Electronic Data Capture In VICH GCP Animal Health Studies

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Electronic Data Capture (EDC) is becoming the data collection method of choice in Animal Health studies conducted to VICH GCP[1]. This is due to the belief in a faster turnaround of the Final Study Report after data collection has been made.

Of course EDC confers many other advantages in this advancing electronic world, but also numerous new challenges to be faced by the auditor. An auditors role is never plain sailing but the big question is 'Would this journey be made smoother if Animal Health had an industry specific guidance for the conduct of EDC studies?'

The First Challenge – What Guidances to Comply With?

Ultimately an Animal Health study conducted to VICH GCP has to comply with the section of the guideline[1] applicable to EDC as below:

Section 8.3.1:

Raw data, whether handwritten or electronic, should be attributable, original, accurate, contemporaneous and legible.

Section 8.3.6:

Similarly, if data are entered directly into a computer system, the electronic record is considered the raw data. A computerised system should ensure that the methods for record keeping and retention afford at least the same degree of confidence as that provided with paper systems. For example, each entry, including any change, should be made under the electronic signature of the individual making the entry, and any changes that are made to data stored on electronic media should be maintained in an audit trail to protect the authenticity and integrity of the electronic records.

Parties conducting studies should have Standard Operating Procedures (SOPs) in place for paper-based data collection systems. This leads to assurance that the data collected meets the conditions of Section 8.3.1. When data is collected electronically how do auditors assure that a data point was recorded by person X on day Y and has not been changed?

VICH GCP does not go into the finer detail of how to achieve this assurance which is why the general consensus within the industry is to endeavour to comply with FDA 21 CFR. Part 11[2] and the corresponding guidance document on electronic source data[3].

These detail the criteria required for electronic records to be used in lieu of paper records. Another helpful source is the FDA Guidance for Computerised Systems used in Clinical Investigations[4] which applies to both human and veterinary clinical studies for the US.

In Europe there is no specific veterinary guidance on the subject. The European Medicine Agency (EMA) reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials[5] is based on the twelve requirements of the Clinical Data Interchange Standards Consortium (CDISC) standards and is a useful guide covering the principles of what should be followed, except it applies to the ICH GCP Guideline (CPMP/ICH/135/95). Animal Health studies differ from some human studies in that the source data (raw data) is predominantly recorded directly into the EDC system and not transcribed.

The Second Challenge – What EDC System is Being Implemented?

There are different types of EDC systems that require specific training and auditors need granted access to the data and metadata held within the EDC database. There are also different physical set-ups of systems that may be encountered. Animal Health studies can be conducted in numerous situations; hi-tech veterinary practices, rural farms with limited connectivity and institutions with shared computers. This can therefore be a factor in deciding which EDC system set-up is chosen and influences how the audit needs to be conducted.

Web-based systems are predominantly used which enable access wherever there is an internet connection. It may be that laptops/netbooks/tablets are provided for data collection and therefore these can be moved around like paper-based files. If connectivity is guaranteed then the data can be recorded contemporaneously into the EDC database eliminating the need for transcription of some data.

An 'off-line' system may be used where hardware may be taken to a rural farm barn with no internet connection and the data is uploaded as soon as connectivity to the internet is established. Electronic pens or ePRO systems used by owners may be in use, which need to be downloaded. Defining the logistics during the planning of the study will help greatly in understanding the flow of data. Auditing of the Data Management Plan will aid in clarifying this. A data flow diagram can be an ideal way of identifying audit targets. It can show human driven and technology driven activities, where delayed time and real time activities exist, for example, consideration of how the laboratory results will be included. The example data flow diagram illustrates this point (see diagram below).

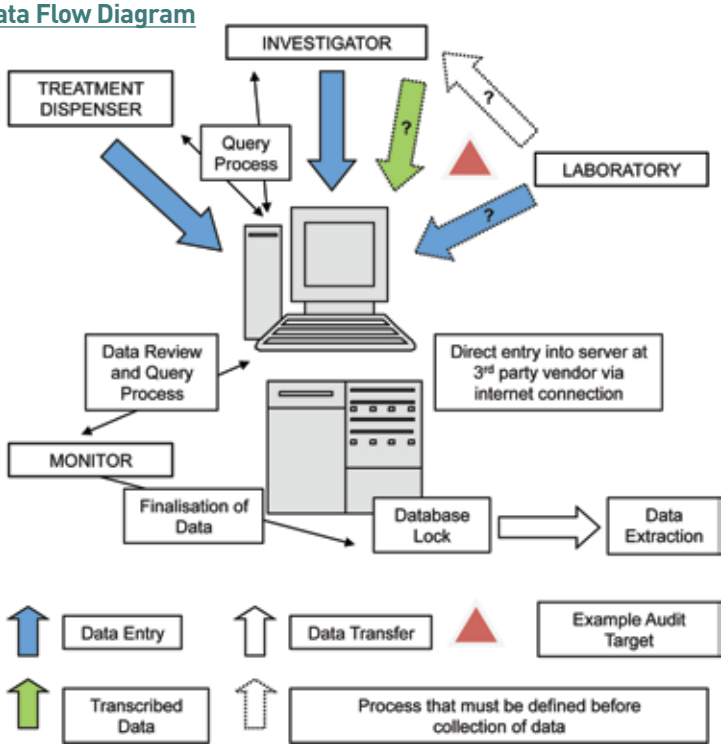
This example shows the laboratory data can be recorded in EDC database either by direct entry by the laboratory or data transfer to the Investigator who will then transcribe data into the EDC database. The process defined will determine which checks the auditor needs to make.

Although it appears easier and beneficial to have the process explained via a walk through, this may not uncover any underlying missing data flow links within the system that are required for compliance.

The Third Challenge – What Data Collection Method is Being Used?

In any study labelled 'EDC' it is unlikely that all data would be collected electronically and in general there will be a hybrid data collection environment, i.e., data collected electronically and data collected on paper. This scenario creates more documentation and therefore additional verification. For example, not only does the study participant signature log need to be checked to confirm participants' identity but also electronic signature agreements need to be confirmed as completed.

Data Flow Diagram



The majority of Data Collection Forms (DCFs) may be electronic (eDCF) but there may be paper ones too. For example, a computer may not be available in the dispensing room and drug accountability would be completed on paper. This data may or may not be transcribed into the EDC database. The protocol should define the data collection method and therefore establish how all raw data is collected.

The protocol should also confirm what data should be transcribed. Ideally the EDC database would have paper-based data transcribed into it, so all data is readily available in one place. However this may not be logical and only the paper-based data may be available, e.g. the owner informed consent. A clear understanding of what needs to be audited is fundamental and this can then be correctly verified within the EDC database and/or the Clinical Study Files.

The Fourth Challenge – What to Audit?

Planning of audits and their scopes in an EDC supported study is equally important as for a paper-based study. Some audits will result in aspects of the EDC system also being reviewed, the process for a forgotten password, user incident management, etc. It is therefore beneficial to combine some aspects of system auditing with a study audit.

Before use by the clinical trials team the EDC system has to have undergone validation, this is confirmed through computer systems validation audit. Before use in a study the systems and routines for the study should be pre-qualified through formal testing, this customisation and testing for a specific study should be open to audit. It is important to assure these activities have been conducted. When auditing a 'live study', core system validation activity assumptions are made, a validated EDC study database; validated eDCF and validated data transfer.

A system audit at site may allow a check of validation certificates but the validation process may also need to be audited to verify the validation records. Iain McPhee's article – Veterinary Quality Assurance and Computer Systems Validation – Quasar 123 (April 2013) addresses some of these issues.

Protocol reviews require more time than for a paper-based study. The protocol will normally have the DCFs appended as with a paper-based study, but there is a second check of whether the eDCFs represent the paper DCFs and therefore the protocol and the requirements of VICH GCP Section 8.3.1 have been addressed. It is at this point that edit checks built into the recording fields should be confirmed and verified, e.g. if a dog is recorded as greater than inclusion weight does a warning show up? Technology driven aspects must also be reviewed, e.g. the cow was classed as a treatment failure automatically by the system because it met X, Y and Z criteria. Another issue is whether there is a risk that the data will be 'too clean' and that bias is introduced. There is a fine line between using drop-down options for efficiency, consistency and completeness, and allowing the Investigator the liberty to record important study information.

During in-phase audit additional checks include whether any protocol amendments affected the EDC database, whether they were implemented correctly, and did not result in a change to previously recorded data; due to, for example, the removal of data fields. It should also be assured that the change control process was adequately controlled and documented. Logging-in should be checked with site personnel and their access rights demonstrated, especially if blinding is involved and connectivity to the EDC database should be evaluated if applicable.

Final data audits are completed after database lock is established so that no changes can be made to the EDC database. Confirmation of the final dataset is essential. The final dataset may consist of the EDC database alone, or it could have been extracted and migrated into a separate study database to include paper-based data not transcribed into the EDC database (inputted separately). There may be two databases to audit; EDC database and the 'paper-based' database. Audits of Final Study Reports for EDC based studies don't require much change to the usual process for paper based systems. It needs to be verified that data extraction was conducted post database lock. A well designed EDC system will allow reports to be generated on selected data fields that can be used to check protocol compliance and data points. The system must also have the capacity to be unlocked if audit observations raise data queries.

Items to be checked post-study include the extraction and archiving of the raw data. The data file extracted needs to contain the metadata so the study can be reconstructed and this must be available in a readable output.

The Fifth Challenge – When to Audit?

As with any paper-based study many different audits may be required. The judgement of when to audit may be reliant upon budget and resource, be based on previous experience or risk assessment.

Remote access of a web-based model can allow the auditor to overview the study in real-time and decide which sites to target through consideration of data trends, for example, a site with high recruitment or a site with a high number of data queries. EDC screenshots can be printed out and taken to site with queries already highlighted, to be checked with the Investigator and Clinical Study Files.

At present with EDC not yet an established method throughout the industry, the risk of non-compliance is higher pre-study. Fundamentally if the EDC database design is incorrect and it has not been correctly validated then there is little point checking whether the Investigators know how to enter the data correctly. Once the EDC system is established and there are SOPs in place and processes have been audited then the focus can shift.

In Summary

Animal Health studies will always require the need for flexibility between paper and electronic data capture due to their nature. EDC studies may require more technical expertise and training beforehand and require more upfront planning. It is also important to remember that electronic checks do not automatically remove the need for review of data by the Investigator, the Monitor and QA, to assure data integrity. Overall, EDC studies allow greater quality oversight. However, the Animal Health industry does need to consistently interpret and apply the same guidelines to stay on a compliant path going forward.

REFERENCES

1. VICH GCP GL9 – CVMP/VICH/595/98-FINAL 4th July 2000
2. FDA 21 CFR Part 11
3. FDA Draft Guidance for Industry: Electronic Source Data in Clinical Investigations, Nov 2012
4. FDA Guidance for Industry: Computerized Systems Used in Clinical Investigations, May 2007
5. EMA Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials, Aug 2010 (EMA/INS/GCP/454280/2010)

Biography

Donna is a University of Birmingham graduate with an honours degree in Biochemistry that included an industrial placement year at Celltech R&D, Slough (now UCB). Post-degree, Donna returned to Celltech as a Downstream Process Development Scientist in a GLP compliant facility. Joining Moredun Research Institute, Edinburgh, in 2004 as a Senior Research Assistant in veterinary immunology gave valuable experience across the disciplines of virology, bacteriology and parasitology leading to a move into monitoring veterinary Clinical Trials at Charles River Laboratories, Cumbria. From 2008 Donna was in the post of Trainee Project Leader, conducting both VICH GCP and GLP studies in a variety of species. As a direct result of site closure Donna took a position of Trial Co-ordinator at the University of Manchester operating a large phase III multi-centre study to GCP in the human field. In 2010, Donna returned to Cumbria and back to Animal Health to a position within Quality Assurance at Triveritas Ltd auditing not only VICH GCP and GLP studies conducted worldwide, but also aspects of GMP and 21CFR11 compliance in product development. Donna joined RQA in May 2011 and became a member of the Animal Health Committee in February 2013.

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