

## **FREQUENTLY ASKED QUESTIONS**

### **1. What is the purpose of the new Clinical Trials Directive?**

The main aim of the Directive is to simplify and harmonise the administrative provisions governing clinical trials by establishing a clear, transparent procedure and creating conditions conducive to the effective co-ordination of such clinical trials in the European Community by the authorities concerned. This would facilitate the internal market in medicinal products while at the same time maintain appropriate levels of protection for public health. Overall, the Directive aims to provide an environment for conducting clinical research that protects participants without hampering the discovery of new essential medicines.

### **2. What are the UK Regulations?**

The Medicines for Human Use (Clinical Trials) Regulations 2004, is the Statutory Instrument that transposed the EU Clinical trials Directive into UK law in May 2004. Each member state will have their own regulations or administrative provisions transposing the Directive into national law.

### **3. Are all clinical trials covered by the Regulations?**

The Directive and the proposed implementing Regulations cover only investigations/studies which are undertaken to ascertain the efficacy or safety of a medicine in human subjects. Non-interventional trials are excluded from the Regulations. To classify a trial as non-interventional, it must meet all of the following criteria:

- are studies involving products with a marketing authorisation that are prescribed in the usual manner and used in accordance with the authorisation;
- when the patient is assigned to a therapeutic strategy within current practice and not according to a protocol;
- the diagnostic or monitoring procedures are only those ordinarily applied to the therapeutic strategy;
- and epidemiological methods are used to analyse the data.

(See the Regulations for a precise definition.)

If a study is not for the purpose of ascertaining the effects of or reactions to a product and the product is simply being used as an aid or tool in the study, it is not a clinical trial covered by the Regulations. For example, in the case of the study of blood flow involving the infusion of vasoactive substances, if the purpose of the study is to monitor the effects of a particular substance to see if it is effective in achieving a particular physiological effect, then it is not a clinical trial. If the infusion is for the purpose of modifying the rate of flow for a therapeutic indication such as

claudication, it would be deemed a trial under the Directive as the purpose of the study is to establish the efficacy of a particular medicine.

#### **4. What steps are being taken to address the concerns of the publicly funded clinical trials community who fear that the transposition of this Directive could unnecessarily delay or stop trials?**

As well as submitting a very full response to the consultation, the MRC submitted an impact assessment to which CRUK and other funders and trialists contributed. This assessment identified six key issues for the MHRA, Government funders and trialists to address with a view to maintaining the UK's record of success in publicly funded trials. The six areas were:

- i. The single sponsor model
- ii. Excessive monitoring and pharmacovigilance
- iii. Onerous trial and manufacturing authorisation and registration
- iv. Transitional arrangements
- v. Trials in incapacitated adults
- vi. Uncertainty about precise requirements and legal liability

#### **MRC/DH joint project**

THE MRC/DH joint project has explored each of these key issues to clarify how the current arrangements for non-commercial trials will be affected taking into account any flexibilities in the Directives, draft legislation and guidance. The project draws up practical guidance to enable those involved in publicly funded trials to comply with the new regulations and take advantage of those provisions that simplify the commencement and conduct of trials such as use of submission of applications and safety reports.

#### **Authorisation for trials and manufacture**

The transitional arrangements allow nearly all trials with current exemptions to roll over as "clinical trial authorisations" under the new legislation without submitting a new application or paying a fee. The arrangements are available on this and on the MHRA website .

#### **Incapacitated adults**

DH are exploring options for obtaining consent for incapacitated adults to enter a trial, including those eligible for research in emergency situations who may be unconscious. DH consulted on a draft guideline, met with stakeholders to explore the ethical and practical aspects of these situations and is reviewing proposals with lawyers.

## **Guidance on precise requirements and consideration of legal liabilities**

The MHRA have prepared guidance to clarify the precise requirements of the legislation for sponsors and investigators conducting non-commercial trials, including aids such as flow diagrams, algorithms and mock applications completed for different type of product and trial. Lastly, the DH/MRC project group has identified arrangements for sponsoring a trial, please see Sponsorship part of this website.

### **5. I have heard that there is no requirement for a single sponsor under the UK Regulations. What are the Regulatory requirements for sponsorship?**

It was clear from consultation that this a major concern in publicly funded trials. The EU Directive does require a sponsor to take responsibility for the initiation, management and/or financing of a trial. In commercial trials it is normal for the owner of the medicine under investigation to take responsibility for all the sponsor's duties. In publicly funded trials the responsibilities are often distributed among the partners.

The UK Regulations allow a partnership or group between them to take this responsibility. Under this approach, the applicant for a CTA can either accept all of the sponsor's responsibilities or to notify the MHRA that its partners accept responsibility for some functions. Regulation 3 specifies how they can do this.

### **6. The Regulations extend to academically led clinical research. Will this impose burdensome responsibilities on doctors who undertake trials?**

The Council and European Parliament intended the Directive to apply to non-commercial research; the recitals to the Directive specifically mention non-commercial clinical trials conducted by researchers without the participation of the pharmaceutical industry. Moreover those drafting the Directive and Commission guidelines constantly considered the impact on non-commercial research.

The purpose of the legislation is to protect clinical trial participants and to ensure that data generated from trials are accurate and verifiable. These issues are equally important, whether the research is commercially sponsored or publicly funded.

### **7. Do the Regulations apply to all products?**

Not all unlicensed chemical entities administered to patients or healthy volunteers would be considered as investigational medicinal products. The

Regulations would apply only to those that are medicinal products and are to be tested or used as a reference in a clinical trial.

### **8. How are clinical trial volunteers be protected under the Regulations?**

The UK Regulations require that each trial has a sponsor who must obtain authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA) and a favourable opinion of an ethics committee before the trial can commence. This gives assurance that the trial will not expose participants to unacceptable conditions or hazards. In addition, there will be a requirement that medicines used in trials are manufactured to standards of Good Manufacturing Practice (GMP) to prevent participants being exposed to unsafe medicines.

### **9. Are medicines used in trials monitored under the Directive?**

The Regulations require that medicines to be used in a trial be manufactured to standards of Good Manufacturing Practice (GMP) to prevent participants being exposed to unsafe medicines. During the trial the sponsor and investigator monitor participants' safety and notify MHRA and the ethics committee of any unexpected serious adverse reactions to the medicines used in the trial so that the effects of unanticipated risks are minimised.

### **10. Are fees charged under the Regulations?**

The Directive required the UK to subject all clinical trials to an authorisation procedure and did not distinguish between commercial or non-commercial trials. The MHRA charges fees to recover the administration costs of assessment, authorisation, issuing of manufacturers' licences and inspection.

### **11. Is it not possible to differentiate between commercial and academic research for the purpose of charging fees?**

HM Treasury rules prevent cross- subsidisation from fees paid by commercial sponsors.

### **12. What are the transitional arrangements for a trial that began before the Regulations were introduced?**

MHRA agreed transitional arrangements for clinical trial authorisations. They also agreed transitional arrangements for manufacturers to apply for licences to manufacture IMPs. Nearly all currently authorised clinical trials were converted to "Clinical Trial Authorisations" without any further

application. For a few trials, more information may be required if they are with unlicensed products on which there is insufficient data to meet the new requirements. MHRA recruited additional staff to handle the increased number of applications.