END OF TRIAL

The European Union Clinical Trial Directive (EU Directive 2001/20/EC) requires the following in relation to clinical trial completion:

"...within 90 days of the end of a clinical trial, the sponsor shall notify the competent authorities of the Member States, or Member States concerned, and the Ethics Committee that the clinical trial has ended..."

"Additionally the sponsor needs to provide a summary of the clinical trial report within one year of the end of the trial to the authorities in the Member States concerned."

The end of a clinical trial should be defined in the protocol and would normally be the last follow-up visit of the last patient. In studies that involve long term follow-up where patients are no longer taking trial medication and the data are obtained as part of usual care, this period could be classified as a non-interventional phase, which would not need to be authorised under the regulations (and not be subject to the annual fees, inspections etc).

Early termination

Several factors can influence the decision to terminate an ongoing clinical trial, including ethical concerns, alterations in accepted clinical practice that make the continuation of a trial unwise, and/or reaching a positive or negative statistical end point earlier than anticipated. Guidelines for early termination of a clinical trial should be established before any data review is undertaken. Interim data analyses, in conjunction with the totality of available evidence, provide the necessary framework from which Data and Safety Monitoring Boards can make informed and prudent recommendations. Clinical trials should not be prematurely terminated for trivial reasons or on economic grounds, particularly if the information to be gained adds substantially to the knowledge base on the therapy of disease states.

Investigator specific considerations are generally more relevant for single center trials but may also influence multicenter trials, particularly if the investigative site in question has been a heavy enroller in the clinical trial.

In the EU, whenever a trial is terminated early, someone acting on behalf of the Sponsor must notify the regulatory authority(ies) concerned within 15 days and clearly explain the reasons for termination. If the Sponsor decides not to commence a trial or not to recommence the trial after halting it, they should notify the regulatory authority(ies) concerned.

Trial close-out

The term "close-out" refers to procedures undertaken to fulfil administrative, regulatory, ethical and participant requirements, after all protocol defined follow-up in a trial has been completed.

A final close-out of a trial can only be completed when both investigator/institution and sponsor files have been reviewed and it is confirmed that all necessary documents are in the appropriate files e.g. Investigator Study File or Trial Master File.

Data analysis

It is important that the final analysis is carried out promptly after the appropriate follow-up period. The analysis should follow a carefully written analysis plan. All outcome measures stated in the protocol should be fully analysed. The analysis should then be discussed by the trial management group to

assist interpretation and to discuss the implications of the findings.

Reports within one year of trial ending

Someone acting on behalf of the Sponsor should also provide a summary of the clinical trial report within one year of the end of the trial to the Competent Authority of the Member State(s) concerned. This is *Good Clinical Practice* and is not a regulatory requirement. The format of this summary should comply with the ICH E3 guidelines for structure and content of a clinical study report as much as possible.

Dissemination of results

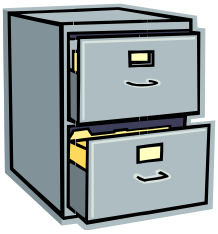
It is important to disseminate the results of clinical research, not only to the research community, but to the general public as well. The obvious route to inform the research community is through publication in scientific journals. It is recommended that the CONSORT guidelines are followed when preparing a manuscript for a clinical trial. This ensures that all relevant information about the trial is reported in the publication.

Different organisations have different strategies for informing the public. The findings from trials can be published on the trial website. Another way is through leaflets in the waiting rooms of hospitals and clinical research centres. Leaflets are a good ways to promote research participation and demonstrate that research findings have improved current clinical practice.

It is important to establish at the outset whether a participant will want to be informed of trial results or whether they would prefer to obtain the results themselves, should they wish to do so.

Archiving

The documents which individually and collectively permit evaluation of the conduct of a clinical trial and the quality of the data produced are defined as **essential documents** according to ICHGCP. These documents service to demonstrate the compliance of the investigator, sponsor and monitor with the standards of GCP and with applicable regulatory requirements. The essential documents should be filed in an organised manner that will facilitate the management of the clinical trial, audit and inspection (Trial Master File).



Essential documents must be retained (archived) for sufficient periods to allow for audit and inspection by regulatory authorities and should be readily available upon request. The Trial Master File should be set up at the beginning of a trial and maintained throughout the trial. **Archiving applies to both the investigator sites and the trial coordinating office.**

Essential records should be maintained in a legible condition and prompt retrieval should be possible. Plans for archiving trial documents should be made in the design phase of a trial and costs of storage should also be considered. Adequate and suitable space should be provided for the secure storage of all essential records upon trial completion. The facilities should be secure, with appropriate environmental controls and adequate protection from fire, flood and unauthorised access. The storage of the sponsor's documentation may be transferred to a sub-contractor (e.g. a commercial archive) but the ultimate responsibility for the quality, integrity, confidentiality and retrievability of the documents resides with the Sponsor.

Access to archives should be restricted to authorised personnel. Any change in the ownership and location of the documentation should be documented in order to allow tracking of the stored records.

An archive index/log should be maintained to record all essential documents that have been entered into the archive and to track

and retrieve documents on loan from the archive. The investigator should make the sponsor/trial organiser aware of the storage arrangements for the documents to be stored at investigator sites. If the investigator becomes unable to store their essential documents the sponsor/trial organiser should be notified in writing, so that alternative storage arrangements can be agreed. If the investigator is no longer able to maintain custody of their essential documents, the Sponsor/trial organiser should be notified in writing and the investigator/institution ensure that appropriate arrangements can be made. Storage of personal data is subject to applicable elements of EU Directive 95/46/EC and the Data Protection Act 1998.

Duration of archiving: The Sponsor or someone acting on behalf of the Sponsor should consider whether the trial results will be, or may be, included in a marketing authorisation application and should take the necessary steps to ensure appropriate retention of the essential documents.

Trials which are not to be used in regulatory submissions:

Essential documents of the Sponsor/trial organiser and investigators from trials that are not to be used in regulatory submissions should be retained for at least five years after the completion of the trial. These documents should be retained for a longer period if so stated in the relevant regulatory requirements or requested by the sponsor or funder of the trial.

Trials to be included in regulatory submissions:

i. Sponsor's responsibilities

The Sponsor or someone acting on behalf of the Sponsor should retain all sponsor specific essential documents in conformance with the applicable regulatory requirements of the country(ies) where the product is approved and/or where the Sponsor intends to apply for an approval.

The Sponsor specific essential documents should be retained until at least two years after the last approval of a marketing application in the EU. These documents should be retained for a longer period if so stated in the applicable regulatory requirements or if requested by the Sponsor.

The requirements of Annex 1 to Directive 2001/83/EC must be complied with.

In addition the GCP requirements CPMP/ICH/135/95 will apply.

ii. *Investigator responsibilities*

Essential documents should be retained until at least two years after the last approval of a marketing application in the EU. However, these documents should be retained for a longer period if so stated in the relevant regulatory requirements or by agreement with the Sponsor. It is the responsibility of the Sponsor or someone acting on behalf of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

In addition the requirements of Annex 1 to Directive 2001/83/EC must be complied with.

Destruction of essential documents

The reasons for destruction of essential documents should be documented and signed by a person with appropriate authority. This record should be retained for a **further** five years from the date that the essential documents were destroyed.

The Sponsor or someone acting on behalf of the Sponsor should notify investigators in writing when their trial records can be destroyed.