Implementation of GOOD CLINICAL PRACTICE principles in EpiData Software

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EpiData Software is released for public use by the non-profit EpiData Association, whose mission is to enhance data quality and analysis in public health through the development and dissemination of tools designed for public health practice and other field work. The software is focused on data entry, data documentation and basic analysis needs for quantitative data. The software can run from any USB stick and is available for free download with extensive documentation from the internet (www.epidata.dk). Major institutions around the world are using the software for either courses, field work or as part of research projects[1].

In clinical trials it is now a requirement that compliance with the "Good Clinical Practice (GCP)" principles is attained[2]. *"Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible"[3].*

Further development is needed for usage of EpiData Software under "GCP compliance". Attaining GCP compliance is part of the overall development plan for EpiData for 2006-2010.

To initiate the GCP development the following import aspects must be considered:
a. Clarification of the term "GCP compliant behaviour of data management ":
b. Collaboration with research and development institutions testing the solutions in the field.
c. The specific contents and parts (see next page) and funding for this.
d. Development of field guides and evaluation of the software by external reviewer. The Danish public offices for GCP compliance supervision[4] have given provisional agreement of doing this.

Since there is no absolute standard or definition of "GCP compliance" the first step is to collect the necessary documents and find the relevant sections in these, see appendix A and B. The collection and identification of core statements have been verified[4] externally. The following GCP definition has been formulated:

Definition of GCP compliant software: The principles of verified software, controlled access, audit trail and traceability covers the period from initiation of the study database to locking of the cleaned database. Parts of the cleaning can be done by running scripts. The contents and running of these must be part of the audit trail documentation. Should the subsequent statistical analysis of anonymous data[5] show data problems or errors, then a new cycle of editing and cleaning of the database will be started under the audit trail governance. Whereas traceability of the analysis will be attained by knowing who was in charge of the analysis and reproducible analysis principles by application of command files[6].

Actual development and release
Development will be done in incremental cycles, where key functionality is designed, implemented and tested first and then in a later phase enhanced. Such that the overall mode of function becomes visible after a relatively short period. Technical details and planning documents have been created and can be delivered.

All software will be released for public testing as soon as sufficiently stable function and mode of usage is attained. Release as open-source will occur following completion of all three cycles.

Documentation will be created with an open internet based principle (prototype www.epidata.org/wiki) and with open debugging as required (prototype www.epidata.dk/php/mantis)

The first cycle will show to the end users how the principles will work and is sufficient for the field testing.
Based on the results and problems during the first cycle an overall progress evaluation will be made including decision of continuation and defining the budget for the remaining cycles. "Complete GCP compliance" according to the stated definition is not attained before all three cycles are completed.

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[1] As documented on http://www.epidata.dk/links.htm
[2] ICH E6: Good Clinical Practice: Consolidated guideline, CPMP/ICH/135/95. See Appendix A and B
[3] Quote from: "http://www.emea.eu.int/Inspections/GCPgeneral.html" - taken on July 3rd 2006.
[4] Public GCP guidance office in Denmark (one of three collaborating offices). Independent of industry: http://www.gcp-enhed.dk/aboutthegcp-unit/
[5] Without revealing any blinding of study subjects.
[6] EpiData Analysis pgm files, Stata do files, Sas Macro's.

Budget and phases[7]

First and Second cycle includes "in-house" documentation of function. Full documentation obtained in third cycle. Budget does not include time for field testing by external collaborators. All prices in Euro (€).

Cycle independent development (Planning and coordination) 20000 Euro

First cycle – single PC

Iteration Phase	Text description of content	From initiation to first field test	
		Budget (Euro)	Time to first test
1.	Restricted Access to data – simple level	10000	2-4 months
2.	Audit Trail Log: entry, edit and double entry Saved on same PC	10000	3-6 months
3	Traceability Reporting from audit trail log in a simple form.	10000	5-8 months

Second cycle – transferring data to a centre

4.	Transport of Data and Audit Trail Log to central centre and inclusion of cleanup phase for data	10000	6-9 months
5.	Full restricted access principle and traceability – reporting from audit trail log	10000	10-12 months

Third cycle - documentation

6.	Publishing overall validity testing documentation	20000	12-14 months
7.	Writing a field guide	20000	12-14 months

Summary requirements for attaining "GCP compliance of EpiData Software".

	Aspect[8]	Currently in EpiData Software
1.	The software must be validated	No
2.	Access to data must be controlled by a restricted access security system (pass word protection) and persons granted access to data must be authorised. (Whole file encryption)	No
3.	Audit Trail. All types of access to data must be recorded, be that creation, editing, searching	No
4.	Traceability. All changes and editing to data recorded in the audit trail can be used, such that individual values as well as complete records can be traced back to first entering of data[9]. Following changes (editing) to data comparison to data at a previous point in time must be possible.	No
5.	Written instructions must exist for setting up GCP Compliance (A field guide)	No
6.	Data quality. Quality of data must be enhanced by built-in error finding, logical consistency check, double entry and/or features for proof reading of data.	Yes
7.	Encryption of ID information of study subjects	Yes
8.	Automatic Back-up of data as part of the process (date stamped)	Yes
9.	Software cannot compromise blinding of subjects	Yes

[7] Each part of the budget is defined with reference to the complete plan and cannot in isolation be created for the indicated sum by itself. Until finalising cycle one all time estimates are provisional.

[8] Software guidance documents a. Guidance for Industry. Part 11, Electronic Records; Electronic Signatures — Scope and Application. www.fda.gov/ohrms/dockets/98fr/5667fnl.pdf. b. Guidance for Industry and FDA Staff: General Principles of Software Validation. www.fda.gov/cdrh/comp/guidance/938.html c. Guidance for Industry. Providing Regulatory Submissions in Electronic Format - General Considerations. www.fda.gov/cder/guidance/2867fnl.pdf.

[9] Does not include typing errors at first time entering of the record if that record was not saved to disk.

Appendix A – Source documents and web addresses

All documents retrieved in the period May 20th to July 3rd 2006 unless otherwise indicated.

Regulatory documents:

ICH E6: Good Clinical Practice: Consolidated guideline, CPMP/ICH/135/95
http://dg3.eudra.org/F2/eudralex/vol-3/pdfs-en/3cc1aen.pdf
http://www.fda.gov/cder/guidance/959fnl.pdf

European Union implementation: Good Clinical Practice Legislative basis Directive 75/318/EEC (replaces 1990 guideline entitled Good Clinical Practice for Trials on Medicinal Products in the European Community (III/3976/88), adopted May 1990.) In particular Part 4, sections B and C of the Annex

Web pages

European Union:	http://www.emea.eu.int/Inspections/GCPgeneral.html
USA:	http://www.fda.gov/oc/gcp/guidance.html http://www.dhhs.gov/ocr/hipaa/

Software guidance documents

a. Guidance for Industry. Part 11, Electronic Records; Electronic Signatures — Scope and Application.
http://www.fda.gov/ohrms/dockets/98fr/5667fnl.pdf
b. Guidance for Industry and FDA Staff: General Principles of Software Validation.
http://www.fda.gov/cdrh/comp/guidance/938.html
c. Guidance for Industry. Providing Regulatory Submissions in Electronic Format - General Considerations.
http://www.fda.gov/cder/guidance/2867fnl.pdf.

Examples of other supporting documents (from WHO):

a. HANDBOOK FOR GOOD CLINICAL RESEARCH PRACTICE (GCP)
http://www.who.int/entity/medicines/areas/quality_safety/safety_efficacy/gcp1.pdf
b. Standard operating procedures for clinical investigators. Http://www.who.int/tdr/grants/grants/files/sop.pdf
c. Council for International Organizations of Medical Sciences (CIOMS).International ethical guidelines for biomedical research involving human subjects ,revised ed. Geneva, CIOMS, 2002 (www.cioms.ch).
d. Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards.
http://www.who.int/tdr/publications/publications/pdf/operat_guidelines.pdf

The document d has an extended list of other supportive documents mentioned.

Appendix B – Extract from the main ICE document on requirements:

ICH E6: *Good Clinical Practice: Consolidated guideline*, CPMP/ICH/135/95

5. SPONSOR

5.1 Quality Assurance and Quality Control

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3 Quality control should be applied to each stage of data handling to ensure that al l data are reliable and have been processed correctly.

5.5 Trial Management, Data Handling, and Record Keeping

5.5.1 The sponsor should utilise appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.5.2 The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).

b) Maintains SOPs for using these systems.

c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail).

d) Maintain a security system that prevents unauthorised access to the data.

e) Maintain a list of the individuals who are authorised to make data changes (see 4.1.5 and 4.9.3).

f) Maintain adequate backup of the data.

g) Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

5.5.4 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.5 The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification of all the data reported for each subject.