such trials will not be authorised without additional expert opinion on whether the effects seen in the TGN1412 case may be repeated in relation to these substances. The Commission on Human Medicine (CHM) will carry out a preliminary review of the proposed trial prior to authorisation, taking into account the expert advice. The MHRA Clinical Trials Unit will write to the sponsor following CHM review.

COREC has also introduced new measures for those applying for ethics committee opinion in the UK. In response to Question 2a of the standard application form, applicants should indicate whether the proposed trial falls into one of the three ‘at risk’ categories. If so, the application for ethical review should include a covering letter explaining what discussion has taken place with the MHRA and – if applicable – how the protocol has been revised in line with CHM advice. A copy of the correspondence with the MHRA should be enclosed. If such discussion has not yet taken place, or is still underway, the applicant is requested not to submit the application for ethical review at this point.