British Association of Research Quality Assurance

DISCUSSION PAPER NUMBER 5 IN A SERIES PRODUCED BY THE GLP COMMITTEE

THE APPLICATION OF GLP PRINCIPLES TO FIELD STUDIES:

STUDY CONDUCT

Author(s) Produced by the Field Studies Committee in 2004 and updated by members of the GLP Committee

The British Association of Research Quality Assurance 2012

This paper may be freely transmitted, copied and used provided that the text is not altered and the attribution of BARQA remains clear.
1 INTRODUCTION

1.1 Scope and Terminology

The information in this paper may be applied to all of the types of field studies defined in Paper Number 1 of 'The Application of GLP Principles to Field Studies' series.15

For the satisfactory conduct of regulatory studies the Good Laboratory Practice (GLP) Principles set out a number of strict requirements which apply in all situations, whether the work is to be performed in an indoor laboratory or a “field laboratory”. This paper attempts to address the specific issues and problems which have to be faced by scientists while conducting studies in which all or part of the work is to be performed out of doors or under glass. Most of the comments will apply equally to those who perform field studies and those who audit them.

The guidance and recommendations included in this paper, based on the knowledge and experience of members of the GLP Committee, is provided purely on an advisory basis to assist in the interpretation of the current GLP regulations to field studies.

2 MULTI-SITE ISSUES

Field studies usually come within the definition of a 'multi-site study' since they require a laboratory as well as a field site (and often more than one field site). For such multi-site studies the current OECD GLP Principles and Consensus Documents make a clear and very helpful distinction between the Test Facility, which is a main laboratory conducting regulatory studies, and Test Sites and trial sites at which a phase of a study is performed. This approach has been clarified still further in the OECD Consensus Document No 13 on multi-site studies.9

2.1 Role and Responsibilities of Study Director and Principal Investigator

The concept of a Principal Investigator (PI), who can act on behalf of the Study Director (SD) by conducting the work for delegated phases or at specified test sites of a multi-site study and who is responsible for ensuring compliance with GLP was, from a practical point of view, a great advance in the sensible application of GLP principles to regulated field work. Appropriate arrangements must always be made for the whole of the study, including the isolated phases, to be under adequate and continuous control. The keys to successful conduct of a multi-site study are a clear allocation of responsibilities at the planning stage and effective communication prior to and during the study.

Generally after the PI completes his/her phase, the PI sends all the raw data with the QA statement and the GLP compliance statement to the SD who will then put the data and information about this phase in the final study report. Alternatively the PI will provide the SD with a phase report for this part of the study. The phase report (or an abstract) can then form part of the final report. This latter option is preferred by some GLP Monitoring Authorities.
2.2 Quality Assurance of Multi-site Studies

OECD Consensus Document No. 13\(^9\) also introduced for the first time in an official
document the terms 'Lead Quality Assurance' and 'Test Site Quality Assurance'. The
Lead Quality Assurance is designated by Test Facility management to take overall
responsibility for a given study, ensuring that there is sufficient QA cover throughout
the study phases. Test Site Quality Assurance describes the Quality Assurance unit
designated as responsible for the part of a study performed at a test site or field
location.

3 OUTDOOR ISSUES

3.1 Climate and Weather

The field environment is not controlled like that of a laboratory and the seasonal and
day to day variations of temperature, sunshine, wind and rainfall are key factors
affecting the progress of all field studies. Well written Study Plans will allow, to
some extent, for this inherent variability. Some of the factors to be considered are
discussed below. Weather patterns will vary considerably from place to place and
from one year to another. Geography, altitude, soil characteristics, previous use and
history of the site are also important determinants.

Even conditions which are ideal for optimum crop growth may be stressful for the
field worker, but under adverse weather conditions the staff and equipment can come
under much greater stress. This may be in situations where support is likely to be less
comprehensive and less readily available than in the laboratory. Therefore field
scientists and QA auditors need to take with them whatever protective clothing,
emergency equipment (first aid, anti-serum, insect repellent, sun cream), water (for
application, cleaning of equipment and for self consumption), supplies of working
equipment and spare parts as appropriate to the nature and remoteness of the field site.

Because the germination and growth rates of crops used as test systems are so
profoundly affected by the weather and other factors the field scientists need to be in
close contact with each test site, sometimes on a daily basis, to ensure that the test
system grows healthily and that study actions are performed at the times or growth
stages specified in the study plan. In a generally cold or wet season one or two days of
hot sunshine may bring forward the growth stage of certain crops with unexpected
rapidity so that, for example, the growth stage specified in the Study Plan could pass
before the test item application has been made.

Refer to the validation of weather stations document for advice on using a weather
station\(^5\) or a data logger\(^6\) at a GLP facility.

3.2 Site Location

The choice of suitable plots or fields for use as test systems is a key part of the field
scientist’s expertise. Selection criteria may be recorded in SOPs or Study Plans. Sites
prone to erosion, flooding or other potential hazards such as major civil engineering
projects, should be avoided. During the course of a study the field staff and QA need
to be alert to unplanned changes at the test sites and surrounding areas (e.g. sudden
flooding or change of use by the owner), and take any necessary action.
3.3 Site Security

In addition to the usual risks of loss of crop (e.g. by disease, infestation, rabbits, deer, drought or flooding), even the remotest of field sites may be vulnerable to deliberate vandalism or unintentional destruction, such as ploughing by a poorly supervised contractor. Appropriate labelling and any other precautions should have been specified in the Study Plan or SOP but during the on-going phase of the study all personnel need to be alert to potential problems, to check the trial sites regularly and to maintain strong communications with farmers and contractors.

3.4 Site Details

Care must be taken to ensure that the specific criteria stated in the Study Plan are fulfilled. The OECD multi-site study guidance document\(^9\) states that the SD must be satisfied with the test sites selected. Clearly this means that the SD needs to be aware of both the quality of the remote facilities and the expertise of the personnel conducting the trials. It could be interpreted that a SD should personally visit and approve every site, but this would be an unrealistic expectation. Efficient communication of information by PIs and regular monitoring of all aspects of a facility should make it unnecessary.

4 TEST SYSTEM ISSUES

Details of the source, date of acquisition, variety, strain, cultivar and other appropriate characteristics must be maintained for test systems. For crop trials it is sufficient to specify a named approved variety, rather than the source of the seeds or plants.

For ecotoxicological tests the requirement to document the receipt and distribution of test organisms can be problematic when the numbers obtained from suppliers are only approximate. For example, test fish or beneficial organisms may be procured in approximate numbers. To minimise handling and consequent stress on the test system, strict accounting for individuals on arrival may not be practicable. In these circumstances the records of ordering and receipt should be maintained and there should be data demonstrating the transfer of specific numbers of test organisms to particular studies and dose groups.

Study Directors, Principal Investigators and Management need to decide which records of test systems constitute facility records and which are study-specific.

5 DISTANCE AND TIME ISSUES

5.1 Travel and Communications

Field scientists may operate across the world and spend a significant part of their time travelling from country to country, from laboratory or hotel to the field and from one field site to another. They may cross time zones, national frontiers and climatic zones. Not only thorough planning but also very strong lines of communication are essential to the satisfactory conduct of fieldwork. Mobile phones, e-mail and fax machines have revolutionised communications but not all geographical areas are covered by reliable cell phone or fixed phone systems and some field sites may be beyond the range of all but satellite phones.

Differences between time zones may cause problems when urgent messages must be passed. Also working hours may differ between countries. In some hot countries
work in the field starts very early, then there is a break in the hottest part of the day and work continues until late in the evening; this pattern may not fit with the normal working hours of the Test Facility in a temperate zone.

5.2 Transport of Test Items and Study Specimens

These issues are dealt with in 'The Application of GLP Principles to Field Studies' Papers 2 and 3\(^1\)\(^2\).

6 PERSONNEL ISSUES

6.1 Line Management

As mentioned in Paper Number 4 of this series\(^3\), when distant test sites need to be used the work may be wholly or partly entrusted to a local branch or facility of the sponsoring organisation, the test facility contract research organisation (CRO) or to another entirely separate organisation, such as another CRO. Even if the planning has been most meticulous, when the PI and/or SD visit the test site during the study he or she needs to be alert to potential or on-going problems.

- are the facilities and equipment truly adequate?
- does the test site really have sufficient qualified, appropriately trained and experienced staff?
- do the staff actually know how to work in compliance with GLP?
- are there viable QA arrangements?
- where non-scientific personnel are employed on a casual basis are experienced established staff instructing and supervising them properly?

The documentation produced while the remote phase is in progress must always demonstrate continuity of control across any organisational interfaces.

6.2 Cultural Differences

All staff participating in field studies away from their own territory need to be sensitive to differences in culture, customs, habits and work patterns of the regions or nations where they are operating. Whenever possible, advice should be taken from a sympathetic local person at one’s own level of management. Regarding general behaviour it is advisable to educate oneself in advance with one of the books which are widely available for business travellers, then observe carefully those around you and copy them where appropriate. In relation to specific problems of study conduct do not forget that the GLP Principles and guidance documents provide a useful common reference text.
6.3 Language

Many organisations and some governments specify a preferred language for Study Plans, SOPs, etc., such as English or Spanish, but SOPs and study records are often written in the local language. Moreover the local field staff are almost certain to speak with the PI or senior field worker in the local language. Scientists from elsewhere who do not speak the local language need to identify someone, preferably the PI, to translate for them as appropriate. Those who visit other countries on a regular basis are recommended to learn something of the local language, even if it is only a few phrases of greeting and thanks, or how to order food and drink; this is always worth the effort.

6.4 Legal Constraints

Care should be taken that international, national and local environmental regulations are observed, for example environmental regulations for use of experimental chemicals, disposal of remaining spray solution, product or treated crop. SDs and PIs need to pay heed to the local management’s policy and practice in matters such as employment and culture and not to assume that the laws and customs will be the same as those at home or in towns and cities.

7 TEST ITEM APPLICATION ISSUES

Great care must be taken to ensure a successful application of the test item. The equipment must be calibrated and primed prior to application, so that an accurate dose can be applied.

With small scale applications, such as residue studies on small plots, hand held gas operated sprayers are usually used; for large scale applications the sprayers or granule applicators are usually tractor mounted or self propelled. The concentrated test item is most often diluted to working strength immediately before being applied to the test system. The rates stated in the Study Plan and dilution procedures stated in SOPs must be obeyed faithfully and documented as the work proceeds. Mixing and filling of the spray tank is usually supervised or performed by the PI or SD; however in some countries and companies it is customary for this activity to be performed by experienced technicians. Calculations and measurements of volumes, etc. should be checked and countersigned. A local supply of water may be used for the dilution, but if no suitable source is available water may need to be carried to the test site.

Adequate space must be allowed between test plots to avoid contamination from spray drift.

It is advisable to check the local weather forecast frequently. Application should not be undertaken in windy conditions, which will cause problems from spray drift, or if rain is expected very soon afterwards. The PI must protect himself/herself, all other people and property and other areas of the field (control plot, remaining field) from any exposure during application. Appropriate protective equipment must be worn (e.g. overalls, rubber boots, gloves, face mask, breathing apparatus) where necessary.

When application is complete the remaining diluted test item must be measured and disposed of in accordance with the relevant SOP and in an environmentally safe manner.
8 DATA COLLECTION ISSUES

8.1 General

Study staff should make a record of events and original observations as they occur. The objective should be to record as much information as possible (including adverse observations) to ensure that these data provide a full and accurate account of the conduct of the study.

It is helpful to provide field observers with pre-designed forms for the recording of data. An appropriately designed form can help to ensure that all of the required data are collected, even where stress caused by difficult working conditions, remoteness from supervision, and large volumes of data, can make the task particularly difficult.

Procedures to be followed when recording data in the field should be described in a SOP. During its collection reasonable precautions should be taken to protect raw data from adverse conditions. The use of bound, tagged or spring-held (not loose-held) sheets can guard against accidental loss. Previously collected raw data should preferably not be taken into the field in case it is lost or accidentally damaged. Some organisations permit only copies of previously recorded data, plot diagrams, etc. to be taken to the field.

All unusual or unexpected observations must also be recorded promptly; hence the study personnel should have the means to make full text records in addition to tables for numbers or observations.

Where subjective assessments such as crop vigour are made, sufficient flexibility in standard procedures needs to be allowed to enable the evaluator in the field to adjust the initial impressions of individual plots so that the judgement may be consistent across the whole group under evaluation. This should be done, however, only while the evaluator remains in contact with the test system being evaluated and while the condition of the test system does not alter significantly. Any change thereafter should not obscure the original recorded value and should be explained and authenticated with the identity of the individual making the change and the date of the change.

The use of digital cameras and camcorders to provide supporting data is now common. These records should be labelled and dated carefully, but it may be necessary to exclude them from the Study Director’s GLP compliance statement.

The safe storage of data during a study is the responsibility of the Study Director or Principal Investigator. A reasonable minimum expectation would be for data to be placed in a metal cabinet when not in use so that it is protected from fire, flood or theft.

8.2 Raw Data

The notes and data entered into notebooks and/or data sheets in the field constitute 'raw data' and are subject to the appropriate GLP principles. There is a well established requirement in GLP that written data should be recorded directly, promptly and legibly in ink. Use of graphite pencil is not acceptable to most GLP Monitoring Authorities and should be avoided. Under wet conditions in the field it might be necessary to use pencil instead of ink, but such a deviation should be explained and authorised in the relevant SOPs and/or raw data and verified permanent
copies should be made as soon as possible. The alternatives of waterproof paper and pens can often be made available.

A formal account written at the end of the observation session could be more comprehensive than the initial notes and may still be valid. It could, for example, record considered impressions based on a period extending over several observations and could reflect a judgement overall where the subsequent evaluation of each data point is dependent on its relation to the others. But as stated above such records need to be made while the observer is still in contact with the test system i.e. while still at the test site.

8.3 Notes to File and Study Plan Deviations

In all situations, truthful and comprehensive records must be made in a timely manner and then signed and dated. Explanations written in the study file, sometimes called Notes to File (although this term does not appear in the GLP regulations or advisory documents) are often used to record additional information or clarification which will help in the reconstruction of the study in the future. It is advisable to make certain that the PI is aware of the existence and contents of all such notes as soon as possible; the SD may also need to be informed sooner rather than later.

All unplanned departures from the Study Plan or SOP, however small, must be recorded as Study Plan or SOP Deviations as soon as they occur. If the PI is not present when a deviation occurs (or is discovered) it is normal practice for study staff to report it to the PI who will then take steps to explain the likely impact of the deviation to the SD and make any recommendations for corrective action. The GLP Principles require that the SD acknowledges all deviations and authorises any necessary corrective action. It may be necessary at this point for the SD to change some future activities of the study by writing a Study Plan Amendment.

8.4 Use of Computers

Where computerised data-collection methods are used in the field, the arrangements must comply with the GLP requirements for the use of computerised systems.

An especially critical point is that of the protection of data against unauthorised alteration. Printing out of a hard copy, which should then be signed and dated by the observer, is a commonly accepted approach.

There is an increasing use of hand-held computers for recording data in the field; where this is done SOPs must clearly state what constitutes raw data. Use of equipment that will lock data electronically is acceptable so long as it contains a full audit trail capability indicating any changes, who made them and when. Standard procedures governing the use of computers must be closely defined, particularly where they relate to downloading of collected data into a larger computer or network. Refer to the BARQA field paper on the use of data loggers.

Where electronic raw data are collected, a SOP should be in place giving guidance on the collection, handling, disaster recovery (in case of loss) and archiving of the data, to meet the guidance given in the OECD advisory document on archiving. The SOP should include a clear definition of what constitutes raw data since the format or location of the raw data might change. The electronic raw data from the field will be transferred to the SD. Where does the raw data reside? Does it reside with the PI or
with the SD? Then after completion of the study the raw data might be transferred to a CD and archived (again in another format). The SOP must define raw data clearly.

Any subsequent collation or transformation of data must be done in such a way that the raw data are not corrupted or erased.

Indications of US government thinking on electronic data recording in GLP situations in general can be found in a rule and associated guidance documents, from the Food and Drug Administration which is internationally recognised as the basis for computer validation requirements. A rule from the US Environmental Protection Agency concentrates on acceptable means of regulatory submission in an electronic format.

8.5 Derived Information and Supporting Records

Field studies often require additional calculations to be made using original observations, for example calculations of the volume of diluted test item applied in the field based on the results of sprayer output tests, time taken to spray or overage (material remaining). The resulting values are not strictly 'raw data', since they are not original observations, but they need to be recorded in sufficient detail to enable the calculations to be checked.

Other types of information generated during a study may relate to concurrent studies, such as chemical stock container usage records or specimen storage temperature details. Such data will form a part of the facility records but, if required, authenticated copies may be placed in study files.

9 SPECIMEN COLLECTION AND RETENTION ISSUES

9.1 Specimen Collection

The collection of specimens in the field for examination or analysis in the laboratory may be an important aspect of the field phase. Sampling schedules, identification, transportation and storage all have to be considered.

The sampling regime (as opposed to the sampling methods) should be carefully defined in the Study Plan. Where, owing to the vagaries of field conditions, the set schedules cannot be strictly adhered to, the SD should, if possible, be informed in advance. Any deviation must be noted immediately in the raw data and endorsed by the PI and SD at the earliest possible time.

The use of pre-printed labels for specimens is the norm. Sets of pre-identified labels can help to prompt the correct collection of all the specimens required. Space may be left on the labels for recording by hand of details such as the date and, if appropriate, the time and place of sampling and the initials of the sampler. However most of the sampling details would be recorded as study raw data. Records of specimens taken and despatched should be kept in the study file as well as on the documentation accompanying the specimens. One useful method for doing this is to supply each pre-printed label in duplicate, one for use on the specimen and one for retention with the field data; a third label is sometimes placed with the specimen inside the sample bag or container in case the outer label should become detached or illegible.
Where preservative (e.g. formaldehyde solution, solid carbon dioxide) is to be added to the specimen before transport to the laboratory or before storage, full instructions should be given in the Study Plan or in the relevant SOP. If appropriate, instructions should include information on safety precautions necessary to protect the study personnel and the environment.

A chain of custody record should indicate the personnel responsible for the integrity of the specimens from sampling in the field to their reception in the laboratory. The record should show the conditions to which the specimen(s) have been exposed during storage and transport, and should account completely for the elapsed time between sampling and examination or analysis. Data on storage conditions should be recorded contemporaneously and the records signed and dated.

9.2 **Storage and Transport of Test Items and Specimens**

This subject is dealt with in 'The Application of GLP Principles to Field Studies' Papers 2 and 4.

9.3 **Specimen Verification**

It is essential for biological specimens to be identified correctly to the required taxonomic level. Identification must be reliable and performed by (or reference specimens checked by) competent study personnel. Where it is deemed necessary to base identifications on published work (e.g. textbooks or specific keys) the appropriate publication(s) used should be cited in the raw data.

9.4 **Specimen Retention**

If biological material that has been collected is not retained, its disposal should be in accordance with the relevant SOP and the facts and reasons recorded.

Most organisations, particularly where remote sites are involved, regard it as prudent to retain duplicate specimens and certified true copies of the raw data. The location of these duplicate specimens and data should be recorded; they provide valuable security against the possible loss of the first set during transit to the laboratory.

When specimens of soil, plant or animal materials are taken for analysis as part of a residues study, the UK regulatory authorities do not regard it as necessary to retain specimens either of the initial or of the 'spent' material. In certain studies, however, it might be appropriate to retain reference specimens (e.g. slide-mounted, pickled or dry-mounted invertebrates). Also, a laboratory may consider it prudent to retain specimens used for assessment and, if appropriate, to retain reserve specimens of all materials until the study is completed.

It is unlikely that specimens taken as part of an environmental study would need to be retained, other than perhaps for use as identification standards in future work. Where specimens of arthropod populations are taken for taxonomic counting, the classification process often involves destruction of the specimen. Moreover, the specimens taken represent only a part of the population from the areas that were under evaluation and retention would not necessarily aid reconstruction of the study. Stored soils (e.g. from soil metabolism studies) undergo changes in the population of microorganisms that they contain. After a period the condition of the soil specimen
population is no longer representative of the conditions of the study and re-examination would not give a meaningful result.

The general subject of long term retention of data and materials from field studies is discussed in more detail in 'The Application of GLP Principles to Field Studies' Paper No 6.

10 CONCLUSION

The practical execution of field studies which meet the regulatory requirements and comply with GLP principles presents a substantial challenge to experimental testing facilities. This paper has offered a discussion of the key issues to be faced by staff while out in the field, drawing on the accumulated practical experience and expertise of people from various sectors of the regulated industry and following careful consideration of the impact of OECD Principles of GLP and the associated Consensus Documents.

11 REFERENCES

BARQA discussion papers: The Application of GLP Principles to Field Studies Series

1 Discussion Paper No 2: Personnel, Facilities and Equipment
2 Discussion Paper No 3: Test, Reference and Control Items
3 Discussion Paper No 4: Study Planning
4 Discussion Paper No 6: Reporting and Archiving
5 Guidance Paper No 7: Procedure for Validating Automatic Weather Stations
6 Guidance Paper No 8: Procedure for Validating Data Loggers used in Field Studies

Other references

11 OECD series on Principles of Good Laboratory Practice and Compliance Monitoring Number 15: Advisory Document of the Working Group on Good Laboratory Practice:
Establishment and Control of Archives that Operate in Compliance with the Principles of GLP ENV/JM/MONO(2007)10 June 2007

12 Food and Drug Administration (FDA), Title 21 "Electronic Records; Electronic Signatures; Final Rule" 21 CFR Part 11. Revised 01 April 2011

13 Environmental Protection Agency (EPA), "Cross-Media Electronic Reporting Regulation" (CROMERR), 40 CFR Parts 3, 9, 51 et al, 13 October 2005