Bird & Bird & Clinical trials regulation

The Proposal for a Regulation of the European Parliament and of the Council on Clinical Trials on Medicinal Products for Human Use and Repealing Directive 2001/20/EC – an update

By Gerry Kamstra, Partner

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Introduction

Although the introduction of Directive 2001/20/EC intended to harmonise the regulation of clinical trials on medicinal products in the European Union, the divergence in its implementation in Member States, the administrative burden imposed by its scope and procedures and the duplication in effort required for multi-State trials (*inter alia*) soon led to much criticism, from clinical investigators through to pharmaceutical companies. Although the introduction of a Voluntary Harmonisation Procedure in April 2009[1] alleviated some of the concerns over multi-State trials, most of the other concerns remained. As a result the European Commission conducted a public consultation in 2009/10 leading to the publication of a summary of responses from stakeholders in March 2010[2] and, subsequently in February 2011, a "concept paper" for public consultation on a revision of the Directive[3].

In July 2012 the Commission published its proposal for a Regulation replacing Directive 2001/20/EC[4]. Its central feature is the setting up of an EU-wide administrative procedure and portal, based upon mutual recognition of assessments prepared by a reporting Member State, that will allow a single application for the approval of a clinical trial to be conducted in multiple EU Member States.

As a result of the proposed Regulation, Directive 2001/20/EC will be repealed. In order to allow for a smooth transposition of the rules of Directive 2001/20/EC to the rules of the proposed Regulation, both sets of rules will apply in parallel for a period of time (possibly three years) after the date of application of the proposed Regulation. This will facilitate the transition, in particular for aspects of the authorisation procedures. The proposed Regulation is expected to apply from 2016.

The proposed Regulation has been considered by the Parliamentary Committees on the Environment, Public Health and Food Safety, on Industry Research and Energy and on the Internal Market and Consumer Protection, resulting in a draft report[5] with suggested amendments for consideration at the first reading by the European Parliament in early April 2014. The EU Council has also prepared a

[1] http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2010_03_VHP_Guidance_v2.pdf
[2] http://ec.europa.eu/health/files/clinicaltrials/2010_03_30_summary_responses.pdf
[3] http://ec.europa.eu/health/files/clinicaltrials/concept_paper_02-2011.pdf
[4] http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf
[5] http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//NONSGML%2BCOMPARL%2BPE-504.236%2B01%2BDOC%2BPDF%2BV0//EN

consolidated text with suggested amendments[6] for the first Parliamentary reading.

This update will first outline the proposed Regulation as put forward by the Commission in July 2012 and then provide a summary of the key amendments proposed by the Parliamentary Committees and by the Council.

I. The Commission's Proposal[7]

Scope

The scope of the proposed Regulation is essentially identical to that of Directive 2001/20/EC. The scope is limited to clinical research on medicinal products, but it is very wide in that it only excludes clinical studies that do not involve an 'intervention' (e.g. surveys amongst medical practitioners without additional intervention or 'data mining').

For 'non-interventional studies' which are post-authorisation safety studies initiated, managed or financed by the marketing authorisation holder voluntarily or pursuant to obligations imposed by the competent authority for marketing authorisations, the rules are set out in Directive 2001/83/EC (i.e. the Community code relating to medicinal products for human use).

The proposed Regulation defines a sub-category of clinical trials falling within its scope, namely "low-intervention clinical trials", which fulfill all of the following conditions:

- the investigational medicinal products (**IMP**s) are authorised
- according to the trial protocol the IMPs are used in accordance with the terms of their marketing authorisation or their use is a standard treatment in any of the Member States concerned
- the additional diagnostic or monitoring procedures do not impose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned

Note that the definition of IMP includes medicinal products which are being tested or used as a reference, including a placebo, in a clinical trial.

The principal differences between the administrative procedures to be applied to low-intervention clinical trials and other clinical trials are simply the quicker processing periods within which the reviewing Member States and applicants must respond (the default position being

[6] http://www.kslaw.com/imageserver/KSPublic/library/publication/ca010814a_1.pdf

[7] This part of this update is substantially based on the Commission's helpful explanatory background notes to the proposed Regulation

deemed acceptance or withdrawal, as applicable). That is to say, apart from the quicker turnaround of applications, low-intervention clinical trials are dealt with in the same way as other clinical trials.

New procedures

The proposed Regulation introduces a new authorisation procedure for clinical trials based on the following concepts:

- A harmonised authorisation dossier, partly codifying the existing Commission guidance contained in EudraLex, Volume 10;
- A 'single portal' to submit an application for conducting a clinical trial linked to an EU database. This portal is managed by the European Commission and is free of charge for sponsors;
- A flexible and swift[8] assessment procedure without establishing a new, central bureaucracy. This assessment is largely controlled by Member States. All Member States in which the sponsor intends to conduct the clinical trial are involved in the assessment, although the primary assessment will be carried out by the "reporting Member State";
- A clear mechanism to appoint a "reporting Member State";
- Clear timelines with a concept of tacit approval in order to ensure compliance;
- A coordination and advisory forum to address issues which may arise in the authorisation procedure. This forum is managed and chaired by the Commission;
- A clear distinction between aspects where Member States cooperate in the assessment (Part I of the assessment report) and aspects of an intrinsic ethical or national/local nature where the assessment is made by each Member State individually (Part II of the assessment report);
- The option, in certain well-defined cases, for a Member State to "opt-out" of the conclusions of an assessment of an application for conducting a clinical trial ("qualified opt-out");
- It is left to each Member State to define the organisational setup and internal competences for assessing clinical trial authorisations, provided that international guidelines on the independence of the assessors are observed;
- A swift procedure to "extend" a clinical trial to additional Member States;

[8] 6 days for the reporting Member State's initial review; 6/10 days for the applicant to respond to questions, 10/25/30 days for the Part I assessment report (depending on whether the application is for a low-intervention clinical trial, other clinical trial or Advanced Therapeutic Medicinal Product clinical trial)

- Where a clinical trial is modified after it has been authorised, this modification is subject to authorisation if, and only if, the modification has a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

To summarise, the Part I assessment (which will follow a "mutual recognition" type procedure) will cover:

- Anticipated therapeutic and public health benefits
- Risk and inconvenience for the subject
- Compliance with requirements regarding manufacture and importation of IMPs
- Compliance with labelling requirements
- Completeness and adequacy of the investigator's brochure

and the Part II assessment (which falls within the competence of each concerned Member State and, in turn, the delegated bodies chosen by it for the assessment) will cover:

- Compliance with requirements for informed consent
- Compliance with requirements for rewarding or compensating subjects
- Compliance with requirements for recruitment of subjects
- Compliance with the Data Protection Directive
- Compliance with requirements regarding the qualifications of investigators
- Compliance with requirements regarding the suitability of trial sites
- Compliance with the requirements for compensation for damage in non-low intervention trials
- Compliance with the requirements for collection, storage and future use of biological samples

Application Dossier

Note that where reference is made in the application dossier to data generated in a clinical trial conducted outside the EU, such clinical trial must comply with the principles in the Regulation as regards subject rights and safety and reliability and robustness of data generated in the clinical trial and have been registered in a public register which is a primary registry of the international clinical trials registry platform of the World Health Organisation. Failing this, such data will not be considered in the assessment of an application.

The language of the application dossier should be that determined by the Member State concerned and Member States are required by the proposed Regulation to consider acceptance of a commonly understood language in the medical field so far as documentation not addressed to trial subjects is concerned.

The EU portal and the European Medicines Agency database for safety reporting

The EU portal for submission of documents relating to applications, or "EU database", is to be maintained by the Commission, and will be publicly accessible unless confidentiality is justified on the grounds of (i) protection of personal data (ii) protection of commercially confidential information or (iii) ensuring effective supervision of the conduct of a clinical trial by Member States. In any event no personal data relating to subjects will be publicly available from the EU database.

Within one year from the end of a clinical trial the sponsor is required to submit to the EU database a summary of the results of the clinical trial, which summary will be publicly accessible from the database.

Sponsors

Note that a clinical trial may have one or several sponsors, that any sponsor may delegate any or all of its responsibilities and that the investigator and sponsor may be the same person. However, only one sponsor shall be responsible for the authorisation procedures and providing answers to questions raised by the relevant Member States and dealing with corrective measures required by a Member State during the conduct of a trial.

Where a sponsor is not established in the EU the proposed Regulation requires it to ensure that it has a "contact person" established in the EU; any communications with that person will be considered as communications to the sponsor. Note the difference from the position under Directive 2001/20/EC, which requires a "legal representative" established within the EU and which has caused some confusion as to the legal liability of persons identified as the "legal representative".

Damage compensation and fees

Member States are required by the proposed Regulation to provide for a national indemnification mechanism for all clinical trials, other than low-intervention clinical trials. This mechanism is to be free of charge when, at the time of submission, the clinical trial was not intended to be used for obtaining a marketing authorisation. For all other trials a fee on a not-for-profit basis, taking into account the risk of the clinical trial, the potential damage and the likelihood of damage, is to be levied.

Whilst Member States may require the payment of fees in connection with applications, they may not require multiple payments to different bodies for the assessment, ie there will be one fee per activity per Member State.

Inspections

Member States will be responsible for inspections and if they wish to conduct an inspection with regard to one or several clinical trials conducted in in more than one Member State they should notify the other Member States concerned, the Commission and the European Medicines Agency through the EU portal – the Agency will be responsible for coordinating cooperation.

The Commission may conduct controls to ensure that Member States correctly supervise compliance with the Regulation and that the regulatory system applicable to trials conducted outside the EU ensures that Good Clinical Practice as required by Directive 2001/83/EC and the ethical principles of the Declaration of Helsinki[9] are complied with.

Clinical Trials Coordination and Advisory Group
A Clinical Trials Coordination and Advisory Group (CTAG) will be established under the proposed Regulation to support the exchange of information between Member States on experience gained with regard to implementation of the Regulation and the functioning of cooperation between Member States.

II. Parliamentary Committee and Council Proposed Amendments

The amendments proposed by the Parliamentary Committees and the Council are largely overlapping and complementary, although in a number of areas the amendments proposed by the Council are more detailed. As little turns upon the source of the proposed amendments they are dealt with together below, except where are notable differences in their proposals.

Scope
Minor changes are suggested to make it absolutely clear that the proposed Regulation only applies to studies relating to medicinal products; and to make it clear that where a study relates to use of an authorised medicinal product outside its marketing authorisation the study only falls to be categorised as a standard clinical trial if the use of the medicinal product is outside normal clinical practice (to exclude studies on standard off-label use from categorisation as standard clinical trials). Correspondingly, in relation to low-intervention trials, it is suggested that clinical trials with IMPs that are being used off-label should only fall within the category of low-intervention trials if the off-label use is supported by sufficient published evidence and/or standard treatment guidelines.

New procedures
As regards the general principles to be applied in allowing a clinical to proceed it is proposed that not only should the data to be generated by the trial be reliable and robust, but that the data should be relevant.

As regards the Part I assessment it is proposed that not only should the anticipated therapeutic and public health benefits be taken into account, but also the quality of life benefits.

It is also proposed that the Part I and Part II assessments by the reporting Member State be submitted within a slightly longer time period than originally envisaged, namely 45 days from the validation of an application

[9] http://www.wma.net/en/30publications/10policies/b3/

– although not commented upon in the Council's proposals, it is hard to see how even these extended deadlines can be complied with given the current resources held by the regulatory and ethical review bodies in the EU at present.

It is proposed that ethics committees should not only be involved in the Part II assessment, but also in the Part I assessment. Various changes are proposed with regard to the constitution of, and the issues to be considered by, ethics committees; in particular (a) they should include not only healthcare professionals and lay persons but also a knowledgeable patient representative and, where applicable, professionals with expertise relating to the vulnerable population group involved in a trial and (b) guidelines on patient involvement in ethics committees should be developed by the Commission. Again, these requirements raise significant questions as to the availability of resources.

As regards the ethical assessment, the Parliamentary Committees appear to be taking a different approach from the Commission and the Council. The Commission's text requires that a clinical trial may only proceed if "the rights, safety and well-being of subjects prevail over the interests of science and society" – this corresponds closely to the text of the Declaration of Helsinki which requires that (point 8) "while the primary purpose of medical research is to generate new knowledge this goal can never take precedence over the rights and interests of individual research subjects". The Parliamentary Committees have proposed that a clinical trial may only proceed if "the rights, safety and well-being of subjects prevail over *all other interests*", whereas the Council has proposed the deletion of the text altogether –presumably relying on other iterations of the requirements of the Declaration of Helsinki in the Commission's text. The text proposed by the Parliamentary Committees ("prevails over *all other interests*") arguably sets the standard too high, inasmuch as this potentially forecloses the conventional basis of ethical assessment (as reflected elsewhere in the Commission's text, borrowing from point 17 of the Declaration of Helsinki) namely that there should be an assessment of predictable risks and burdens to the subjects in comparison with the foreseeable benefits to them and to other individuals affected by the condition under investigation. In short, it appears that the Commission and Council proposals are more in line with the Declaration of Helsinki.

It is proposed that the informed consent given by a trial subject may include consent to use his or her data outside the protocol of the clinical trial in question for scientific purposes, provided that the use of the data is in accord with data protection legislation. This is a useful endorsement of current practice and avoids the need to go back to trial subjects for consent when potentially useful new analyses of data are proposed.

Finally, proposals are made which set out in more detail the conditions under which clinical trials involving incapacitated subjects, vulnerable population groups, minors, pregnant and breastfeeding women and those in emergency situations may be carried out. These proposals are broadly in

line with current statutory requirements and ethical guidelines in (for example) the UK.

Application Dossier

It is proposed that where an application dossier relies on data generated in an earlier trial, such data must (a) have been gathered in a trial that complies with the Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research Involving Human Subjects[10] and (b) be registered in a public register which is a partnered registry of the international clinical trials registry platform of the World Health Organisation[11].

The EU portal and the European Medicines Agency database for safety reporting

It is proposed that not only should the sponsor of a clinical trial submit a summary of the results of the clinical trial to the EU database within one year from the end of the trial, but that this should take place irrespective of the outcome of the trial (so for example adverse findings must be made public) and in a form that is understandable to the lay person. It is proposed that failure to provide this summary to the EU database should be met with financial penalties.

In addition, it is proposed that where a marketing authorisation is sought for the IMP the clinical study report should be submitted to the EU database within 30 days after the marketing authorisation has been granted or the application is withdrawn. These proposals address the public debate that has been conducted over recent years between advocates of clinical trial transparency (for example the Cochrane Collaboration) and the pharmaceutical industry. It is worth noting that the proposed 30 day deadline is substantially shorter than the one year period advocated by (for example) the International Federation of Pharmaceutical Manufacturers & Associations.

As for safety reporting, more detailed requirements and deadlines are proposed. It is proposed that the European Medicines Agency rather than the Commission should be responsible for controlling the EU database, and that it should be responsible for avoiding unnecessary duplication between the EU database and the EUdraCT and EudraVigilance databases.

Sponsors

It is proposed that where a sponsor delegates any or all of its tasks to an individual, this should in a written contract.

As regards responsibility for a clinical trial, two very significant changes are proposed by the Council:

First, that the principal investigator will be responsible for ensuring the compliance of a clinical trial at a clinical trial site with the requirements of

[10] http://www.recerca.uab.es/ceeah/docs/CIOMS.pdf
[11] http://apps.who.int/trialsearch/

the proposed Regulation. This proposal would impose a significantly higher level of responsibility upon principal investigators than heretofore, as compliance with *all* of the requirements of the Regulation will include matters normally within the remit of the sponsor alone.

Second, the Council has rejected the Commission's proposal that a sponsor which is not established in the EU should have just a "contact person" within the EU and instead proposed that such a sponsor must have a "legal representative" responsible for ensuring compliance with all of the sponsor's obligations under the proposed Regulation. This would make the requirement for a "legal representative" for non-EU based sponsors even more onerous than at present under Directive 2001/20/EC. Somewhat oddly, the Council also proposes however that Member States may each (or collectively as regards a multi-State trial) opt out of the requirement for a "legal representative" and only require a "contact person". It seems unlikely that any Member State seeking to encourage clinical trials of new IMPs in its hospitals would require a "legal representative" rather than a "contact person".

Damage compensation and fees

The Council has rejected the Commission's proposal that there should be a free national indemnification scheme established in the Member States, no doubt reflecting Governmental concerns about the costs of such schemes. Instead it proposes that Member States should simply ensure that systems for compensation in the form of insurance or a guarantee are in place – this would allow the arrangements that are commonly used currently to satisfy the Regulation.

Clinical Trials Coordination and Advisory Group

It is proposed that in addition to the establishment of the CTAG the Commission should facilitate cooperation and sharing of best practice between ethics committees.

III. The key amendments to be put to the European Parliament in April 2014

As regards the obligations of the Member States the key proposed amendments are:

- The deadlines within which the national medicines agencies and ethics committees will have to work and the increased involvement of ethics committees
- The rejection of the proposal for free national indemnification schemes

As regards the European Medicines Agency the key proposed amendments are:

- The proposal that it should be responsible for the EU database and that it should avoid unnecessary duplication with the EUdraCT and EudraVigilance databases

As regards pharmaceutical companies the key proposed amendments are:

- The requirement that a lay summary of the clinical trial results be filed with the EU database within one year from the end of the trial
- The requirement that the clinical study report be filed with the EU database within 30 days of the grant of the marketing authorisation or its withdrawal

As regards non-EU sponsors the key proposed amendments are:

- The requirement in the case of those Member States that do not opt for just a "contact person", that the sponsor should have a "legal representative" responsible for the sponsor's compliance with the Regulation

As regards the clinical research community the key proposed amendments are:

- The requirement that the principal investigator be responsible for ensuring the compliance of a clinical trial at a clinical trial site with the requirements of the proposed Regulation, in particular the unqualified wording of the proposed amendment

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