CQAdvisor

A NEWSLETTER FOR THOSE WHO CARE ABOUT THE QUALITY OF CLINICAL TRIALS

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New UK clinical trial regulations 2006

The UK's clinical trial regulations have been amended. The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 were finalised on 13 July 2006 and laid before Parliament on 20 July. The new regulations will enter into force on 29 August 2006. As well as incorporating EU Directive 2005/28/EC into UK law, the new regulations introduce some controversial requirements, including the need for the sponsor to report serious breaches of GCP to the governing body. Prior to finalisation of the changes, the Medicines and Healthcare products Regulatory Agency (MHRA) ran a consultation exercise on the proposed revisions to the 2004 regulations between 15 November 2005 and 7 February 2006. The feedback received asked mainly for clarification on the following: additional guidance on the retention time for ethics committees' documents; the definition of a serious breach of GCP that has to be reported to the MHRA; specific modalities that will apply to non-commercial trials; the format and content of the investigator's brochure; and the content of the trial master file.

The MHRA has produced a useful Annex that outlines the concerns raised as well as its responses. This is available on the website <www.mhra.gov.uk>. The new regulations will be reviewed in the next issue of the newsletter.

FDA meetings on the up

The growing number of meetings between the FDA and sponsors should support drug development objectives, but there are concerns about whether the agency can cope with the demands being placed upon it. More details on page 6 ▶

Excessive payments to investigators uncovered

A case of overly high payments to a doctor performing post-authorisation studies has been uncovered in Sweden. The sponsor involved has been forced to review the size of its payments to investigators evaluating a psoriasis drug. In a separate case in the USA, a National Institute of Mental Health official has been investigated after allegedly receiving payments as consultancy and lecture fees from a major pharmaceutical company.

The Swedish doctor in the psoriasis study had managed to find 60 patients to evaluate, whereas other centres had found it hard to recruit subjects at all. The case was reported to the Swedish National Anti-Corruption Unit, which began preliminary enquiries into bribery. Full story on page 2 ▶

Pan American Health Organization releases draft GCP guidelines

Most of the countries in the Americas are not part of the three ICH regions. However, the Pan American Health Organization (PAHO) is committed to ensuring that clinical trials in its region follow strict ethical and scientific principles to safeguard trial subjects, consistent with the Declaration of Helsinki. To facilitate this aim, draft GCP guidelines for the region have recently been issued. "Good Clinical Practices: Document of the Americas" has been developed by a Working Party comprising representatives from South and Latin American countries; the USA was also represented, by former FDA officials David LePay and Stan Woollen. Report on page 3 ▶

New guidelines to improve the conduct of early-stage trials

Giving one subject a single dose of a new product of the first day of a study is one of the recommendations of a report published by a taskforce set up by the Association of the British Pharmaceutical Industry (ABPI) and the BioIndustry Association (BIA). See page 5 ▶

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Overpayments to investigators exposed in Sweden

A pharmaceutical company has allegedly paid unreasonably large remunerations to doctors evaluating a new psoriasis medication. The company has been forced to review its strategy after an investigation upheld the claims.

A doctor in Sweden is said to have received 2.4 million kronor (over US$ 300,000) after he treated and evaluated 60 patients with a psoriasis product in a 2-year period. The sponsor and doctor have been investigated by the Swedish National Anti-Corruption Unit.

The Pharmaceutical Supervisory Committee (Läkemedels Förmånsnämnden) requires marketing authorisation holders (sponsors) to perform post-authorisation studies. The sponsor had planned to follow up 300 patients in Sweden and Demark, but there was a low degree of interest in taking part, especially at university clinics.

However, one doctor in Halmstad, Sweden, prescribed the treatment to 60 patients, far more than anyone else. During 2005 and the first quarter of 2006, these patients accounted for almost half of all prescriptions for the product in Sweden.

Unreasonable rise in costs

According to the Swedish newspaper *Sydsvenskan* (27 July 2006), the Head of Pharmaceuticals at Halland County Council began to suspect a problem when the costs for the new medication rose unreasonably. When this was traced to a single doctor, he raised the alarm. The case was then reported to the National Anti-Corruption Unit, which began investigations into bribery. Sweden's Rural and District Council and Pharmaceutical Industry Association (Lif) guidelines suggest that doctors should be remunerated at 1000 – 1500 kronor per hour. In the case under review, it was reported that the sponsor offered the doctors prepared to evaluate the product a sum of 20,000 kronor for every patient included in the study. They were to receive a similar amount when the evaluation was completed after 2 years' of treatment. This was considered to be unreasonable by Lif's ethical committee. The same sponsor has already received a fine for overpayments to doctors.

In the news report, Lif's managing director Richard Bergström said, "The problems we have to address are partly that the sums paid to doctors must be reasonable, and partly that the studies themselves should not lead to an unreasonable increase in the use of the medication concerned. Scientific studies should not be seen as a way of marketing a particular medication by the back door".

The Halmstad doctor has been stopped from including so many patients in his study in order to avoid a skewed distribution among the patients. In addition, the sponsor's target of 300 patients for evaluation has been reduced to about 200. The remuneration to the participating doctors has been cut to a total of 25,000 kronor per patient, after agreement by the sponsor – following an accurate calculation of how much time doctors need to spend on the evaluation – that its initial payment "wasn't quite right".

Other news reports suggest that the same sponsor may be under investigation for similar incidents in other Member States, including the UK.

US official under investigation

In another example of financial exposure, a report in *Clinical Trials Advisor* (29 June 2006) alleges that the chief of the geriatric psychiatry branch at the US National Institute of Mental Health (NIMH) is being investigated. It is said that he received over US$ 500,000 in consultancy fees, lecture fees and honoraria from a major pharmaceutical company. A congressional investigation is underway. The company's activities had been made open, and were acknowledged in papers and speeches; however, appropriate clearances should have been in place. Conflicts of interest are a major issue in the USA. Some believe that this case violates the fundamental principle that the public interest must be separated from private gain, and specifically that the NIH must be "a Camelot of ethical purity".

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Draft GCP guidelines published for Pan American region

The Pan American Health Organization (PAHO) recognises the need for harmonised standards within its Member States to safeguard subjects involved in clinical research. Draft GCP guidelines for this region have therefore been issued.

PAHO (<www.paho.org/>) is an international public health agency working to improve health and living standards in the countries of the Americas. It is also the Regional Office for the Americas of the World Health Organization (WHO) and represents the Member States listed in *Table 1.*

Among its publications, PAHO has issued an undated (and no version number) document entitled "Good Clinical Practices: Document of the Americas", which acknowledges the need for national and international standards to guarantee the scientific and ethical soundness of clinical pharmacology research. It states that guidelines should be established to guarantee that study data are adequately stored and that they can be confirmed, regardless of where the study is conducted. The document goes on to outline how the ICH Guidelines for GCP came into being.

Despite most of the countries in the Americas not being part of the three ICH regions, PAHO is committed to ensuring that clinical trials in its region follow strict ethical and scientific principles to safeguard the physical and mental integrity of the subjects involved, consistent with the Declaration of Helsinki. The document notes that the number of patients involved in clinical trials in the region has increased in the past decade and that harmonised criteria for GCP in the Americas are crucial. The document was therefore drafted to propose guidelines for GCP that can serve as a foundation for regulatory agencies, and be used by investigators, ethics committees (IECs), universities and businesses in the PAHO region.

Supporting information

The content of the main body of the PAHO GCP guidelines closely follows that of the ICH GCP guidelines. However, there are notable additions within the supporting Annexes, which are summarised below.

Given that PAHO is a regional office for WHO, it is not surprising that Annex 1 – 'Operational Guidelines For Ethics Committees That Review Biomedical Research' – references two WHO publications:

- Operational Guidelines for Ethics Committees That Review Biomedical Research – <www.who.int/tdr/publications/publications/pdf/ethics.pdf>
- Surveying and Evaluating Ethical Review Practices: a complementary guideline to the Operational Guidelines for Ethics Committees That Review Biomedical Research –

Table 1. *PAHO Member States.*

Antigua and Barbuda	Colombia	Guyana	Saint Lucia
Argentina	Costa Rica	Haiti	St Kitts and Nevi
Bahamas	Cuba	Honduras	St Vincent and the Grenadines
Barbados	Dominica	Jamaica	Suriname
Belize	Dominican Republic	Mexico	Trinidad and Tobago
Bolivi	Ecuador	Nicaragua	Uruguay
Brazil	El Salvador	Panama	USA
Canada	Grenada	Paraguay	Venezuela
Chile	Guatemala	Peru	

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<www.who.int/tdr/publications/publications/pdf/ethics2.pdf>.

Annex 2 includes a self-evaluation questionnaire for IECs, which may be useful when defining the procedures of a new IEC or reviewing those of an existing IEC. The checklist can also be used to verify compliance with written procedures in the following areas:

- institutional authorisation for the establishment of the IEC
- definition of the purpose(s) of the IEC
- the principles that govern the IEC in assuring the protection of research patients
- the authority of the IEC
- the IEC's relationship to other parties
- IEC membership, management, functions, operations and documentation/record requirements
- information the investigator provides to the IEC
- emergency research consent exception.

Annex 3 provides operational guidelines and help on preparing the Model Informed Consent (MIC) (the informed consent document for the subject and the model consent for signature), as well as guidelines for the responsible clinical investigator and research team on how to obtain consent. Advice on preparing the MIC is consistent with that given in the ICH regions, but is written in a readable and accessible way and is supplemented by a useful checklist of the requirements for the informed consent document and the informed consent form.

Annex 4 is a guide for inspectors and regulatory authorities on planning, conducting and reporting clinical investigator inspections. It addresses planning the inspection, the selection of studies, the identification of inspectors, and preparing for, scheduling, conducting and concluding the inspection.

Source: <www.paho.org/english/ad/ths/ev/GCP-Eng-doct.pdf>

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Guidelines released to improve the conduct of early-stage trials

Give one subject a single dose of a new product of the first day of a study, recommends a report published by a taskforce set up by the Association of the British Pharmaceutical Industry (ABPI) and the BioIndustry Association (BIA).

The ABPI/BIA taskforce was established to provide industry input to Professor Gordon Duff's expert working group set up to learn from the adverse events of the TGN1412 Phase I trial in March 2006. Following the taskforce's deliberations, a report was published on the ABPI website on 24 July 2006, outlining recommendations to enhance and clarify the existing guidelines governing the testing of new medicines in humans.

The ABPI/BIA taskforce has highlighted aspects of those guidelines that are particularly important for the very small proportion of clinical trials in which novel agents stimulating the immune system are given to humans for the first time. Within this arena, recommendations cover the whole range of the Phase I development sequence, from comments and advice on the compound's mechanism of action and biological activity, through to the education and training of those involved in safety assessment.

The taskforce's recommendations, which are based on existing best practice within the industry, have been submitted to the scientific expert group chaired by Professor Gordon Duff that is reviewing early-stage clinical trials. Membership of the expert working group comprises bioscience and pharmaceutical industry experts in fields such as immunology, biopharmaceutical development and clinical trials.

The ABPI/BIA taskforce's recommendations include

- use of an alternative initial dose-setting assessment for certain novel agents
- giving only one subject the active medicine on the first day
- following this with 'staggered dosing' as doses are increased
- conducting such studies at a hospital with intensive care facilities
- providing all investigators with appropriate training in such studies
- giving particular emphasis to manufacturing controls to ensure safety, quality and efficacy of the finished product.

'Points to consider'

The ABPI press release includes quotes from key personnel. "As a responsible industry, we were shocked and want to ensure a similar event never occurs again, and that is why we have developed these 'points to consider' for first-in-human clinical studies," said Dr David Chiswell, Co-Chairman of the taskforce. "In order to safeguard patient safety, we want to make the guidelines available to the research-based industry and – if either the UK or the European regulatory bodies find this useful – to help develop them into a more formal set of 'points to consider'."

The taskforce carefully examined existing regulatory guidance for biopharmaceuticals. Co-Chairman Sir Colin Dollery commented: "On the one hand, it was clear that there are no major safety-related issues not addressed in the existing guidance – as demonstrated by the fact that there have been tens of thousands of such trials without any major incident. However, it was also clear that the specific wording of certain points could be clarified and that some may need greater emphasis, primarily in relation to novel biological agents or medicines based on a novel way of working. Decisions about the first administration to man of agents that stimulate the immune system need especially careful scrutiny."

FDA meetings on the up

The growing number of meetings between the FDA and sponsors should support drug development objectives, but there are concerns about whether the agency can cope with the demands being placed upon it.

As drug development has become more complex, sponsors have sought to meet earlier and more often with the FDA to ensure that their protocols meet agency requirements and that trial data will support product approval. An article in *Applied Clinical Trials* outlines when the FDA routinely meets with sponsors and how this might change in the future.

The Prescription Drug User Fee Act of 2002 encourages early and frequent communication between the FDA and sponsors. It sets timeframes for the FDA in which to respond to sponsor requests and schedule meetings at set milestones in the development process:

- the pre-investigational new drug application meeting to assess whether preclinical safety data support first studies in man and that the initial protocol appears sound
- the end-of-Phase II (EOP2) meeting to discuss whether the Phase III plan is likely to demonstrate effectiveness, test appropriate populations and address safety concerns
- the pre-new drug application meeting to review the data that the FDA will expect in the marketing application and whether the sponsor has addressed concerns raised earlier.

Other meetings might take place at the end of Phase I to assess the clinical testing of fast-track products or unique therapies or after filing. Furthermore, the FDA usually meets with sponsors to negotiate final product labelling.

All in all, FDA drug review divisions hold an average of nine meetings each day, with each session requiring 200–500 FDA staff hours for preparation.

Uniform standards

The FDA clearly wants all meeting sessions to be productive and to support efficient drug development and approval. Its Office of New Drugs (OND) is therefore undertaking the clarification and standardisation of how the FDA review divisions handle meeting requests, internal pre-meeting discussions and subsequent communication with sponsors. Currently, OND review offices follow varying policies for sharing information with sponsors on internal deliberations, with some offices allowing sponsors to review draft meeting minutes, while others are less keen.

To gain more uniformity, OND is developing a guidance on Good Meeting Management Practices, which aims to clarify

- procedures for FDA reviewers to schedule and prepare for internal pre-meetings, including checklists of topics for different disciplines to address at milestone meetings
- timeframes for reviewers in which to respond to a sponsor's preliminary questions ahead of a scheduled meeting. This should focus the meeting on the most critical issues and allow FDA staff to resolve some easier issues in advance, in order to reduce a meeting's agenda
- who at the FDA chairs a meeting, who should attend and the process for setting the agenda
- the issues to cover in a meeting wrap-up session, to identify any remaining areas of confusion
- the FDA responsibility for preparing official meeting minutes, with opportunities for sponsors to review draft minutes to ensure understanding and agreement.

More meetings

The volume of meetings could increase further if the FDA implements recommendations from a report on its First Cycle Review Performance (<www.fda.gov/OHRMS/DOCKETS/98fr/OC05257-

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rpt0001.pdf>). The report examines the factors that allow the FDA to approve a new molecular entity in one rather than multiple review cycles; it concludes that more, early agency–sponsor meetings make a difference in the production of quality applications that do not require more information later from the sponsor. Thus, the analysts

- suggest adding a mid-Phase III meeting when it is still possible to alter studies to address any inadequacies
- encourage the development of checklists to guide meetings for each therapeutic category
- urge more follow-up to meetings based on the review of minutes.

Source: <www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=316471>

Notice board

- **British Association for Research Quality Assurance (BARQA) Annual Conference**
  1–3 November 2006, Royal Bath Hotel, Bournemouth

BARQA Professional Development Courses

- **Monitoring Clinical Laboratories**
  7 September 2006, Heathrow
- **Good Laboratory Practice for Study Directors, Principal Investigators, Study Staff & Management**
  12–13 September 2006 and 28–29 November 2006, Cambridge
- **Good Pharmacovigilance Practice**
  19–20 September 2006, Wyboston Lakes, Bedfordshire
- **Good Clinical Practice Auditing – Principles & Practice**
  25–27 September 2006, Cambridge
- **Implementing Good Clinical Laboratory Practice (GCLP)**
  4–5 October 2006, Cambridge
- **Process Mapping as a Management and Auditing Tool**
  5–6 December 2006, Cambridge

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News *in brief*

WHO Director-General

Dr Lee Jong-wook, Director-General of the World Health Organization, died suddenly on 22 May in a Geneva hospital. United Nations Secretary General Kofi Annan said, "The world has lost a great man today". Until new elections are held, Dr Anders Nordstrom, WHO's Assistant Director-General for General Management, will serve as acting head of the organisation.

WHO initiative to harmonise registration of clinical trials

WHO has announced the development of a Registry Platform designed to standardise the information on clinical trials publicised on the Internet. The Platform is not a registry itself, but will identify a set of standards to which all registries should adhere. Currently there is little coordination among the many registries on clinical trials to be found globally. The Registry Platform seeks to bring participating registers together in a global network, to provide a single point of access to the information they hold.

A web-based search portal will be launched later this year where stakeholders, including patients wishing to enrol in a clinical study, can search among participating registers for clinical trials taking place or completed throughout the world.

The Registry Platform will assign a Universal Trial Reference Number (UTRN) to prevent confusion over those clinical trials that are currently to be found on more than one registry; investigators and sponsors will be encouraged to register their studies on only one participating registry.

Registries participating in the scheme will be members of a Network of Registers, and would qualify according to criteria adopted by the International Committee of Medical Journal Editors (ICMJE), a group representing 11 prestigious medical journals. Other registries could establish agreements with Member Registers to coordinate trial registration.

WHO feels that it is best suited for initiating such a scheme since it is a global, neutral, independent organisation with convening capacity. The organisation has worked with stakeholders – including the pharmaceutical and biotechnology sectors – in developing the Platform, and will continue to do so until the search portal is launched. The timing of disclosure of information about clinical trials, especially early-phase trials, has been a discussion point of particular interest to sponsors and investigators, who believe that early disclosure may infringe their intellectual property rights. More information can be found at <www.who.int/ictrp/en>.

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R&D productivity doldrums

According to the Tufts Center for the Study of Drug Development (CSDD), big pharma may finally be turning the corner in their efforts to improve R&D success. Tufts found that top US pharmaceutical companies have increased the number of new clinical trials by more than 50% since 2002 and it believes that this could herald a resurgence in R&D productivity. During the period 2003–2005, the rate at which the 10 top US drug companies initiated clinical trials for new drug candidates rose by 52%, following a 21% decline from 1993–1997 to 1998–2002. Time will tell if this revival will be sustained and whether a reduction in late-stage development terminations will ultimately boost overall clinical success rates (ie. the share of investigational new compounds entering clinical testing that eventually receive marketing approval from the FDA). The results of this analysis are reported in the May/June *Tufts CSDD Impact Report.*

Source: <http://csdd.tufts.edu/NewsEvents/>

Reducing time and costs

The Tufts Center for the Study of Drug Development (CSDD) believes that new approaches to assessing drug safety could lead to dramatic improvements in drug development efficiency, ie. getting more new medicines to market and reducing the time it takes to get them there. A *Tufts CSDD R&D Management Report* published on 24 April 2006 suggests that more flexible approaches to clinical trials, utilising real-time data collection and analysis, will help to shorten the long and costly clinical development phase. According to Tufts, the average clinical phase time for new drugs receiving market approval in the USA in the period 2002–2004 was 7.0 years. While slightly faster than the average of 7.2 years for the period 1993–1995, total development time has, in general, lengthened steadily since the mid-1990s. In addition, average clinical development costs currently represent 58% of total development costs, compared with 32% for products developed in the 1980s. The panel suggested that as the pharmaceutical industry evolves its R&D practices, the safety function will resemble the way organisations address efficacy. Panellists suggested that safety will need to have dedicated project management and informatics support, which will develop statistics for deriving the probability of toxicity on a real-time basis. Instead of being a separate department within research organisations, as is often the case today, drug safety evaluation needs to be integrated seamlessly across all phases of drug development and commercialisation. Tufts CSDD claims that, "Lowering late-stage attrition requires developers to collect higher quality safety data and speed the communication of those data to the right people within the organization, so that a decision can be made as early as possible in the development program whether or not to terminate the project."

Source: <http://csdd.tufts.edu/NewsEvents/>

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FDA Warning Letters
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Websites regularly reviewed includes:

DG Enterprise, EFPIA, EMEA, FDA, ICH, IFPMA, MHRA, WHO

Aims & Scope:

- to publish news and information about the results of GCP audits and inspections in the ICH regions
- to provide news, views and opinions about ICH GCP implementation
- to provide answers to readers' CQA questions and the views of inspectors
- to summarise and make readers aware of relevant articles and information in other publications, press releases and information on the Internet
- to provide information about meetings, conferences, training courses and publications.

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