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## Protection of trial subjects in clinical trials

### **Moderators: Dr Ramli Ghani, Malaysia, and Dr Rolf Spang, Switzerland**

Clinical research is developing in terms of sophistication of scientific approach, ethical complexities, number of trial subjects, and multicountry involvement. Given the need for greater numbers of subjects, it may happen that soon much of clinical research will take place in developing country locations. However, research carried out in poor communities, particularly when funded by more affluent sponsors from developed countries, may raise complex ethical and legal questions for participants, regulators and ethics committees. Recently, many countries have either updated their Good Clinical Practice guidelines (GCP) or started more effective implementation of GCP principles. Regulators have an important role to play in protecting trial subjects. This session deals with the regulatory challenges resulting from this shift, and the need for a constantly improving regulatory framework for clinical trial management.

### **Cross-border movement of clinical trial subjects Dr Alar Irs, Estonia**

In 1998-99, a cross-border clinical trial took place involving 135 healthy volunteers recruited and screened in Estonia. The subjects were transported to Switzerland for the early phase of the trial which was carried out by a contract research organization (CRO) and sponsored by several major pharmaceutical companies. The Swiss drug regulatory authorities and an independent ethics committee (IEC) in Switzerland were notified of the studies.

The Estonian State Agency of Medicines (SAM) learned about the study and an inspection was carried out at the premises of the recruitment in Estonia. As a result, the SAM concluded that since the study had begun in Estonia, it should have been approved by an Estonian ethics committee and by SAM. Inspection also revealed that the subjects had not been provided with sufficient patient information, neither in Estonia nor in Switzerland. Consent forms were in English or German, languages that many of the subjects did not understand and monetary compensation had been paid to the subjects for the 1-2 week study equivalent to several months' salary in Estonia. In one case, it emerged that a recruitment doctor had recommended to a patient not to inform the investigators at the CRO of concomitant therapy, although this could undermine the validity of the data. No medical follow-up was provided to the trial subjects.

All activities in Estonia related to the trial were stopped by the inspection and a report was forwarded to the Swiss regulatory authority which conducted further investigations in Switzerland.

The Estonian Medicinal Products Act was subsequently amended by parliament, because it was found that the point of commencement of a clinical trial was not specified in legislation. The Act now states that "Dissemination of information concerning a clinical trial to possible trial subjects or performing of procedures related to the trial is deemed to be the commencement of the clinical trial", thus requiring ethical and SAM approval before the recruitment of subjects can start. This is in line with good clinical practices (GCP).

The following conclusions can be drawn from the above case:

- It remains open whether the benefits of such research justify the risks involved.
- Review of a trial by an ethical committee in a different country to that where recruitment takes place does not comply with international guidelines. Also, such a procedure cannot adequately evaluate the influence of travel and monetary compensation (even if appropriately addressed in the application) on subjects from vulnerable or low income groups.

- It is also difficult to address informed consent procedures and medical follow-up in such “mobile studies”.
- Cooperation between drug regulatory authorities is absolutely vital to ensure the protection of clinical trial subjects and the integrity of data in international pharmaceutical research.

## **Cross-border movement of clinical trial subjects and regulatory communication**

### **Dr Rolf Spang, Switzerland**

Switzerland is located in the heart of Europe and is divided into 26 cantons which each license physicians and establish ethical committees. Before the recent establishment of a federal authority it was the responsibility of the InterCantonal Office for the Control of Medicines to oversee clinical trials and good clinical practices (GCP).

Switzerland keeps a register of all clinical trials and it is the responsibility of the Swiss Agency for Therapeutic Products to consider applications. Sponsors have to submit documents, such as approval by the ethics committee, the study protocol, the investigators’ brochure and the contract between the sponsors and the contract institute.

Since Switzerland has common borders with several EU countries, there are frequent cross-border movements linked to recruitment of subjects for clinical trials. However GCP regulations have not been developed with this particular situation in mind. When the Swiss authority learned of the clinical trial described, certain issues were identified:

- Direct communication and exchange of information between regulatory authorities is needed when overseas recruitment is discovered.
- Consent documents should be written in the local language understandable to the individual subject.
- The trial subjects should be followed up once the trial is finished, in order to safeguard their health.

## Ethical principles and protection of trial subjects in China

### Dr Guowei Sang, China

The State Drug Administration (SDA) was established in 1998, directly under the State Council, to improve the regulation of pharmaceutical products and medical devices, including the regulation of clinical trials and the protection of trial subjects in China.

On 1 December 2001, the newly revised Drug Administration Law was enacted in order to:

- ensure the protection of the rights, safety and welfare of human subjects;
- conform with internationally recognized ethical standards and scientific principles for clinical trials;
- ensure the clinical trial process is standardized and the results are scientific and credible;
- ensure that clinical trials of all drugs, including biotechnology products and traditional Chinese medicines, and in all phases, including human bioavailability or bioequivalence studies, are performed according to Chinese GCP.

Ethics committee approval and informed consent are measures used to ensure the protection of trial subjects.

SDA is responsible for drug administration nationwide. No clinical trials can be conducted unless all the related data have been submitted to the SDA for approval. In China, all clinical trials must follow Chinese GCP. The Department of Drug Registration and the Department of Drug Safety and Inspection are within the structure of the SDA and are jointly responsible for the evaluation and inspection of clinical trials of new drugs. Penalties are imposed for illegal activities in drug research and application.

Since 1992, China has recognized that GCP is an international ethical and scientific standard for the design, conduct, recording and reporting of clinical trials that involve human subjects. An internationally accepted GCP is also important to China, since it

allows participation in international cooperation in medical and pharmaceutical science, technology and trade. Therefore, the Chinese GCP is based on the International Guidelines for Biomedical Research Involving Human Subjects, prepared by the Council of International Organizations in Medical Science and WHO. The Chinese GCP was adopted by the SDA and enacted in September 1999. In 2000, a number of GCP training and teaching activities were organized and related materials published.

While the Drug Administration Law and the Chinese GCP have improved clinical practice in China and led to greater protection of trial subjects' rights, benefits, and safety, special guidelines are needed for clinical trials of biotechnology products and vaccine, taking into account their specific characteristics. It is also strongly recommended that a general training programme be conducted for medical doctors, manufacturers and the public on the ethical principles and protection of subjects in clinical trials, so that clinical trials in China will achieve an internationally recognized standard.

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## Recommendations

1. Drug regulatory authorities have an important role in protecting trial subjects. Drug regulatory authorities are required to keep a complete register of trials carried out in the country and, when possible, these registers should be made public (e.g. through the agency website).
2. When trials are carried out in several countries or where part of a study is carried out in a different country, direct communication between the regulatory authorities of the countries involved should be established. Contact data of responsible people should be available on the agency website.
3. Drug regulatory authorities should pay attention to the informed consent procedure and ensure that complete information is provided to the trial subjects in conformity with international guidelines, in addition to requiring national or local ethical review.

4. WHO should develop guidelines for the effective control of trials by the regulatory authority.

5. WHO should strengthen protection of human trial subjects by developing good clinical practices (GCP) training tools for drug regulatory authorities, promoting training of GCP inspectors, and providing assistance to Member States in setting up GCP inspectorates.

6. Progress should be reported back to the ICDRA.