The Academy of Medical Sciences | FORUM

European Clinical Trials Directive

A summary of papers presented at the Symposium organised by the Academy Forum on 3 June 2003, London

July 2003

European Clinical Trials Directive Symposium

Participants in order of programme

Sir John Skehel FRS FMedSci
Chairman of the Academy Forum and Vice-President, Academy of Medical Sciences and Director, National Institute for Medical Research

Professor Alasdair Breckenridge CBE FRSE FMedSci
Chairman, Medicines and Healthcare products Regulatory Agency (MHRA)

Sir Colin Dollery FMedSci
Treasurer, Academy of Medical Sciences and Senior Consultant, GlaxoSmithKline Research & Development

Dr Brian Davis
Clinical Trials Unit Manager, Medicines and Healthcare products Regulatory Agency (MHRA)

Mrs Moira Daniels
Director of Global Regulatory Information & Intelligence, AstraZeneca Research & Development

Professor Patrick Vallance FMedSci
Registrar, Academy of Medical Sciences and Head of Division of Medicine, University College London

Dr Richard Sullivan
Head of Clinical Programmes, Cancer Research UK

Professor Sally Davies FMedSci
Head of Research and Development for London, Department of Health

Professor Terry Stacey
Director, Central Office for Research Ethics Committee (COREC)

Dr Simon Thomas
Senior Lecturer, Wolfson Unit of Clinical Pharmacology, School of Clinical and Laboratory Sciences, University of Newcastle upon Tyne

Mr Stephen Hasler
European Regulatory Operations and Systems, GlaxoSmithKline

Abbreviations used in the Report

Abbreviation	Meaning
ADR(s)	Adverse drug reaction(s)
AE(s)	Adverse event(s)
CA(s)	Competent Authority(ies)
CIFD	Coming into force date
COREC	Central Office for Research Ethics Committees
CRUK	Cancer Research UK
CTA	Clinical Trial Authorisation
CTC(s)	Clinical Trial Certificate
CTMP	Clinical Trial in a Marketed Product
CTX(s)	Clinical Trial Exemption(s)
CV	Curriculum vitae
DDX(s)	Doctor and dentist exemption(s)
Directive	The European Directive on Good Clinical Practice in Clinical Trials 2001/20/EC
DMC	Data Management Committee
DSMB	Drug Safety Monitoring Board
EC(s)	Research Ethics Committee(s)
EMEA	European Medicines Evaluation Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good clinical practice
GMP	Good manufacturing practice
HVT	Healthy volunteer trials
IB	Investigator's brochure
ICH	International Conference on Harmonisation
IMP(s)	Investigational Medicinal Product(s)
LREC(s)	Local Research Ethics Committee(s)
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
ML	Manufacturing license
MRC	Medical Research Council
MREC(s)	Multicentre Research Ethics Committee(s)
MS(s)	Member State(s)
NHS	National Health Service
QP	Qualified person
RGF	Research Governance Framework
SI	Statutory Instrument
SmPC	Summary of product characteristics
SOP(s)	Standard Operating Procedure(s)
SUSAR	Suspected, unexpected, serious adverse reaction
UK	United Kingdom

Introduction

Prioritising the concerns: what needs to be resolved?

The European Directive on Good Clinical Practice in Clinical Trials (the Directive) (2001/20/EC), which will be implemented in the United Kingdom in May 2004, has broad and important implications for the way in which studies involving human subjects will be conducted in the United Kingdom. Ethical, legal and practical aspects of trials involving both patients and healthy volunteers, whether sponsored by academia, industry, research organisations, charities or government bodies, will be affected.

While Clinical researchers support the intention of the Directive in emphasising the importance of adhering to the principles of Good Clinical Practice so that all clinical research is conducted to a high standard, the Academy of Medical Sciences and others in the research Community have expressed serious concerns about the potential impact of the Directive on publicly-funded trials [1] [2]. It has been noted that, unless the Directive is implemented sensitively and pragmatically, there will be onerous new responsibilities for clinical researchers. Key issues include manufacturing authorisation and Good Manufacturing Practice (GMP), trials sponsorship, bureaucracy in trial authorisation and registration, intensity of data verification and pharmacovigilance. In some respects, the Directive has created a focal point for discussion that was overdue – what is necessary to correct UK problems associated with lower quality research and inadequate quality assurance?

Clinical research is dynamic and there is the fear that procedural rigour will constrain innovation. Extra review may bring unintended consequences; not just extra costs but less discovery. If research is lost from the UK then this is a loss for the research community, but also a loss more generally to UK healthcare if the work now done elsewhere is not applicable to the UK.

Action points for the UK

The purpose of the meeting organised by the Academy of Medical Sciences on 3 June 2003 in London was to explore many of these implications and to discuss the practical aspects which will arise when the Directive is implemented. The programme was designed to present the views and concerns of key stakeholders and to provide extensive opportunities for discussion and clarification.

Continuing role for the Academy of Medical Sciences

In order to take forward discussion and resolution of the issues raised in this report, the Academy is reviewing the opportunities for follow up work across the research community. Some of the specific points, for example for the regulation of challenge studies and for clinical research infrastructure, are already being addressed by Academy initiatives (Working Groups on *Microbial Challenge Studies* and *Strengthening Medical Research*). The Academy now welcomes further input as feedback to this Report.

In addition to the specific issues elicited by the Directive, it is important that the research community learns some general lessons. For example, to become better aware of developments at the EU level and to recognise the importance of communicating coherent and timely strategic messages. These broader challenges are also an opportunity for future work by the Academy.

Forum

Sir John Skehel welcomed the speakers and participants to the Academy Forum's first Symposium and explained the thinking behind the Forum initiative.

The Academy of Medical Sciences recognised the need to work with all players involved in the health care sector and sought in particular to increase the involvement of industry in its activities. As a result, on 31 March 2003, the Forum was launched to promote and increase the interaction of academic and industrial biomedical scientists and engineers, and other groups committed to the pursuit of research excellence and improvements in health care through research. The Forum has eighteen subscribing members including several pharmaceutical companies, biotech companies, trade associations, a venture capitalist, a research

[1] P Vallance, *View from the Top: Small, innovative clinical trials are under threat*, Research Fortnight, 14 May 2003, p.21
[2] Evans, Meredith and Duker, GCP journal, June 2003, p.7

council and a major research-funding charity. The Forum is an active network bringing together Forum members and Academy Fellows through a range of activities to influence the national medical science policy agenda and to provide an international perspective, especially within Europe, when issues have a wider relevance. The Forum aims to add strategic value by building on what is already distinctive of the Academy: its commitment to impartiality and its independence from vested interest. The overall objectives of the Forum is to deliver the benefits of medical research more rapidly to patient care, to foster the economic benefit of research, and to support the biomedical research profession.

Defining the Impact – What is Endangered and What is the Cost?

Professor Alasdair Breckenridge chaired the morning session. He commented that it has been only in the last few months that the academic community, the NHS and research funding bodies have become fully aware of the significance of the Directive to clinical research in the UK. He emphasised that the Directive will affect the development of medicines, some aspects giving grounds for concern to the public sector, e.g., the new requirement of approval for phase I trials, the definition of sponsor, quality control of material and conduct of trials, while other changes are to be welcomed such as specification of time scales for ethical opinions. Professor Breckenridge emphasised the importance of this Forum event to inform the further input from the Academy to the UK Consultation on implementation.

Key Points from the Symposium

1. The European Clinical Trials Directive is written on the implicit assumption that the purpose of performing a clinical trial is to produce data for a Marketing Authorisation application to a national or international regulatory authority. However, the Directive requires anyone who performs a clinical research study in the EU that involves the safety or efficacy of a medicinal product to comply with its regulations.

2. Academic clinical researchers and the medical research charities in the UK were consulted informally about the Directive but it is a matter of regret that a strong enough case was not mounted by UK representatives to convince the Commission that non-commercial clinical studies require a modified and less bureaucratic system of regulation along the lines of the existing doctors and dentists exemption (DDX) and the clinical trials exemption (CTX) procedure in the UK.

3. The Directive must now be implemented into UK law but strenuous efforts must be made to minimize its impact upon non-commercial clinical research. No other EU Member State has the volume or quality of non-commercial funding for clinical research, which takes place in the UK. Much is at stake.

4. The Academy takes this opportunity to re-emphasise its support for the principles of Good Clinical Practice in order to maximize the value of clinical research for the researcher and funder, and for patients and the NHS. However, the government needs to produce a flexible, coherent, pragmatic and durable approach to developing policy and procedures for implementing the Directive that involves all the interested parties, assures patient safety but keeps bureaucracy to a minimum.

5. The Directive will increase the costs of non-commercial clinical research considerably (most major pharmaceutical companies already have these processes in place). Substantial local investment will be needed in the non-commercial sector for installing management systems, training staff and documenting processes. Unless the government offers assistance, the volume of clinical research in the UK will fall.

6. Verbal assurances that “Mechanistic” studies are not covered by the Directive even if they involve use of a medicinal product (provided that the aim is not to ascertain efficacy or safety) need to be clarified in writing.

7. The development of the flow charts, processes, documents and charters is a major undertaking that must take place before 1st May 2004. In particular, versions of the documents termed “Good Clinical Practice” and “Good Laboratory Practice” that are appropriate for non-commercial clinical research must be developed. The extremely detailed versions used for regulatory (marketing) clinical trials are unnecessarily complex. Simpler versions need not compromise safety.

8. The Directive imposes responsibilities on the trial sponsor (with the implicit assumption that it is a pharmaceutical company). In academic circumstances, there is a risk over onerous interpretation. In the non-commercial sector the issue of who should be the sponsor is extremely contentious and many organizations are unprepared to accept this role. Medical schools and main teaching Trusts need to be clear as to who will take the various responsibilities outlined in the Directive’s definitions. NHS R&D should play a major role in developing a national template and facilitating the process. NHS R&D money that comes to Trusts from the R&D budget can be used to create the infrastructure necessary to support the Directive, this must be made clear.

9. The position of the UK competent authority (MHRA) is that there is nothing in the Directive, which the non-commercial sector cannot follow, and the implementation and monitoring of the EU Directive in the UK will be done sensibly. While the Academy accepts these assurances are given in good faith, the history of regulation suggests that it will become more onerous as time passes.

10. With less than 10 months to go before the Directive becomes law urgent action is needed by all concerned lest clinical research in the UK suffers a serious and long lasting constraints.

11. There are concerns that the EU clinical databases (for trial registration and for pharmacovigilance) are not being given sufficient strategic attention – and funding – by the Commission. There is a danger both that researcher views will not be sufficiently taken into account in the design of the databases and that the procedures will not be in place to enable researchers to gain familiarity with the system before the formal start date. It is important that the UK seeks clarification on the status of the databases from the Commission.

Draft UK Legislation to Implement the Clinical Trials Directive

Brian Davis, Clinical Trials Unit Manager, Medical and Healthcare products Regulatory Agency (MHRA)

Dr Davis opened his presentation with a brief history of the development of the Directive. It was written by the European Commission and was meant to be an umbrella Directive to cover procedures in all Member States (MSs). The resulting document is a composite of many different agendas.

After a brief explanation of the workings of the Commission and its working parties, Dr Davis concentrated on the transposition of the Directive into UK Law. The Medicines for Human Use (Clinical Trials) Regulations 2003 and a consultation paper, MLX 287, were published on 21st February 2003. The consultation period was 12 weeks. However, the Academy of Medical Sciences has been given a short dispensation to allow time for consultation and feedback from academia. Once comments have been received the Statutory Instrument (SI) will be prepared, pass through the parliamentary procedures and be expected to come into force by late summer 2003. Transitional arrangements will exist until May 2004, with full implementation on 1st May 2004. The system for granting Manufacturer's Licenses (MLs) should be in place before full implementation.

The Directive changes the way clinical trials are controlled in the UK from one where control is on the supply of an Investigational Medicinal Product (IMP) to one where the clinical trial itself will be controlled. Clinical Trial Certificates (CTCs), Clinical Trial Exemptions (CTXs), Clinical Trials in Marketed Products (CTMPs) and Doctor and Dentist Exemptions (DDXs) will go. For the first time in the UK Phase I studies will be included in the MHRA's review and require competent authority (CA) authorisation.

Application requirements	
Used within the conditions of the Marketing Authorisation (MA):	Application form, Summary of product characteristics (SmPC) and Protocol
Used outside the conditions of the MA:	Application form, SmPC and any appropriate additional data, and Protocol
No new data available since CTA:	Application form, Letter of cross-referral to CTA and Protocol
New data available since CTA:	Application form, Update of CTA with new data and Protocol
New chemical or biological entity:	Application form, IMP Dossier, Quality data, Non-clinical data, Clinical data and Protocol

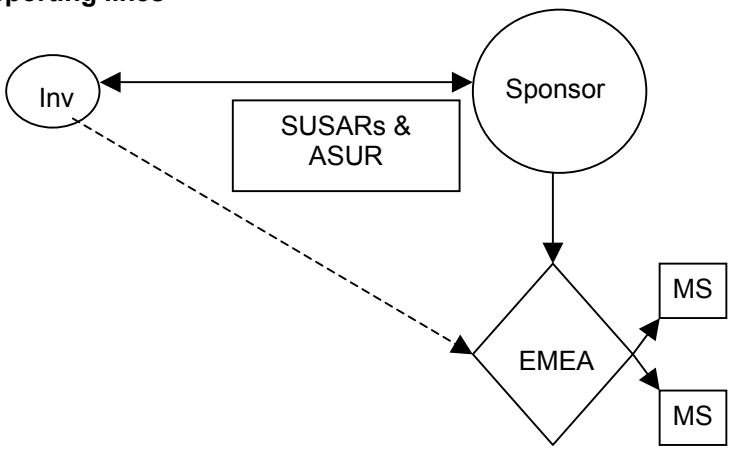
After the authorisation for the clinical trial to proceed has been granted, amendments will fall into two categories; non-substantial and substantial. The Regulations provide a comprehensive guide to those amendments which are considered to be substantial, and sponsors should decide what is to be submitted to both the CA and the ethics committee (EC), and keep a log of all amendments not submitted. Substantial amendments are those which affect subject safety, physical or mental integrity, scientific value of the trial, conduct or management of the trial, and quality or safety of any IMP used in the trial. The agency has the right to impose amendments for urgent safety measures, to introduce compulsory amendments, to suspend or terminate the trial and co-ordinate regulatory decisions with other MSs. The MHRA does not want to be overwhelmed with amendments which do not affect the above criteria, but the sponsor should record all amendments occurring which have any importance to the trial.

A clinical trial must be conducted under the principles of GCP. The Commission will introduce the GCP Guideline as a Commission Directive, but no date has yet been given for this. ICH GCP should be taken into account but is not a part of this European Legislation. The position of the agency is that there is nothing in the GCP guidance that an academic cannot follow. Conditions and principles of GCP which are still under consultation in the UK are persons not able to consent (minors and incapacitated adults), legal

representation and emergency research. Inspection for GCP is meant to be educational, as inspectors will produce reports and then work with the institution to rectify any causes for concern.

With regard to pharmacovigilance, the agency does not want to be inundated with reports. Only suspected, unexpected, serious adverse drug reactions (SUSARs) should be reported which covers anything not in the SmPC or listed in the Investigator's brochure (IB), depending on the stage of development of the IMP. The Eudravigilance database will eventually take information from 25 MSs and be the biggest pharmacovigilance record in the world. It is expected that this will be an important tool in spotting safety signals. Sponsors are required to submit annual safety update reports per protocol. Therefore, for a multicentre clinical trial all the adverse reactions (ADRs) should be collated. There will be an information exchange across all the MS, the European Commission and the European Medicines Evaluation Agency (EMEA). For non-commercial trials a procedure outlined in Figure 1 might be considered if the Sponsor decides to delegate the responsibility for reporting SUSARs to the investigator.

Figure 1 SUSARs reporting lines



In order to supply an IMP a sponsor must obtain a ML for clinical trial products. This will give assurance of manufacture to GMP standards. The IMPs require release by a Qualified Person (QP). An exemption from the need to have an ML will exist for certain aspects of manufacture in hospital or healthcare centres.
Unlike the present CTX system, the new Clinical Trial Authorisation (CTA) will not need to be renewed on a regular basis for the trial to continue. However, notification of the end of the trial and the process is laid down in the Commission guidelines which provide a declaration form, and explain the timings, premature termination and suspension. A sponsor should define the end of the trial in the protocol and should cover all circumstances, if possible.

The MHRA will impose a fee structure which is not without implications for academia and the health service. There will be an annual service charge for each drug that the sponsor has under trial. The proposed fees for 2004/2005 are presented in Table 1.

Table 1: Proposed fees for MHRA CTA authorisation 2004/2005

Category of Application	Proposed Fee 2004/2005 (£)
Phase IV initial application or cross-referral to known CTA	140
Additional clinical trial protocol authorisation	100
Other amendments to IMP dossier	100
Annual service charge per initial application	200
Phase I initial application	610
Phase II & III initial application unknown IMP	2700
Phase II & III initial application known IMP	2250

Transitional arrangements in the UK are expected to be in place from late summer 2003 when the Regulations come into force. For applications authorised before the 'Coming into Force Date' (CIFD), CTC,

CTX, CTMP trials will be converted to CTAs from 1st May 2004 with no fee charged. DDX trials will be assessed to the same standard as a CTA then converted to a CTA, again with no fee. Otherwise, a sponsor will need to be identified in order to apply for a CTA before this date.

For applications after the CIFD**,** but before 1st May 2004, for CTC, CTX, DDX, CTMP and Healthy volunteer trials (HVT) trials the agency would like sponsors to start to apply for CTAs as soon as possible. There will be a fee charged. Exemptions granted from the CIFD will expire on 30th April 2004 and after 1st May 2004 the CTA applies. For those continuing to apply for exemptions until then there will be no fee. However, for ongoing studies a CTA will have to be in place before 1st May 2004. For the HVT pilot scheme (which is not legally binding) sponsors should submit with a fee.

IMP Manufacturing Authorisations after the CIFD require applications for MLs with the same fees proposed as current MLs. These will be based upon the size of the company, the number of relevant employees and the size and complexity of the manufacturing operation. There will be an inspection programme of manufacturing sites.

The MHRA's communication plan will begin with letters to all CTC, CTX and DDX holders, an article in MAIL and an announcement on the MHRA website. A 'Tool Kit' and guidance will be provided. The MHRA will encourage all exemption holders to apply for a CTA as soon as possible after the CIFD to avoid the deluge in February to April 2004.

Discussion

- During the discussion which followed, the perception that the UK was more advanced than other MS in implementing the Directive was noted to be no longer correct. In the last few months other countries (e.g. Holland, Germany, Denmark, Sweden) have published draft legislation and are rapidly catching up.
- Clarification was given on the relationship of long-term follow up monitoring of patients and its relationship to the end of trial declaration. These follow-up studies should be regarded as part of the overall protocol and included in the original application as a follow-up phase of the study.
- Concern was expressed that for products from academia without marketing authorisations, the cost of the toxicology assessments, fees, etc., will be a burden that cannot be afforded.
- The GMP guidance suggested to many that some special case studies, e.g., PET investigations, might not be possible. Dr Davis assured the audience that the guidance notes would be flexible.
- The objective of the Directive was to harmonise the way in which clinical trials are performed across 15 MSs. Therefore, other regional regulations (e.g., United States FDA) have not been taken into account in the Directive's development. However, the ICH guidelines have introduced harmonisation on many aspects**.**

Impact of the Clinical Trials Directive on the Research-based Pharmaceutical Industry

Moira Daniels, Director of Global Regulatory Information & Intelligence, Astra Zeneca Research & Development

Scope and scale: a missed opportunity for the EU?

Moira Daniels covered the history of the Directive, but felt that there had been too many compromises to achieve its objective of harmonisation of the procedures for clinical trials across the European Union. Due to the delay in the issuing of the final guidelines, no MS had been able to transpose the Directive into their own laws in time. There is concern that each MS may define 'non-interventional studies' (excluded from the Directive) in different ways: however, most studies will have to be performed under a CTA. The Directive applies not just for the pharmaceutical industry, anyone performing a clinical trial must comply with its regulations, including academia and the NHS. Industry would like a definition of a 'valid' application and when the clock will start for the assessment times.

There will be no single decision across Europe for a multi-national, multi-centre study, but each involved MS will assess the application and reach its own decision, potentially creating conflict as well as duplication. A single, positive opinion per involved MS ethics committee (EC) must be received and 'no grounds for non-acceptance' from the CA. Concern remains that both the CA and EC will be looking at the same dossier and that no clear remit of each has yet been published – again there is potential for ambiguity and conflict.

The role of Guidelines and reduction to practice

After a brief explanation of the application process and timings involved for both CAs and ECs the guidelines to the Directive were reviewed. There will be 12 guidelines but only 5 have been finalised and published to date. The content of these has been significantly improved but there are still issues for further clarification. They require detailed review and changes to process. Within industry it is felt that these are manageable, with the slight adaptation of processes. However, there may be considerable problems for academia to bring their practices into compliance with the Directive and its guidelines. The final, published Guidelines for CA and EC applications illustrate the differences in national requirements and delay in publication of the rest is causing delay to the start of the IMP ML application and inspection process.

When considering the Good Manufacturing Practice (GMP) procedures introduced by the Directive, industry feels that there is much work to be done in order to be ready in time for implementation: amendment of Directive 91/356/EEC Principles and Guidelines on GMP for medicinal products; update to EC Guide to Good Manufacturing Practice Annex 13, Manufacture of Investigational Medicinal Products; and manufacturing and/or import authorisations for IMPs for human use (MLs). Annex 13 is still under review and general points on which clarification is sought include labelling, the product specification file, Qualified Person activities, premises & equipment, documentation, production, release of batches and shipping. Concern was expressed about the resource and time needed to train both GMP and GCP inspectors across the EU as they must not apply Marketing Authorisation standards to IMPs. It is important for inspectors to be pragmatic.

Manufacturing Site Authorisation will be required for each manufacturing or importation site. This applies equally to comparators and all investigational products, including Phase I material, but there will be no re-testing required once available in the EU, based on QP release. The labelling should be in the national language. Issues for manufacturing and/or import authorisation for IMPs include clarification of the process to obtain site authorisation in advance. Will there be an expiration period for the ML? How will MSs provide GMP certificates at manufacturer's request? Will supply to 'Named patients' remain unaffected in MSs in which it is allowed? The present thinking within industry is that CTA will put the EU at a disadvantage compared to the USA as a location for clinical research, particularly in new technology areas where academic institutions may be involved.

Industry wanted a notification procedure to CAs, but there will be an authorisation process. Guidance is still needed concerning the classification and submission of substantial amendments. No differentiation of

guidance at different phases of development has been given and there appears to be duplicate and unnecessary information and possible conflicts in decisions plus a lack of clear guidance on timelines and process. Could there be possible delays in the 60-day CA assessment period if extra time is taken for validation of the submission package? For the sponsor there could be possible delays and increased workload, e.g., translation of documents into 11 languages. There is significant duplication of summary information between the IMP dossier and the IB. Time and resource will have to be given to the education of personnel involved in completing the application forms etc. Also, the end of study notification information, which is now requested, is more than that described in the Directive leading to increase workload.

The EC Guideline exceeds the scope defined in the Directive and ICH GCP, e.g., no clear division of responsibility between the EC and CA; no definition of the maximum set of documentation (addition of Module for Ethics Committees); no guidance on how a single opinion will be obtained in a MS; no definition of substantial amendments; no clear definition of who should interact with the EC and different MSs have different practices to which they may adhere.

The Guideline contradicts adverse reaction/event reporting requirements as defined in the Pharmacovigilance guidance and ICH, and reporting SUSARs to ECs will increase workload with no obvious benefit to patient safety. However, the Guidance has been significantly improved from the earlier version. The outstanding issues are causality assessment by drug and by design; clarification of how the sponsor should inform all the investigators; guidance for reporting of comparator SUSARs; different reporting requirements to ECs in MS, and annual reporting on short duration studies. Concerning information to the investigators, industry does not want to follow the model of the USA with their individual investigator letters per ADR but would prefer an update of the IB on a regular basis. Investigators in Europe need to be clear on how they want to receive this information.

In order to apply for a CTA the sponsor must obtain a number from the CA database, EUDRACT. There appears to be major issue with respect to database funding from the Commission. Even more worrying is that no contingency plan has been published. The content exceeds requirements of the Directive. However, there is a joint working party dealing with user requirements and functionality (see later).

Implications for Industry

Are these significant changes? For the research based pharmaceutical industry they are not, as the data were previously required by some or all MSs in EU. Some of MS and the US FDA required approval of Phase I studies and GMP authorisation of IMPs: the most change will be experienced in the UK.

The UK regulations are detailed but the explanatory text clearer than for other MSs. Practical details require clarification and the transitional arrangements proposed are seen as complex. Industry would recommend a simple transfer of CTX to CTA and no retrospective application of requirements to studies ongoing in May 2004. It is felt that the GMP requirements are onerous and need to be relevant to the risk.
In summary, industry's major concerns are that:

- The lack of agreement on the principles has resurfaced in the guidelines. The complementary role of CAs and ECs is not clearly differentiated, leading to poor accountability.
- The increased bureaucracy and administrative burden will impact upon Europe as a preferred location for clinical research. Many MSs are inexperienced in the assessment of clinical trial applications. The massive increase in workload for ECs means risk for delays in gaining approval to start clinical trial. There are conflicts and disconnects in the requirements and systems for reporting ADRs.

Major outstanding issues are seen as:

- No real compromise from MSs, still numerous national requirements;
- No consideration given to the EU accession countries;
- Process for release of comparator products is complex;
- EUDRACT database may not be available in May 2004;
- Duplication of reporting requirements between Sponsor and CAs and the database.

Requirements for industry to continue to want to sponsor trials in the EU:

- Implementation is planned;
- Transitional arrangements are clear;
- Documentation requirements are detailed but no more than currently required (please note the benefit of using single summary document for ECs and CAs);
- No plans to change decisions on placing studies.

Discussion

- Clarification was sought concerning whether challenge agents and other products which are impossible to manufacture to GMP are IMPs. The MHRA legal opinion is that not all products are covered by the Directive (e.g. challenge agent is not itself being studied for efficacy and safety). Further guidance will be sought (see subsequently).
- Legislation covering 'named patient' supply is separate from the Directive and will still apply.
- It is understood that the accession countries will have to accept the Directive and, if a MS of the present Community has granted a CTA, this will be accepted by the new members. Poland has already put the Directive in place.
- The roles and responsibilities of who will report ADRs should be clearly defined by the supplier of the IMP and the sponsor (if different). Therefore, there should be an agreement between the pharmaceutical company and the investigator regarding who is responsible for each part of the CTA process. Pharmaceutical companies in responding to investigation requests to use a product are unlikely to want to become the sponsor for such research.
- Concern was expressed that GMP release for placebo preparations will increase the cost to academia still further. Dr. Davis reminded the audience that MLs apply to specific forms of drugs, e.g., tablet production, and not to individual products. This should mean that the manufacturer of the active product should also have an ML for producing placebos.

EC Directive and Investigator-led Clinical Research: which studies are at risk?

Patrick Vallance, Head of Division of Medicine, University College London

Implication for academia

Professor Vallance opened his talk with the title of a recent paper 'The Death of Academic Clinical Trials'[3]. While many of the principles underlying the Directive are welcome, there are many areas of concern in relation to how the Directive may impact upon clinical trials performed by academia, in particular: mechanistic studies, studies to obtain pilot data for a grant application and studies of existing medicines in clinical practice. The Directive will mean that many clinical studies that previously required only ethics committee approval or a DDX will now require a full application to the MHRA and extensive paperwork. Before imposing such an additional burden on academic clinical investigators it would be desirable to show that it would improve patient safety or trial conduct or reduce fraud, and that it is practically possible without impeding research progress.

The Directive implies that the purpose of performing a clinical trial is to produce data for a Marketing Authorisation application, giving credence to the image that the Directive was largely written for industry. The implications for academia are not reflected in the Directive and some key concerns are:

- A sponsor is required for every study. Who, in academia, will want to be a sponsor with its legal requirements? There may be problems obtaining the necessary insurance and indemnities.
- Increased paperwork. A matter for resource and infrastructure with financial implications.
- Need to apply to a CA (the MHRA) for every study and amendment including updates to the IMP dossier and the IB.
- Increased study and research infrastructure costs from manufacture, GMP, GCP, fees, etc.
- Manufacturing problems – particularly if the product is to be prepared or packaged without a commercial partner (and particular issues, e.g. for PET agents, radiopharmaceuticals)

What research may be threatened?

Mechanistic studies

It is not clear whether mechanistic studies are included in the Directive. The definitions of a 'trial' and an 'IMP' are broad and it might appear as though any trial using any pharmacologically active substance would fall within the legislation. However, there are many studies where a compound is used to probe a biological mechanism – are these really captured by the Directive? Examples were given of using acetylcholine to study endothelium-dependent relaxation in healthy volunteers or patients, and where a newly discovered peptide is infused to test hypotheses about appetite regulation. It seems as though such studies should be exempt because the aim is not "to study the efficacy or safety of the medicinal product" – a key definition in the Directive. This view was confirmed as correct by Dr Brian Davis but academia needs urgent written confirmation, as inclusion would result in cessation of a large number of mechanistic studies in healthy volunteers or patients and an increased reliance on data from animal studies or in vitro investigations.

Pilot Studies

Pilot data are usually essential before grant funding is obtained. These are small scale studies, often with an early protocol and often undertaken with little funding. The Directive could delay the onset of this type of study and cause considerable cost at a time when there is no financial support. This will deter original investigator-led studies.

Clinical studies of existing drugs

What about studies in clinical practice? These are often large scale studies on 'everyday drugs' and where industry has little interest. Two examples were given, UKPDS and ISIS II, studies that were of fundamental

[3] Lancet 2003;361:1568

importance in changing UK clinical practice. Problems under the Directive for these could include approval for drugs, GMP labelling implications, GCP, reporting of adverse events, finding a sponsor and the burden of monitoring and site visits.

Academic studies explore questions important to patients, clinicians and health services which may not reflect priorities for individual companies. Within the clinical setting a large number of drugs are used outside their licensed indication and not all those therapeutic studies which change practice are large scale or designed for MA support, e.g., adenosine to treat SVT, apomorphine for refractory Parkinson's disease. Special groups, e.g., paediatrics and tropical medicine, often rely on academic research.

In summary, Academia needs to have answers to the following questions:

- Are mechanistic studies covered? The boundaries must be clarified, particularly in relation to the key phrase, that a clinical study is covered only if it is done "with the object of ascertaining the safety and/or efficacy of the medicinal product";
- Is full implementation necessary for a trial that is not part of drug discovery/development and generating data that will not be used for application for MA?;
- Will full implementation constrain innovative research and the development of evidence-based practice?

Discussion

Dr. Davis (MHRA) clarified the following points:

- Mechanistic studies are not part of clinical research into efficacy or safety of the medicinal product, therefore, they are not included in the Directive. However, they will require a positive ethics opinion;
- Pilot studies. The risk to the patient has to be assessed even though the study may be small. Currently these are covered by the Directive and will need full application;
- The reason that the Directive concentrated on Marketing Authorisations is because CAs has to ensure there is no threat to public health and safety is addressed throughout the development of data to support such an application;
- In large studies, parts of the study can be delegated, e.g., to safety monitoring committees. As long as it is clear in the application and protocol who will be responsible for assessing adverse events and who will report them, this is acceptable and may lighten the burden of paperwork on one section of the clinical study team;
- Psychotherapy trials are not covered by the Directive unless comparison of such clinical practice is made against a drug;
- Does the Directive apply to a diet trial? If dealing with a very specific product, e.g., treating a group of patients suffering from Parkinson's Disease with Vitamin C, then this would fall within the Directive (regulated similarity to current practice). However, manipulating diet in a group of diabetics would not be covered by the Directive as no drug is involved;
- At present, ionising radiation is not considered to be subject to the Directive;
- What is an IMP, e.g., can vitamins, trace elements, etc., all with different standards of manufacture, be classified as an IMP? At the moment a drug is defined in the Medicines Act but the Directive definition will replace this. The EU definitions have already been clarified for herbal products so there is little change;
- The MHRA will continue their process for clarifying discussions with sponsors prior to CTA submission;
- It is acknowledged that UK academia did not engage EU institutions and the EU Commission in the discussions during development of the Directive and a more coherent approach from this sector is needed. An opportunity had been missed and implementation must proceed, but it will be handled at the local level to decide policy for academia/NHS;
- Not all the other EU MSs have the public funding for clinical research which is available in the UK, resulting in fragmentation of representation. There is now a great opportunity to work together with the MHRA to gain clarity.

The Impact of the new Legislation on Non-commercial Trials: a major funder's perspective

Richard Sullivan, Head of Clinical Programmes, Cancer Research UK

At present there are 212 ongoing, publicly funded studies in the UK, about 50 of which are with drugs with MAs and SmPCs, but the majority use MAs outside their SmPCs. In the last 5 years CRUK alone has funded 65 large, Phase III, clinical trials with 6,000 patients per annum. In cancer alone there are 145 NCRN trials (in early 2003). It is estimated that there are approximately 6,000 publicly funded Clinical Trials across Europe (EORTC).

Why does research need to be sustained?

Public funded clinical trials are particularly important in:

- Helping to save many lives;
- Researching areas where there is little prospect of commercial gain, orphan diseases and paediatric applications;
- Comparator trials to establish best practice;
- Evaluation of generic products;
- Addressing unmet clinical needs;
- Exploring long-term outcomes and Quality of Life indicators;
- Understanding the biology of the disease.

Patient safety and trial quality is upheld in UK trials and current procedures are rigorous. All the funding bodies, e.g. CRUK, MRC, HTA, BHF, when considering funding a particular trial, review the scientific method, ethics, assess the Principal Investigator (PI) and research sites to assure the reliability of the data and results, and their public dissemination.

Healthcare policy in Europe is a diverse and difficult area. The decision-making apparatus for healthcare policy in the EU (MSs, Commission, Parliament & Council of Ministers) is complex. In reinforcing points made by previous speakers it was clear that academic input to the formation of the Directive was very limited. The intention was to harmonise and simplify clinical trials in Europe but the working parties consisted of only MS Cas and the final detailed Guidance Notes were not published until 9 weeks into the MHRA 12 week consultation period, giving little opportunity for the public sector to be engaged.

The role of the sponsor has given rise to much discussion. It is defined by reference to ICH GCP and because ICH GCP has been incorporated into Rules Governing Medicinal Products this sets the standard for GCP and thus the legal position of sponsor. This is a commercially driven definition and operationally, means that commercial systems are deemed the legal standard for the protection against liability. It fails to recognise de-centralised systems for trial safety and quality in publicly funded clinical trials and is a major issue for insurance.

Cost and opportunity costs

A further issue is the cost: benefit of the proposed legislation. What has not been addressed in the regulatory impact assessment is the lack of significant benefits to patient protection many of the proposed changes to regulations will bring. Overall, CRUK assessment has revealed that cost across phases I to III) would be quadrupled.

Thus, the impact of this legislation on publicly funded clinical trials could be considerable and many questions remain unanswered. Are the putative benefits proportional to the risks? Where is the harmonisation across Europe, particularly in the approach to orphan diseases? What processes actually protect patients? There could be fewer high quality clinical trials to offer patients and some diseases may not be covered at all if the legislation is implemented in its current form. There is also the issue of opportunity costs. Money spent on regulations might this be better spent on research nurses, data managers, education, etc [4] [5].

4 CentreWatch Europe 2002, 9, 9-12

5 Controlled CT 2002, 23:29-41

The wider context

The UK is very successful in biomedical research and publicly supported clinical trials are a major factor in the UK's success[6]. National public health initiatives, e.g., NCRN & NTRAC, are at risk as well as the future of exploratory biology. The Directive also needs to be viewed within the wider context of other recent regulations such as Human Tissues, 1998 Data Protection Act & Section 60 and the Research Governance Framework (RGF) which is adding yet other pressures an already overburden research community. All sectors want to work with the MHRA to ensure that the legislation will be implemented in a pragmatic manner. For the future, it is also imperative to engage better at the EU policy-making level to be aware of future developments and to communicate UK perspectives.

Discussion

- There are differing views on how public bodies could act as trial sponsors. The 'owner' of the clinical trial needs to be recognised ownership of the trial is not an easy matter outside the industry model.
- There are substantial problems with insurers withdrawing from the clinical trials market and there has been a major increase in premiums. Although this cannot be blamed on the Directive the EU needs to consider this further.

Practical Consequences of Transposition: Opportunities and Challenges for Sustaining UK Strengths in Clinical Research

The afternoon session was introduced and chaired by Sir Colin Dollery, Treasurer of the Academy of Medical Sciences and Senior Consultant, GlaxoSmithKline Research and Development.

Following the initial discussion of the impact of the Directive on UK research, the Forum Symposium now explored some of the procedural issues and the opportunity afforded by implementation to address quality issues in responsible research.

6 Grant J et al. Science 1997, 278:878-80

Implications of the European Clinical Trials Directive on R&D in the NHS

Sally Davies, Head of Research and Development for London, Department of Health

The Directive provides the legal framework for managing, control & accountability of clinical trials involving IMPs. It should protect patients and promote quality, both in the commercial and the academic and health service sectors and will sit alongside the Research Governance Framework.

Issues for the Sponsor

The role of the sponsor, is to take ultimate responsibility for the study, initiate ethics review, peer review, MHRA authorisation (to conduct the study), finance and declaration of end of trial, ensure standards to GMP & GCP, host inspections - systems versus trials (every 2-3 years). The sponsor will be responsible for the data monitoring committee and reporting adverse events and reactions (plus annual reports), ensure submission of substantial amendments and logging of others, and report the end of the trial.

NHS R&D – Opportunities and challenges

Who should be the sponsor? An NHS Trust cannot be instructed that they should or should not be a sponsor. One possibility is the R&D office on behalf of their NHS Trusts. Medical schools are another possible group to take on this role. Can there be collaborative sponsors? There is no reason why there cannot be a primary sponsor who then delegates responsibilities to others i.e., 'Fit for Purpose'. There is a need to train more people as research managers for these roles.

There are system changes which the public sector must embrace, but the Directive focuses on issues that were already of concern, e.g. variability in research quality and the changes should be seen as an opportunity to improve accountability and R&D management.

Promoting Quality Assurance

The pharmaceutical sector gathers a mass of documentation in order to ensure compliance with GCP but is this necessarily "good clinical practice" or aimed at ensuring liscensing? PICTF information shows that there are missing data from clinical trial audits within the public research areas. Among the weaknesses in the quality issues are:

- Informed consent: missing, not timely or according to protocol
- Study conduct: not eligible, protocol violations, data missing
- Medical records: missing, participation not recorded, poor security
- Case record form: incomplete, conflict with source records
- Staff: inadequate GCP training
- IMP: inappropriate transport, storage, dispensing & patient use
- Ethics: poor documentation

Pharmacovigilance is also giving cause for concern within the health service. Will there be over reporting? As yet, processes are not in place to set up data monitoring committees, produce annual reports, investigate each serious event & report. There is little knowledge about the Eudravigilance database within the public sector, but it will focus on the exchange of information on clinical trials and ADR reports between MSs, ECs and the EMEA. There is a risk of over interpretation of pharmacovigilance data, particularly as Yellow cards & National Patient Safety Agency reports continue.

To reiterate, most of these issues existed before the Directive but now we need to recognise and resolve them, and reflect the needs and roles in job descriptions.

The clinical community has foreseen the problems with consent issues, particularly for those with 'incapacity', in 'emergency medicine', ITU & neonatal, cluster randomisation (where a non-intervention arm may be unaware), diagnostic agents & physiological probes (e.g., PET tracers), research in children and pregnant women, and the field of psychiatry, e.g., schizophrenia. The Department of Health, however, believes these issues can be solved at local levels between academia and the NHS.

In summing up, Dr. Davies believed that the key questions for the public sector are:

- Should the Trust or Medical School be sponsor?
- What are the advantages for Trusts to take on sponsor role?
- Who will fund extra costs?
- Will manufacturers assist in authorisation submissions to MHRA for “academic” studies?
- How will QP & GMP work for small companies and academia?
- Can NHS specialist pharmacy production units supply? (Yes if GMP)
- Will there be impact on the biotechnology sector?
- GCP: what is the standard?

Since the meeting, the Department of Health and the Medical Research Council (MRC) have announced a joint project to address important issues raised by the academic trial community. More information is expected to appear on their websites.

Discussion

- Individual Trusts can decide which trials to take: probably the Trust covering the main PI will take the sponsor role.
- While funding for research infrastructure, stimulated by the Directive, might be seen as diverting money awary from that already allocated to research projects, it was posited on efficient use of NHS R&D capacity if better quality research resulted.

Application for ethical review – opportunities

Terry Stacey, Director, Central Office for Research Ethics Committee (COREC)

It is recognised that many of the problems in clinical research have existed long before the Directive. The Directive will give more focus to the ECs and how they carry out their work, but this should be seen in a positive light. The EC remit is to review the proposal and ensure it reaches an ethical standard.

ECs in the UK have a long history. In 1991 they were set up within the NHS (HSG(91)5) and in 1997 Multicentre Research Ethics Committees (MRECs) were established (HSG(97)23) which give a single opinion in the UK. At present the average time taken for EC review is less than 60 days. Student research has been an issue for ECs in that all proposals are submitted in batches each year. Therefore, ways of handling ethical review for educational purposes are being investigated.

Streamlining ethical review

Article 6 of the Directive states that all MSs will have to establish mechanisms for delivering a single ethical opinion for a clinical trial. In the UK the UK Ethics Committee Authority (UKECA) will be created. This will consist of the 4 Ministers of Health in England, Northern Ireland, Scotland and Wales. The draft Regulations give UKECA the power to recognise research ECs and COREC will probably play a role in this. This recognition will ensure that the EC is competent to fulfil its duties within the terms of the Directive. It is intended that all ECs will work to a standard system: We need criteria for them to perform their role, to ensure there is an appropriate system and to make their work transparent.

In time, the number of committees is likely to be less than at present. They will give a single opinion on a submission within the UK and be able to ask one set of questions. The applicant should be a key named person responsible for the ethical conduct of the study. The Directive does not instruct the ECs with respect to pharmacovigilance, but there is no mechanism for an EC to stop a trial on grounds of safety. Monitoring of the clinical trials will be done mainly by annual safety reports and end of trial reports.

There has been a change in some of the language used. A Chief Investigator is the lead investigator for a whole MS and signs the application. The term 'Principal Investigator' cannot be used as the Directive defines this as the person in charge of the trial at a local site.

Roles and responsibilities for human subject protection

The considerations of the EC will be much as before, with a greater focus on two vulnerable groups, i.e., minors (below the age of 16 years) and incapacitated adults. There is need for further discussion relating to the latter group and what constitutes a legal representative. The handling of emergency studies needs further clarification.

The Directive presents opportunities for the UK: it clarifies the system, presents common structures, common documentation and common application forms. There will be no problem in separating the responsibilities of the UK EC and MHRA. Consistency between ECs is still a slight worry but is a matter of training.

Possible threats include a destabilisation of the research ECs as local research ethics committees (LRECs) may no longer review enough applications each year to maintain their competence. There could be a potential for errors if the ECs are only allowed one review period. There will be less tolerance of incomplete applications or patient information not transcribed properly: There will be little time to correct these faults and the application will be rejected.

Indemnity for each EC will come from the body which has established them.

Discussion

- It is anticipated that ECs will move towards discussion with the DSMB or DMC when assessing SUSARs.
- The Directive requires the EC to review the scientific design of the study, i.e., provide the process for quality assurance for the science of the study. Academia needs to be more rigorous in its review of their proposals and the protocols themselves prior to submissions.
- Guidelines to the Regulations will give details of the reporting process, etc.

The challenge of Local Implementation of the European Clinical Trials Directive

Simon Thomas, Senior Lecturer, Wolfson Unit of Clinical Pharmacology, School of Clinical and Laboratory Sciences, University of Newcastle upon Tyne

Implementation of the EU Clinical Trials Directive as currently proposed by the UK consultation letter (MLX287) will present considerable challenges to local institutions conducting research in the UK. It is unclear at present how many studies annually would be affected, but the numbers involved would be significantly larger than those currently requiring MRHA approval. This is because approval will now also be required for Phase I and many other healthy volunteer studies involving the administration of drugs or other investigational substances, whether commercial or investigator initiated. Although the Directive may exclude physiological and mechanistic studies, studies investigating the clinical pharmacology or pharmacokinetic of drugs do appear to be affected, including those involving administration of single doses of drug or collection of additional samples or measurements from patients receiving drugs under their normal conditions of use.

Indirect influence of the Directive

The directive will also have a significant indirect influence on non-pharmacological research in the UK. The Research Governance Framework (RGF), which governs all types of research, and the Governance Arrangements for Research Ethics Committees (GAfREC), have been written with the EU directive in mind. As a consequence, many of the directive's principles are now indirectly applied to all research, for example need for independent scientific review, ethics committee arrangements, the need for an identified sponsor etc.

Compliance with the principles of ICH-GCP

The need to perform research to the principles of ICH-GCP has been a requirement for the pharmaceutical industry for some time and is essential for studies that are to be used in submissions for marketing authorisation. However, these principles will be difficult to implement for non-commercial researchers. While all research should already comply with many ICH-GCP principles (e.g. consistency with the Declaration of Helsinki, respect of the rights and protection of subjects, the need for informed consent and confidentiality of information), compliance with other principles will require a change in the way research is conducted. Examples would be the production of protocols to a standard format, maintaining evidence of staff qualifications and training (signed and updated CVs), accurate and audited clinical trail data, clinical trial monitoring, standard operating procedures and use of products produced to 'Good Manufacturing Practice' standards. While there is merit to these principles, the cost-benefit of rigorous application of ICH-GCP to many academic studies, particularly small scale or single dose studies is questionable. In interpreting the guidance, clear guidance on what constitutes the '*principles of ICH-GCP'* would be helpful.

Sponsors

The role of sponsors (as opposed to funders) of research is specified in the directive and in the RGF. Sponsors could be the pharmaceutical industry, a funding body, universities, a NHS Trust or another organisation. The sponsor must take on legal responsibility for the research, including arranging scientific review, submission of applications to the MRHA and REC, study management, monitoring, and appointments of DSMBs when appropriate. They are also responsible for the reporting of serious unexpected suspected adverse reactions (SUSARs) arising during the research to the REC, MRHA and study investigators and this must be done within strict time limits. For fatal or life-threatening events, initial information must be passed on within 7 days with additional information available in a further 8 days. For less serious reactions 15 days are allowed. Sponsors are also responsible for providing annual safety updates including listings of individual reports, and an overall report of safety. They also need to manage inspections and meet the costs of these. It is a responsibility that 'substantial' protocol amendments should be submitted to the REC. The sponsor should think carefully about what constitutes such a change, e.g., changing the timing of blood sampling during a study is regarded as substantial amendment and would need authorisation.

Independent scientific review

The requirement for provision of independent scientific review will not be difficult when open peer review is a component of the funding process, e.g. for studies with charitable or research council funding. However, sponsors will need a mechanism to provide review of other research. Provision of independent scientific review may be difficult for the pharmaceutical industry in view of their need to maintain the confidentiality of commercially sensitive information.

Documentation

Implementation of the directive requires the maintenance and updating of considerable documentation by sponsors, as well as other institutions or researchers involved in the study (Table). This information is required whether the study involves 6 patients or 6,000 and whether the drug is given once or over several years.

Documentation to be held by Sponsor and/or investigator/institution for clinical trials

- Investigators brochure (+ updates) or SmPC
- Protocol and amendments (signed)
- Information sheet and consent form (+ updates)
- Financial aspects
- Insurance statements
- Signed agreements between parties
- EC opinion and composition
- MRHA authorisation
- Investigators CVs
- Medical and laboratory tests, including normal ranges
- Medicine labels
- Instructions for medicine use
- Shipping records
- Certificates of analysis
- Decoding procedures
- Master randomisation list
- Monitoring reports (pre-trial, initiation, close-out etc)
- List of persons responsibilities delegated to (+ updates)
- CRFs and corrections
- SAE notifications from investigators and to EC and MRHA
- EC/MRHA annual reports and final reports
- Subject screening log
- Subject identification code list
- Subject enrolment log
- IMP accountability at site
- Record of retained tissues
- Documentation of IMP destruction
- Completed subject identification code list
- Audit certificate
- Clinical study report

(Detailed guidance for the principles of GCP in the conduct in the EU of clinical trials on medicinal products for human use. ENTR/6416/01, July 2002)

Employers of researchers

The research governance framework also sets out responsibilities for employers of researchers, including the need to encourage a quality research culture, consider data protection and information handling, and ensure financial probity and management. Health and safety must be addressed. Employers need to ensure that research carried out has appropriate ethical approval, and they are responsible for adherence to recruitment arrangements and protocol, as well as agreements with other research partners. Employers must also consider and arrange approval for student research and have mechanisms for detecting and dealing with research misconduct and fraud.

Research Ethics Committees

The organisation and functions of research ethics committees have been changed substantially as a result of the EU directive. As previously, RECs must examine the relevance and design of the trial, weigh up the risks and benefits, consider the recruitment and consent arrangements for subjects and ensure that adequate indemnity is in place. What is new is that clinical trials will be subject to review by a single committee and

approval will cover the research throughout the UK. Assessing the suitability of staff and locations at distant sites becomes virtually impossible and is likely to be delegated to the host institutions. As a result, independent review of locality issues for multicentre studies will be lost. The directive sets out a legal framework for the inclusion of adults unable to provide their own consent and RECs will need to consider the justification and arrangements for this. More detail will be asked by RECs about the rewards given to investigators and subjects, and the agreements between sponsors and trial sites.

Each EC will require recognition by UKECA, having fulfilled their requirements, and will be centrally funded. There numbers of applications will be limited to 12 per meeting, allowing more detailed review of each project by RECs, some of which have previously had to consider up to 40 at a sitting. The parallel processing of projects by the MHRA and the EC will reduce the time required for approval but if either one requests changes to the protocol, these will then have to be approved by the other.

Prior to submission to the EC the applicant needs to book a slot with an appropriate REC and provide documents within 4 days of the date of booking the slot. The EC can be chosen on the basis of its location, expertise or experience with similar applications; alternatively the first available REC slot can be selected. The EC will perform a validity check on receipt of the application to ensure that it: meets the remit, contains approved application form and all attachments including a full protocol, documents for participants and other professionals affected, questionnaires, chief investigators CV, evidence of scientific review and a fee, if appropriate. Student projects will require a named supervisor and their CV and confirmation that the supervisor is willing to act as sponsor.

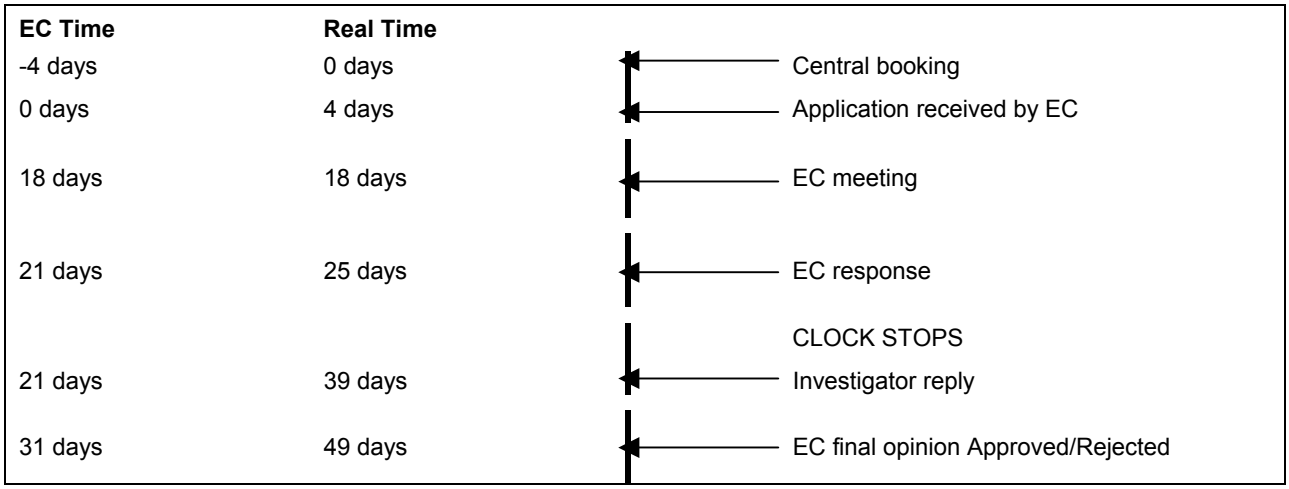
Having received a valid application the REC will be limited to 60 days for review (except gene therapy, somatic cell therapy or genetically modified organisms) and can make only a single request for supplementary information. It is helpful if a researcher can be available at the time that the REC considers the application, but they must be familiar with the submission and in a position to respond to questions and advice from the committee. The time-limited review process is reasonable and most properly organised and supported committees will not have difficulty in meeting this time frame for all but the most complex applications. However, it seems inevitable that if the sponsor cannot address the concerns of the REC within the 60 day limit the application will be rejected, otherwise the REC will be working outside the legal framework set out by the directive.

Conclusion

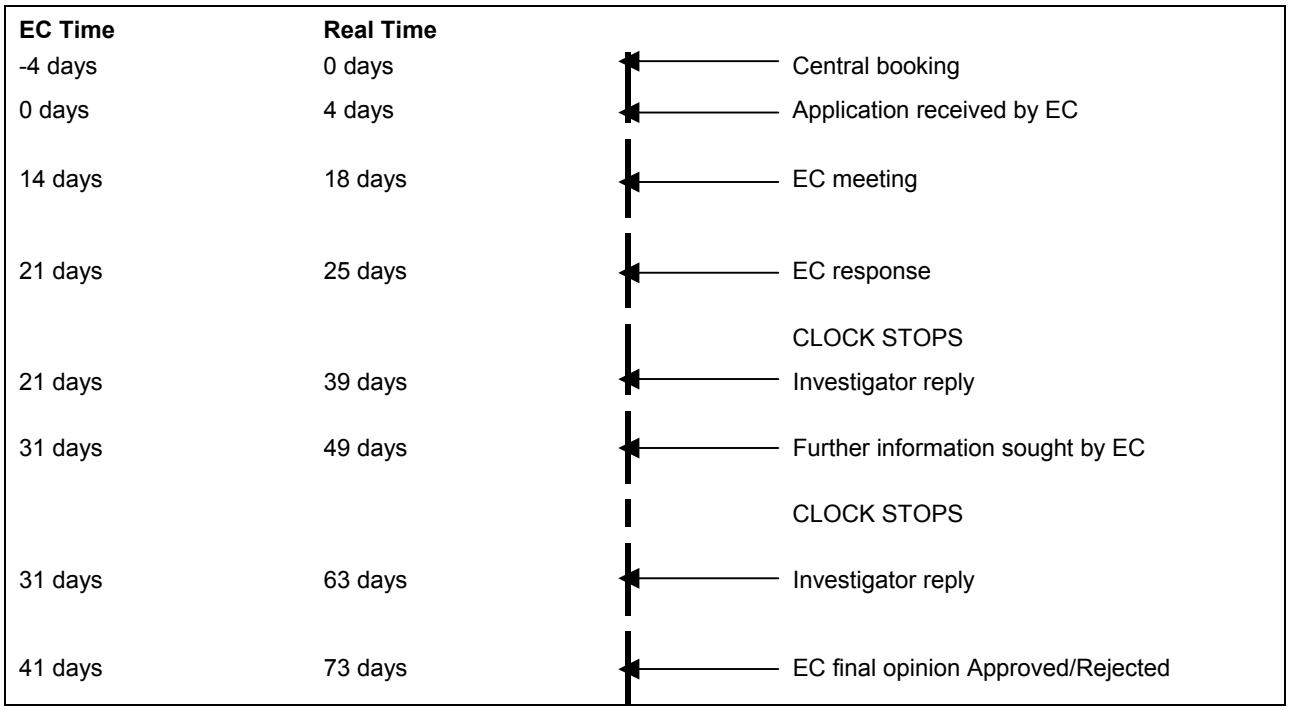
In conclusion, the EU clinical trials directive will have very substantial implications for local organisations conducting research. The documentation required will be considerable and for a large number of research projects it seems unlikely that this increased burden on researchers, sponsors, host institutions and RECs will improve the safety or probity of the research affected to an extent justified by the additional costs involved. Substantial local investment will be needed for training of staff, developing new research procedures and appointing new staff to deal with the additional administrative burden. There is a real risk that valuable research will be lost as a result, particularly investigator initiated exploratory or pilot studies, and some institutions may no longer be in a position to host clinical trails. Any opportunities to clarify the guidance and to soften its impact on research, particularly on non-therapeutic studies that are unrelated to applications for marketing authorisations would be beneficial. In particular, the directive's requirements with respect to research involving single doses or a limited duration of exposure to licensed products need clarification so as to avoid the stifling of research by the over vigorous implementation.

Figure 2: Potential timings for EC review of an application for a CTA (examples)

(A) Single REC response



(B) Further clarification sought by REC



Discussion

- ECs are keen for all research to be reported but this is often difficult within academia and the health services. Some projects are never started but this is not communicated to the EC.
- Short, non-GCP protocols often go to LRECs who are reluctant to reject research but validation and the 60 day rule could stop this.
- Funding has to be in place before research can go to the EC but some funders are reluctant to commit without an EC approval.
- There are training issues within the health service, e.g., junior doctors and students are often in a placement for only 6 months. It will now be more difficult to include them because of the need to show they are adequately trained to do research.

Working with the European Clinical Trials Database

Stephen Hasler, European Regulatory Operations and Systems, GlaxoSmithKline

EUDRACT is the agency database which will be a register of all clinical trials being conducted in the EU. It will contain information on each clinical trial (content, commencement, termination, inspections) and will facilitate communication on these clinical trials between the sponsor and the CA. It will enable CA oversight of clinical trials and IMPs and will provide enhanced protection of clinical trial subjects receiving IMPs. The Eudract system comprises a data entry and viewing area, the quarantine area, which is accessible to sponsors and CAs, and the database itself, which is only accessible by CAs and the European Commission. The responsibility for developing, implementing and maintaining the database rests with the European Commission who have delegated the work to the EMEA.

Process standardisation, accountability and audit

The sponsor needs to register with the system (access control mechanism). This provides security from unauthorised access and authentication of submitted information and also provides access to the quarantine area.

A single Eudract number is issued per protocol regardless of how many MSs are involved in the clinical study. This can be obtained up to one year in advance of the full set of data being sent to the agencies. The limited information consists of trial identification, sponsor identification and information on the IMP. If the sponsor does not complete the application after 12 months the data are wiped from the database. The CA will not review any application until the full set of data has been submitted. When a second application is made to another MS for the same protocol, the common data will be accessed from the database and the sponsor inputs data which is different for second MS. At any time before the CA reviews the Clinical Trial Application, sponsors will be able to see and edit their own data and should ensure that it is up-to-date before making a CTA submission to a CA.

The CA will validate the submission form: when this validation is complete the CA will move the sponsor data from the quarantine area to the database itself. A copy of the data will remain visible to the sponsor in the quarantine area but this file will be locked.

GCP and GMP inspection details by a MS will also be captured in the database.

Staff responsible for data entry need to be suitably trained and should have SOPs available to them. Quality control and assurance procedures will need to be in place to verify accuracy of data and integrity of data entry.

What needs to be resolved?

Key outstanding issues are:

- Development of User Manuals and “How To” Documents
- Ensuring sponsors are assured of system usability, confidentiality, user support arrangements, system availability, system stability and system bandwidth
- Definition and implementation of Transitional arrangements for the change to use Eudract from 1 May 2004
- Definition of the reports to be generated from EudraCT and how these will be used and published
- Building and piloting of database

The database should be available 24 hours per day, 7 days per week. However, it is not clear what transitional arrangements are being considered by the EMEA.

EudraVigilance is the other key database to be created by the Directive. It is the database which records the SUSARs on IMPs for trials being carried out in EU. It will facilitate the review and safety of use of IMPs in these clinical trials plus communication between authorities. It will provide enhanced protection of clinical trial subjects receiving IMPs as authorities will have oversight of both the clinical trials and IMPs. There will be a link between Eudract and EudraVigilance because a SUSAR has to relate to an IMP. They, therefore, share a few common fields.

Strategic concerns

The EMEA have agreed to set up a Joint Working Team for EudraCT and have established another for EudraVigilance, the first meeting of which was in mid May 2003. From a sponsor perspective the EudraCT Joint Working Group proposed remit is to establish business process design and implementation, ensure needs of clinical trial sponsors are represented, assess EudraCT design and implementation (confidentiality, security, accessibility, usability, stability, availability, etc), have input to the "User Guide" and run a pilot EudraCT in advance of full implementation, if possible. However, there may be a major issur in providing database infrastructure. The EMEA have indicated that they have insufficient IT budget to build EudraCT but the system design, by external consultants, should have continued to its planned end of May 2003. Further progress beyond May 2003 is unclear: if EudraCT does not exist on 1st May 2004 it is not obvious how the EMEA will support the Directive requirement for this database.

Discussion

- Database entry supports the creation of the application form which can then be printed and attached to the rest of the package of documents for both the CA and the EC.
- International Standard Randomised Controlled trial numbers will not be the same as the Eudract number but they will be included in the form.
- EMEA are keen to include representatives of all key stakeholders in the EudraCT Joint Working Group. However, it is not clear how academia has been consulted.
- Sponsors can be different in different MS, but there will be a unique identifying number for all applications across Europe.

General Discussion

The Directive may have an indirect effect on charitable donors for medical research who require to know what proportion of their grant will be spent on research and how much on bureaucracy. There could be greater increases in the overheads of small trials than in larger studies.

There is no proposal at the moment for electronic submission of clinical trial applications to the MHRA. Although Eudract and Eudra Vigilance will be expensive to develop and implement, implementation of EudraVigilance has started and it is expected that EMEA will implement Eudract sooner or later. Standards of electronic data transfer have been set up within ICH for the transmission of adverse event data and the guideline on EudraVigilance, associated with the Directive, makes it clear that SUSAR reports will be submitted electronically. A web interface to EudraVigilance will be developed to facilitate the electronic submission of SUSARs and will be open to use by all clinical trial sponsors. There is nothing in the Directive to require electronic submission of Competent Authority or Ethics Committee applications but the Commission guidelines expect applicants to complete part of these applications electronically online using the Eudract system and submit the paper version.

Concerns were again raised that while the Directive was intended to address issues in commercial product development, it also captures other research and many are still worried that it will impede research. However, if the opportunity is taken to improve the NHS as a clinical trial test-bed then an environment will be created to attract additional industry R&D investment. Will the new bureaucracy be a net impediment to research volume or the stimulus to build the better research environment? The academic community must collaborate in ensuring that an appropriate “road map” informs the process.

Will the MHRA treat academic studies differently from those from industry? Inspectors will look at the systems of Trusts, etc., to see that the research is creditable and publishable. If they find something wrong in the trial they will raise with the sponsor, investigator, etc., and make many attempts to have it rectified. The goal is to advise rather than punish but if the fault persists, the sanction would be an infringement notice.

In summary, it has been recognised that the academic community missed an opportunity in influencing the development of the Directive. It will be necessary to do better in the future, in identifying impending European developments and in articulating the messages of the clinical research community. Many researchers are concerned about what is perceived as a progressively more regulated environment. With regard to the specific implementation of the Directive in the UK, academic research centres and NHS Trusts need to decide who will take the lead and prepare for the impact of implementation; for example, in terms of clarifcation of process steps, joint construction of templates (research protocole) and training staff.

PROGRAMME

THE EUROPEAN CLINICAL TRIALS DIRECTIVE SYMPOSIUM

Tuesday 3 June 2003, The Royal College of Pathologists, 2 Carlton House Terrace, London SW1

The European Directive on Good Clinical Practice in Clinical Trials, that will be implemented in the UK in May 2004, has broad and important implications for the way in which trials involving human subjects will be conducted in the UK. Ethical, legal and practical aspects of trials involving both patients and healthy volunteers, whether sponsored by academia, industry, research organisations, charities or governmental bodies, will be affected. The purpose of this meeting is to explore these implications and to discuss the practical details that will arise when the Directive is fully implemented in a year's time. The programme has been designed to present the views and concerns of a number of key stakeholders and to provide opportunity for discussion of these issues.

9.00 – 9.30 Registration

9.30 – 9.35 Welcome and introduction by Sir John Skehel FRS FMedSci, Chairman of the Forum and Shadow Vice-President of the Academy of Medical Sciences and Director of the National Institute for Medical Research

MORNING SESSION: chaired by Professor Alasdair Breckenridge CBE FRSE FMedSci, Chairman of the new Medicines and Healthcare products Regulatory Agency (MHRA)

9.35 – 9.40 Introduction by Professor Alasdair Breckenridge CBE FRSE FMedSci

9.40 – 10.05 ***Draft UK legislation to implement the Clinical Trials Directive***, Dr Brian Davis, Clinical Trials Unit Manager, Medicines and Healthcare products Regulatory Agency (MHRA)

10.05 – 10.20 Discussion

10.20 – 10.45 ***Impact of the Clinical Trials Directive on the research-based pharmaceutical industry***, Dr Moira Daniels, Director of Global Regulatory Information and Intelligence, AstraZeneca Research & Development

10.45 – 11.00 Discussion

11.00 – 11.25 Coffee

11.25 – 11.50 ***EC directive and investigator-led clinical research; which studies are at risk?***, Professor Patrick Vallance FMedSci, Head of the Division of Medicine, University College London

11.50 – 12.05 Discussion

12.05 – 12.30 ***The impact of the new legislation on non-commercial trials: a major funder's perspective***, Dr Richard Sullivan, Head of Clinical Programmes, Division of Clinical Research, Cancer Research UK

12.30 – 12.45 Discussion

12.45 – 13.45 Lunch

AFTERNOON SESSION: chaired by Sir Colin Dollery FMedSci, Treasurer of the Academy of Medical Sciences and Senior Consultant, GlaxoSmithKline Research & Development

13.45 – 13.50 Introduction by Sir Colin Dollery FMedSci

13.50 – 14.15 ***Implications of the European Clinical Trials Directive on R&D in the NHS***, Professor Sally Davies FMedSci, Head of Research and Development for London, Department of Health

14.15 – 14.30 Discussion

14.30 – 14.55 ***Application for ethical review – opportunities and threats***, Professor Terry Stacey, Director, Central Office for Research Ethics Committees (COREC)

14.55 – 15.10 Discussion

15.10 – 15.35 Coffee

15.35 – 16.00 ***The challenge of local implementation of the European Clinical Trials Directive***, Dr Simon Thomas, MD, Clinical Senior Lecturer and Consultant, Wolfson Unit of Clinical Pharmacology, University of Newcastle

16.00 – 16.15 Discussion

16.15 – 16.40 ***Working with the European Clinical Trials Database***, Stephen Hasler, European Regulatory Operations and Systems, GlaxoSmithKline

16.40 – 17.10 Discussion and general discussion

17.10 – 17.20 Summary by Sir Colin Dollery FMedSci

17.20 – 18.30 Reception

The Academy gratefully acknowledges the support of AstraZeneca.

10 Carlton House Terrace
London SW1Y 5AH

Tel: 020 7969 5288
Fax: 020 7969 5298

Email: apollo@acmedsci.ac.uk
www.acmedsci.ac.uk