Clinical trials on medicinal products in Malta following EU accession

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Abstract

Following EU Accession, Malta has to adopt EU Directives as part of its own legislation. Three such directives concern the conduct of clinical trials in European countries – 2001/20/EC, 2003/94/EC and 2005/28/EC. These directives, and the respective guidelines explaining their implementation, have considerably changed the way clinical trials are conducted. While the participation of Malta in clinical trials is to be encouraged for various reasons, these have to be regulated according to the legislation set out by the European Union. In themselves, what these Directives strive to achieve are mainly the safety of the study subject and the protection of the investigators from serious consequences. This short article aims to give a brief overview of these changes to prospective investigators and hospital administrators.

Overview

Following Malta's accession to the European Union, the directives and guidance documents published by the European Commission concerning research on human subjects were adopted locally.

The legislation concerning clinical trials consists of Directive 2001/20/EC[1] (transposed as Clinical Trials Regulations, 2004[2]), Directive 2003/94/EC[3] (transposed as Good Manufacturing Practice in Respect of Medicinal and Investigational Medicinal Products for Human Use Regulations, 2004[4]) and Directive 2005/28/EC[5] which come into force at the end of January 2006.*

Keywords

Clinical trials, Medicines Authority, Ethics Committee, Legislation

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Directive 2001/20/EC[1] and the Clinical Trials Regulations, 2004[2] apply to all interventional trials (Phase I - IV) involving investigational medicinal products in the Community (including non-commercial ones) beginning on or after 1 May 2004. This legislation applies to both the public and private sector.

According to article 2(a) of Directive 2001/20/EC[1] and Regulation 3 of the Clinical Trials Regulations, 2004[2] a clinical trial is 'any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal products, and/or to identify any adverse reactions to one or more investigational medicinal products and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal products with the object of ascertaining their safety and/or efficacy.'

Article 2(e) of Directive 2001/20/EC[1] and Regulation 3 of the Clinical Trials Regulations, 2004[2] define sponsor as an '*individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial.*' In the case of academic investigator-led trial, the principal investigator is often the sponsor. In commercial trials, applications are usually handled by the pharmaceutical company or the clinical research organisation (CRO) that is heading the trial, rather than by the investigator. In academic research the application is usually handled by the researcher or his delegate.

Companies, CROs or researchers applying to regulatory authorities for a clinical trial can download a clinical trial application form[6] from the European Commission's EudraCT database sponsor portal on: http://eudract.emea.eu.int/. This database contains information on all clinical trials being conducted in the Community from 1 May 2004. The database may be accessed by the competent authorities of the European Union member states, European Medicines Agency and European Commission.

In order to conduct a clinical trial in Malta separate copies of the application form must be submitted to the Medicines Authority and to the Health Ethics Committee. The applications to the Medicines Authority and Health Ethics Committee may be submitted in parallel or sequentially, as the sponsor wishes. A clinical trial may only start if the Health Ethics Committee has issued a favourable opinion and the Licensing Authority has issued an authorisation. Following successful validation, applications are assessed within a time frame as stipulated in Directive 2001/20/EC[1] and the Clinical Trials regulations,

2004.[2] As part of the assessment the Medicines Authority or the Health Ethics Committee may require further information or clarification and in the meantime there may be a clock stop until the applicant answers.

Furthermore, substantial amendments to an approved application should be implemented only after being separately authorised by the Medicines Authority and / or Health Ethics Committee (depending on the nature of the amendment). Amendments are considered to be substantial when they fit into the criteria set out by the applicable guideline.[7] An amendment application form[8] has been published by the European Commission. The Medicines Authority and Health Ethics Committee should also be notified when a clinical trial has ended or is halted. An end of trial form[9] has also been published by the European Commission.

Directive 2001/20/EC[1], Clinical Trials Regulations, 2004[2] and the guidance documentation[10,11] published by the European Commission also define pharmacovigilance aspects and responsibilities with respect to pre-marketing and post-marketing clinical trials conducted within or outside the European Community. Reporting mechanisms and timeframes are also defined. Sponsors should also submit, on request as well as once a year throughout the clinical trial, a safety report to the Medicines Authority and the Health Ethics Committee.

Medicines Authority

The European Commission has published a guidance document[7] for the initial submission, amendments and end of trials. One should note that a number of documents need to be included with the application to allow assessment. These are listed in a guidance document[7] published by the European Commission. The Medicines Authority has also published guidance notes[12] so as to explain the procedures within the local context. The Authority recommends that the documents published by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use should also be followed, including the Guideline for Good Clinical Practice.[13]

According to Directive 2001/20/EC[1] and the Clinical Trials Regulations, 2004[2] the sponsor should send electronic reports concerning Suspected Unexpected Serious Adverse Reactions (SUSARs) to the European Medicines Agency (Eudravigilance clinical trials database, accessible on: http://www.eudravigilance.org) and the Medicines Authority. The Medicines Authority has also published guidance documents[14-16] to explain further these pharmacovigilance obligations.

Pharmacovigilance obligations also hold for clinical trials which have started before 1 May 2004. For this reason clinical trials which started before 1 May 2004 and are still ongoing need to be notified to the Medicines Authority. After 1 May 2004 any new trial needs to be approved as detailed above before it can commence.

Health Ethics Committee

The ethics committee involved in the review of clinical trials in Malta as per the Clinical Trials Regulations, 2004[2] is the Health Ethics Committee, as established by the notice in the Malta Government Gazette of 29th April 2005.[17] The members were appointed by the Director General (Health). The list of members of this Committee may be seen at the HEC website on www.sahha.gov.mt, under the heading 'Statutory Bodies'. This Committee meets every month.

Article 6(3) of Directive 2001/20/EC[1] and Regulation 7(2) of the Clinical Trials Regulations, 2004[2] list the points which the Health Ethics Committee should consider when assessing an initial clinical trial submission:

'In preparing its opinion, the Ethics Committee shall consider, in particular:

(a) the relevance of the clinical trial and the trial design;
(b) whether the evaluation of the anticipated benefits and risks is satisfactory and whether the conclusions are justified;
(c) the protocol;
(d) the suitability of the investigator and supporting staff;
(e) the investigator's brochure;
(f) the quality of the facilities;
(g) the adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research on persons incapable of giving informed consent;
(h) provision for indemnity or compensation in the event of injury or death attributable to a clinical trial;
(i) any insurance or indemnity to cover the liability of the investigator and sponsor;
(j) the amounts and, where appropriate, the arrangements for rewarding or compensating investigators and trial subjects and the relevant aspects of any agreement between the sponsor and the site;
(k) the arrangements for the recruitment of subjects.'

The informed consent, patient information leaflet as well as any other documentation which has to be completed by the patient should be in both Maltese and English.

The European Commission has published a guidance document[18] for the initial submission of documentation for an ethics committee opinion. One should note that a number of documents need to be included with the application to allow assessment. These are listed in this guidance document published by the European Commission. Additional information may be found in the guidance notes[19] which were published by the Health Ethics Committee. Applications of substantial amendments together with notifications of SUSARs and terminations of clinical trials should also be sent to the Health Ethics Committee.

Any researchers planning studies not involving clinical trials are invited to submit their proposals to the Medical School Research Ethics Committee as is customary.

Conclusion

The Health Ethics Committee and the Medicines Authority are well aware that these regulations may have radically changed the way that clinical trials are conducted in Malta. Even though these regulations may be interpreted as an unwelcome imposition from the European Union, they have been instituted to protect both study participants and investigators from any unwelcome consequences that have caused deaths and ruined the reputation of some researchers in the past.

As mentioned initially, these technicalities are usually tackled by the industry, that is pharmaceutical companies and CROs, that approach investigators with an invitation to join a clinical trial. These companies are very familiar with the above procedures and are also aware that the requirements in Malta are similar to those of other European agencies and ethics committees. Clinicians and health care professionals, as investigators or representatives of clinical trial centres, should be aware of these regulations so as to know the extent of their duties and responsibilities.

The Medicines Authority and Health Ethics Committee did not add any requirements other than those requested by other European agencies. Separate sets of documents are required for the two bodies to conduct separate assessments as expected by the legislation. These two bodies have to meet obligations and responsibilities.

Investigators are invited to contact the Medicines Authority (prelicensing.mru@gov.mt) and/or the Health Ethics Committee (hec@gov.mt), should they require further advice. The Health Ethics Committee also invites investigators to contact the Committee, preferably in writing, should they wish to discuss issues with the Committee during one of their meetings.

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* Directive 2005/28/EC has been transposed as Good Clinical Practice and Requirements for Manufacturing or Import Authorisation of Investigational Medicinal Products (Human Use) Regulations, 2006 (LN 119 of 2006), under Medicines Act, 2003. Available from: http://www.doi.gov.mt/EN/legalnotices/2006/05/LN119.pdf