HMA
Heads of Medicines Agencies
Management Group

8th January 2010

To: European Commission
Unit ENTR/F/2,
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Subject: RESPONSE OF THE HEADS OF MEDICINES AGENCIES (HMA) MANAGEMENT GROUP TO THE COMMISSION'S CONSULTATION ON REVIEW OF THE CLINICAL TRIALS DIRECTIVE

Introduction

Since the implementation of the Clinical Trials Directive in 2004, the Heads of Medicines Agencies have established a Clinical Trials Facilitation Group (CTFG) to assist the operation and harmonisation of the Directive in Member States.

The CTFG has submitted to the HMA Management Group a consolidated document responding in detail to the Commission's consultation on the review of the Clinical Trials Directive, which is attached as a technical annex. This covering paper summarises the main points, and has the endorsement of the HMA Management Group.

Since there have been a number of national initiatives to promote clinical trials research, individual Member States may also submit consultation responses to assist the Commission in its review.

General Comments

CTFG notes that the implementation of the Directive has achieved benefits which are not adequately recognised in the Commission's document. The scrutiny of Clinical Trial Authorisation applications has led to a greater attention to issues of patient safety and data quality. Although only a small minority of applications are finally rejected, it is common for improvements to be required in the protocol before the CTA is granted. Scrutiny varied considerably between MS before the Directive, and Phase 1 normal volunteer studies were in many cases outside regulation (apart from Ethics review). Bringing clinical trials into regulation has inevitably has some impact on the resources required, but in the view of CTFG this has brought added value to the quality of research. The task now is to lighten regulatory burden wherever possible without a major new legislative initiative as much has already been achieved by the co-operation of Member States within the existing legal framework. There is scope to adopt best practice from Member States to improve the clinical research environment of the EU.

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KEY ISSUE N°1: MULTIPLE AND DIVERGENT ASSESSMENTS OF CLINICAL TRIALS

Since only 25% of trials in the EU are multinational, and there has been a low rate of disagreement between MS, the problem of divergent assessment has been overstated. In addition, divergences between Member States are mainly related to clinical practice differences (and consequent ethical considerations) and not related to pure regulatory or scientific review by NCAs .While it is true that multiple assessments of the same CTA added to the time taken to initiate multinational trials, this is now being addressed by the introduction of a Voluntary Harmonisation Procedure co-ordinated by CTFG. The greatest avoidable delay in recruitment of the first patient is not regulatory, but clinical. It should be noted that the implementation of the Directive has streamlined and accelerated the Ethics review process in many countries.

Because the majority (75%) of clinical trials are authorised in a single Member State, we do not support a centralised CTA process which would add delay and complexity to the system as a whole. Individual MS staff would need to support both a national and a central review procedure, or else a single centralised process would need to be imposed on the great majority of trials which are solely national.

The Ethical review process must remain at national level, to reflect national differences in culture and healthcare provision. We would, however, advocate strong formal links between the Ethics review structure and the Competent Authority within each country to ensure that their respective roles are clearly defined. We would also support better networking of Ethics bodies across the EU to share best practice.

KEY ISSUE N°2: INCONSISTENT IMPLEMENTATION OF THE CLINICAL TRIALS DIRECTIVE

There has been a lack of clarity on the definition of certain terms:

- Substantial amendment
- Non-interventional trial
- SUSARs

These could be resolved by revising the guidance on the existing legislation. They do not require re-casting of the legislation as a Regulation; indeed, it is not clear that such a change would assist researchers and regulators in reaching consistency.

The problem of inconsistent definition of a ‘non-interventional trial’ could be minimised by adopting a risk-based approach to the CTA and monitoring processes. Those studies carrying little or no risk in excess of usual clinical care could, with revised guidance, be regulated in a ‘light touch’ way (see below).

There is some responsibility on the research community to avoid wherever possible the resubmission of trial protocols as ‘substantial amendments’. Researchers should also avoid reporting as SUSARs a large number of events which do not justify that term. Finally, it would be a valuable simplification if SUSARs were to be reported only to the

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Competent Authority and not also to the Ethics committee, since it is the former which is best equipped to reach a judgement on their significance.

KEY ISSUE N°3: REGULATORY FRAMEWORK NOT ALWAYS ADAPTED TO THE PRACTICAL REQUIREMENTS

CTFG is working with the EU Inspectors Group to develop a reflection paper on risk-based Quality Management in clinical trials. This may form the basis for a more risk proportionate approach to the regulation of clinical trials in the future which could offer great benefits to researchers without reducing the safety or quality of clinical trials. It could be actively supported through revised guidance and without needing changes to legislation.

As regards the sponsor role, several MS have made arrangements for formal sharing of the sponsor responsibilities between several different bodies (for example, the funder and the host hospital), linked by agreements on roles and responsibilities. For multi-state trials this could also be done between MS to ensure that the whole trial is managed effectively and the responsibilities of the sponsor are clearly allocated and coordinated,

We see no logical basis for treating commercial and 'non-commercial' (or 'academic') sponsors differently in legislation. In any clinical trial, participants are entitled to a similar degree of protection. Similarly, any clinical trial has the potential to influence future clinical practice and must therefore deliver results which are reliable whether or not they are to be used in support of an MA application. What is required instead is a risk-based classification of clinical trials, so that appropriate (but not excessive) levels of scrutiny are applied both at authorisation and during monitoring. The level of risk can be proposed by the sponsor and confirmed (or amended) by the NCA.

KEY ISSUE N^{o} 4: ADAPTATION TO PECULIARITIES IN TRIAL PARTICIPANTS AND TRIAL DESIGN

CTFG refers to the implementation in several MS of arrangements to enable clinical trials in paediatric populations and under emergency conditions. These could be used as a model for other countries and could be supported by amendment of the existing EU legislation.

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KEY ISSUE N° 5: ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES ("GCP") IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

It is unacceptable that subjects anywhere in the world should be exploited by participation in clinical trials which are inadequately controlled to protect patient safety and data integrity. The EU can take legal powers to enforce GCP for any study which is to be submitted as part of a MA application within the EU, but has no powers to enforce a global standard of GCP otherwise. Progress can then only be achieved by collaborative action between regulators world-wide and by international training links built on a voluntary basis.

Yours sincerely,

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