Competence in Clinical Trials – the Regulators Perspective

(Jennifer Martin Senior GCP Inspector, 9 June 2014)

Requirements

Statutory Instrument 2004/1031 (as amended)

- **Regulation 28(2):**
  The sponsor (and delegate) shall put and keep in place arrangements for ensuring in a trial that the conditions and principles of GCP (that is Schedule 1, Part 2) are satisfied and adhered to

- **Schedule 1, Part 2**

  2. Each individual involved in conducting a trial shall be qualified by education, training and experience to perform his tasks
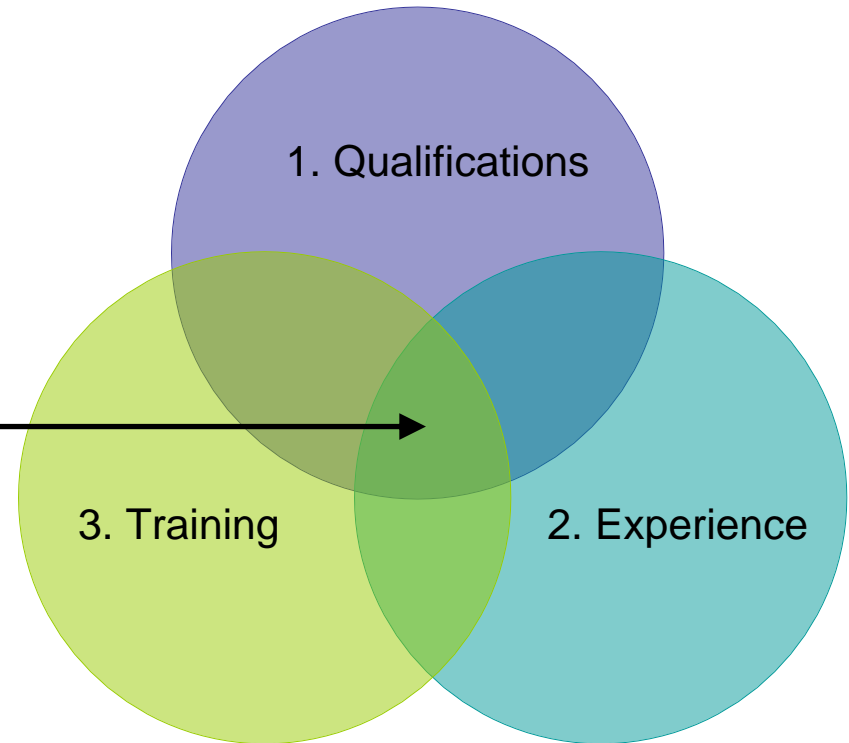
CPMP/ICH/135/95 (ICH GCP E6)

2.8. Each individual involved in conducting a trial shall be qualified by education, training and experience to perform his tasks
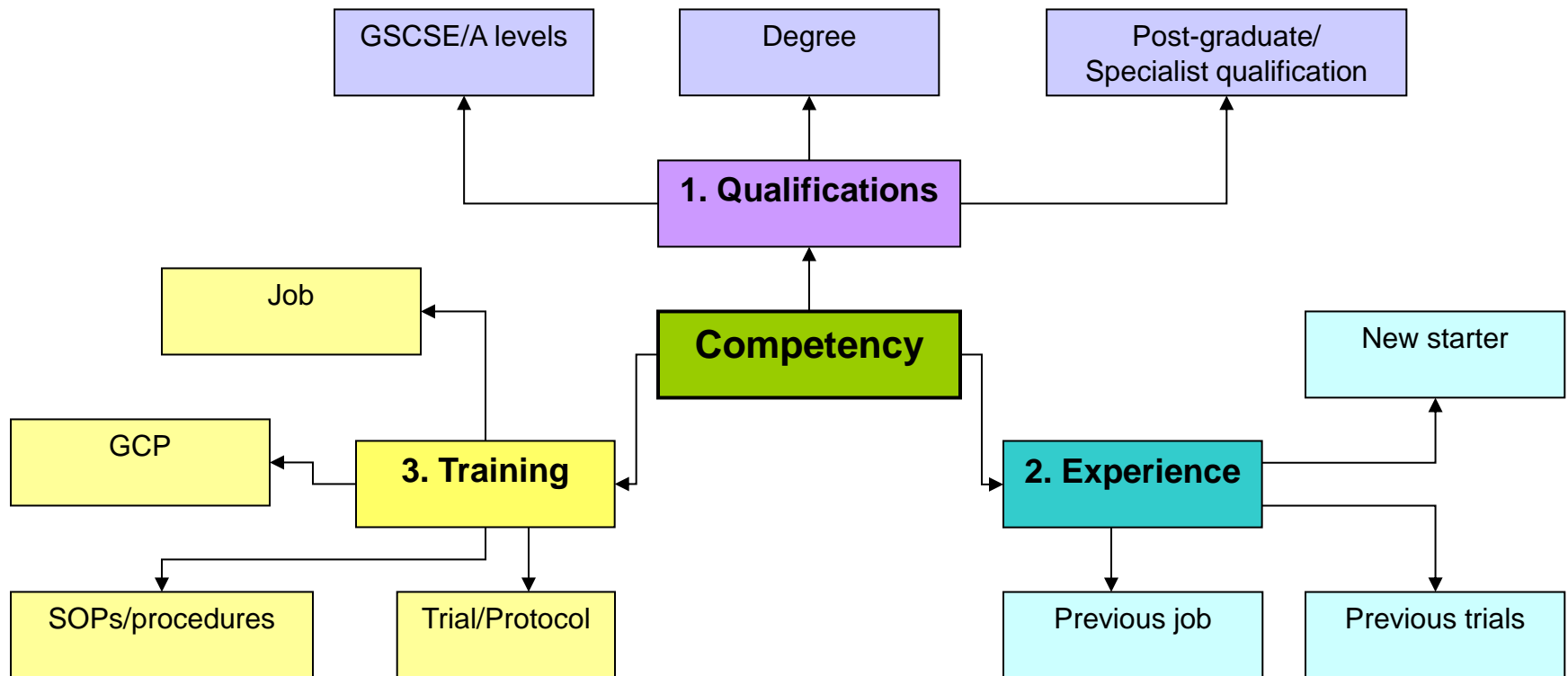
Requirements

The 3 key legislative aspects!

4. Competency **should** equal all 3 combined

1. Qualifications

2. Experience

3. Training

Training Expectations

MHRA Expectations for meeting these requirements:

1. Qualifications

The qualifications needed for people working in clinical trials will vary dramatically. For example:

- Named archivist or trial administrator responsible for the trial master file: may not need a degree, but should have relevant qualifications to allow them to perform this duty to a suitable standard

- A laboratory technician may not require a degree if they are processing samples, but, may require a relevant scientific qualification if they are performing complex analyses or method validation.

- A monitor, project manager or medical writer, etc. it may be desirable to be educated to degree level or equivalent (but this is not essential, as may work up through other roles)

Qualifications

The qualifications needed (cont.)

- In the MHRA phase I accreditation scheme, those who wish to be a PI on a first in human trial must be a medically qualified doctor and hold a relevant post-graduate qualification in pharmacology

- Research nurses would be expected to have a general nursing qualification plus any specialist qualification if they work in a specialist field (e.g. midwifery, chemotherapy etc.)

- Other health care professionals (e.g. radiologist, pharmacist etc.) would be expected to have a relevant qualification or degree associated with the job they are employed to perform

Qualifications: Discussion

Discuss & highlight how suitable mechanisms to verify the qualifications held by staff/trial team

Example of some answers:

- Request copies of relevant certificates (degree, life support, post-graduate courses etc.)

- Documentation/check of affiliations to any associations or registrations (i.e. GMC, NMC etc.)

- Check CV (**_not adequate in itself,_** as this could contain false information – examples have been identified)

2. Experience

The experience of people working in clinical trials will also vary dramatically, from a new starter to very experienced.

Therefore, it is important for staff to gain experience in a supervised manner, for example:
- Mentoring/coaching
- Review/assessment of work
- Audit
- Accompanied visits (if appropriate)

Experience: Question 1

No matter how experienced, will you ever know it all?

- **No**

Why?

- **Change!!**

Experience: Question 2

So, what things can change over the course of a trial or your career?

- Regulations and/or associated guidance
- Company procedures/re-structuring
- Tools used (templates or technology)
- Your job
- Science (new analytical techniques/diagnostics)
- Medicine (ATIMPS, gene therapy etc.)

Experience: Discussion

Discuss how you ensure you maintain your experience or how your staff maintain their experience

Example of some answers:

- Keep abreast of any changes to regulators website for updated regulations and guidance (this should be more formalised for larger organisations, for circulation to all relevant staff and impact on SOPs)

- Ensure up to date knowledge of company procedures and associated forms/templates/tools

- Ensure appropriate training/mentoring to perform any new functions associate with your job/role.

3. Training

What training is expected?

Each person involved in a clinical trial of an investigational medicinal product (CTIMP) must receive training in:

a. Good Clinical Practice (GCP)
b. Written procedures (SOPs/guidelines etc.)
c. Trial-specific
d. Job (i.e. the task and functions you perform): *experience*

....commensurate with their roles and responsibilities.

3a. GCP Training

What level of GCP training is needed?

Depends on the role of the individual within the trial!

Range from a detailed knowledge of GCP principles, UK regulations & European guidance to awareness of particular GCP principles.

In some cases, no GCP training may be needed, e.g. if an activity is part of a person's normal clinical role and all other protocol activities are performed by a member of the research team.

GCP Training: Discussion

Common Query: Who needs to be GCP trained?
Discuss if full or reduced GCP training is required:

A. Pharmacy staff only dispensing an IMP in accordance with standard daily practice under the oversight of a clinical trial pharmacist.

B. Clinical Supplies staff in the local affiliate office involved in reviewing IMP labels to ensure compliance with Annex 13.

C. A Statistician advising on trial design and statistical methodology and analysing clinical trial data.

D. A ward nurse only responsible for taking blood samples from subjects at an investigator site in accordance with standard ward procedures.

E. Chemotherapy nurses administering IMP in a chemotherapy unit.

GCP Training: Answers

ANSWER: (A, B, C, D, E) Reduced GCP training may be appropriate for ALL these roles.

A. Pharmacy staff only dispensing an IMP in accordance with standard daily practice under the oversight of a clinical trial pharmacist.

D. A ward nurse only responsible for taking blood samples from trial subjects at an investigator site in accordance with standard ward procedure.

A&D. No GCP and study-specific training required.

It may be appropriate that these staff only receive an overview of the clinical trial in the form of a written summary; or they could simply be made aware of the local trial team contacts and have an awareness of (rather than detailed knowledge of) GCP requirements, in particular adverse event reporting, documentation expectations.

GCP Training: Answers

ANSWER: (A, B, C, D, E) Reduced GCP training may be appropriate for ALL these roles.

B. Clinical Supplies staff in the local affiliate office involved in reviewing IMP labels to ensure compliance with Annex 13

C. A Statistician advising on trial design and statistical methodology and analysing clinical trial data.

B. Training in Annex 13 and its requirements surrounding labelling.

C. Training in GCP principles relating to corrections and verification of data. Awareness of and/or training in ICH Topic E9.

GCP Training: Answers

ANSWER: (A, B, C, D, E) Reduced GCP training may be appropriate for ALL these roles.

E. Chemotherapy nurses administering IMP in a chemotherapy unit.

E. Depends on the role of the chemotherapy nurse in the trial:
  - If the only activity undertaken by the chemotherapy nurses is the administration of the IMP as per standard treatment and all other protocol activities are undertaken by a member of the research team, then no or reduced GCP training may be required.

  However
  - If the chemotherapy nurse is to undertake any other trial duties (e.g. asking about adverse events and completing forms or questionnaires, performing or documenting assessments in the source notes), then training on the relevant areas of GCP should be undertaken to cover the activities delegated.

3b. Written Procedures

Written procedures are the organisations formal quality system.
These are usually made up of:

- Policies
- Standard operating procedures (SOPs)
- Working practices/guidelines and associated forms/templates

[However, (1) organisations may use other terminology
(2) for activities not undertaken routinely, there may be no need for written procedures
if they are contained elsewhere (e.g. the protocol, hospital policies etc.)]

Purpose of written procedures, is to ensure tasks are performed:

- Correctly and consistently, especially if they are undertaken by another member of the organisation in the absence of those more experienced or that usually perform it
- In compliance with regulations and associated guidelines

Written Procedures

Discuss and highlight:

1. What should be considered when preparing and following written procedures (whatever form they take)?

2. When training staff in written procedures, what considerations should be given to what and how training should be implemented

Written Procedures

1. **When preparing and following written procedures the following need to be considered:**

I. Reflect the activities that are being performed

II. Satisfy the principles of GCP and the regulations

III. Need to be complied with

IV. Cross reference other appropriate procedure(s)

V. Don't contradict other procedures or hospital policies

VI. What happens when you don't follow them (e.g. documentation, notification, impact assessment)

VII. Include an appropriate review period to ensure they remain up to date

Written Procedures

2. Training in written procedures should be:

I. Undertaken before commencing the task associated with them

II. Are specific to the roles and responsibilities of a particular individual or job description (i.e. as specified in training grids and/or matrices)

III. Can vary depending on the role and the procedure (e.g. face-to-face training, 'read and understand', associated exam/test); the suitability of method should be assessed prior to implementation

3c. Trial Specific Training

Trial specific training includes training in the protocol and any supporting trial manuals and guidance necessary for the role in relation to the activity to be undertaken. This enables both the sponsor/CRO and trial site staff to understand the clinical trial in relation to their particular tasks. For example:

- Therapeutic area

- Assessments to be performed and when

- eCRF / IVRS/ ePro devices etc.

- Informed consent training

- Use of a particular piece of equipment (ophthalmology, lung function etc.)

Trial Specific Training

Training must be undertaken before commencing the task and documented in the trial file:

- Training log
- Delegation log (if at an investigator site) to demonstrate the PI has authorised in advance appropriately trained and qualified individuals to undertake certain trial-related tasks

Note:

Large departments (e.g. pharmacy) may have activities delegated by the PI to a named person (e.g. clinical trials pharmacist) who has responsibility for the conduct of that activity by the department, which has its own mechanism for identifying those working on the trial (e.g. generic log)

Trial-specific training and delegation of responsibilities may not always be required (e.g. if the task is no different to normal clinical practice, requires no knowledge of the protocol and the normal practice of record keeping is consistent with GCP)

Training Discussion

Role		GCP	SOP	Trial	Del. Log
A.	A chemo nurse is administering standard of care chemotherapy only	✘ [1]	✔ [2]	✘	✘
B.	An investigator laboratory is handling routine blood samples on trial subjects, then sending the samples to a central laboratory facility for analysis	✔ [3]	✔ [2]	✔ [4]	✔
C.	A radiologist is taking a particular image and interpreting it in line with a protocol-defined scale (e.g. RECIST)	✔ [5]	✔ [5]	✔ [5]	✔
D.	A CRA responsible for monitoring trial sites	✔ [5]	✔ [5]	✔ [5]	✘
E.	Person responsible for archiving	✔ [6]	✔	✘ [7]	✘

(1) Although recommended some basic awareness of trial and GCP related to documentation/ AEs; (2)Organisations standard SOP/policy; (3) GCP: Handle source data in line with the relevant principles of GCP [Schedule 1, part 2(9)] & subject confidentiality [Schedule 1, part 2(13)]; (4) Relate to sending labs only; (5) Full training in GCP, trial and any applicable SOPs; (6) Relevant to trial records retention; (7) Unless there were any trial specific aspects differing to those covered by organisations SOPs

Training: How and When?

All activities should be considered as part of a risk assessment and documented where there is no or limited GCP/SOP/trial specific training required.

How: Various formats (e.g. face-to-face, web-based or self-directed reading)

When: Before undertaking activity/updates to procedures have occurred

Frequency: Not defined in the regulations, so what is expected?

Training: How and When?

How often training is given, and in what format is a business decision, however the recommendation is:

- It is given at appropriate intervals to ensure that staff maintain current awareness of the UK Regulations and applicable European guidelines
A fixed frequency such as every two years may not always be appropriate
- Systems are in place to allow for ad hoc training in between scheduled training events, e.g. in the event that there are significant regulatory updates, or to provide refresher training, e.g. when staff have been on extended leave.
- Requirements for GCP training should be documented in the organisation's procedures

4. Competency

Is there any expectation to have a 'competency sign-off', which indicates that a person is competent in a process?

- **No** regulatory requirement to have a specific 'competency sign-off'.

However, for an organisation to provide evidence that they meet SI2004-1031*, schedule 1, part 2(2) the responsible organisation should have in place processes# to assure themselves that their staff are indeed competent to perform their assigned tasks.

*including all its subsequent amendments
#As per 2004/1031, regulation 28(2)

Competency

This can be approached in several ways. However, the first aspect to consider is an assessment covering:

- What the nature of your organisation is, therefore what task(s) are performed
- What is the criticality and impact of those task(s) in relation to GCP and the clinical trials
- Who is performing those task(s) within your organisation
- Standard organisation policies and requirements for assessment of competency (NHS)

Then, deciding and documenting what level of training is needed for each task (e.g. from "read and understand" to a formalised and documented competency assessment and sign-off)

Competency

Mechanisms already discussed:

- Qualifications:
  - Verifying that staff have the qualifications they claim to have

- Experience:
  - Assessing what previous experience staff have gained either within or prior to joining your organisation

- SOPs/Trial training:
  - ensuring that SOP/trial training provided to staff is appropriate and effective (some organisations have a check following training, i.e. test or questionnaire to assess staff learning)

- Updates:
  - ensuring that updates to training are provided as needed, particularly if trial or organisation processes or the protocol changes, or in the event of regulatory changes

Competency: Discussion

What else?

Discuss & provide examples of ways to provide evidence of competency

Competency: Answer

Some examples of ways to show competency:

- Documentation of thorough checks carried out to ensure that on completion of training, staff are indeed carrying out their duties according to requirements and/or procedures:
  - Co-monitoring visits
  - Peer review of interpretation of results (e.g. labs, ECGs, RECIST etc.)
  - Peer review of the quality of documents produced (CSR, study plans or guidelines, trial specific documents etc.)

Competency: Answer

Some examples of ways to show competency (cont.):

- Formal competency sign-off procedures and associated forms in training record, covering:
  - When person observed task being performed
  - Supervised assessment of person performing the task (who and when)
  - Documented assessment by nominated "trainer" of person ability to perform task unsupervised (i.e. competent)

Competency: Answer

Some examples of ways to show on-going competence:

- Documentation of on-going checks carried out to ensure that staff maintain adequate knowledge to carry out their duties according to up to date requirements and/or procedures:
  - Audit
  - Co-monitoring visits
  - Management review of monitoring/audit reports
  - Spot checks of activities by supervisors/experts

- If appropriate, a "complaints" mechanism for the identification of non-compliance with procedures, protocol, etc.:
  - Identification and reporting of issue and personnel
  - CAPA, including retraining requirements to rectify
  - Documentation when and how competency revoked/reinstated

Competency Example (MHRA)

New GCP inspectors:

- Expected to have a degree (Life Science) or equivalent qualification and relevant previous experience in clinical trials

- Assigned a mentor/coach

- Receive classroom training (e.g. legislation, key GCP aspects, inspection techniques, as applicable)

- SOP training (usually "read and understand")

- Have on-the-job training with feedback from accredited inspectors

- Formal assessment and sign-off in each area of GCP by Expert (commercial, non-commercial, Phase I, etc.)

Competency Example (MHRA)

Accredited GCP inspectors:

- Regular inspector audits (inspection technique and reports)
- Peer review of inspection reports
- GXP training week/ regular technical meetings
- SOP update training
- Monthly technical meetings

To maintain competency inspectors are reassessed if coming back from long term leave (e.g. maternity, secondment to another area, sick leave).

We also have a complaints process!

Documentation Needed

- To demonstrate that training has occurred and staff are competent, documentation must be maintained and retained for all staff involved in the conduct of clinical trials and, where appropriate, for staff involved in supporting functions

- Records must be maintained as trial supporting documents (either centrally or with the individual) for as long as they may be needed to support historical reconstruction of the trial

Documentation: Discussion

Common query: What records should be maintained?

Discuss & provide examples for what records should be maintained

Documentation: Answer

The extent and content is a **business decision**, but typically:

- Current **job description** dated and signed by the post-holder and line manager (demonstrating when current roles and responsibilities were agreed)

- **CV** (demonstrating current/previous education and experience, ideally signed and dated to confirm the document date and ownership by the post-holder)

- Confirmation of **GCP training** taking place (including clear reference to the framework used in the training, e.g. UK Statutory Instruments/EU Directives)

- Documented **training in written procedures** (relevant to the post-holder's duties/clinical trial role(s) and responsibilities)

- Documented **trial-specific training** (relevant to the post-holder's duties/clinical trial role(s) and responsibilities in a particular trial)

- Documented **competency sign-off** (for specific duties requiring it)

Documentation: Answer

Remember :

GCP requires evidence of who were involved in the clinical trial and that they were appropriately trained

Therefore:

Records should be reviewed before an individual leaves the organisation to ensure retained records that are archived are complete and accurate.

Questions

Competency Verification

Topics to cover competency verification:

- Requirements

- Training Expectation

- Mechanisms

- Documentation Needed

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