

Quality Assurance
in
Bio-availability /
Bio-equivalence studies.

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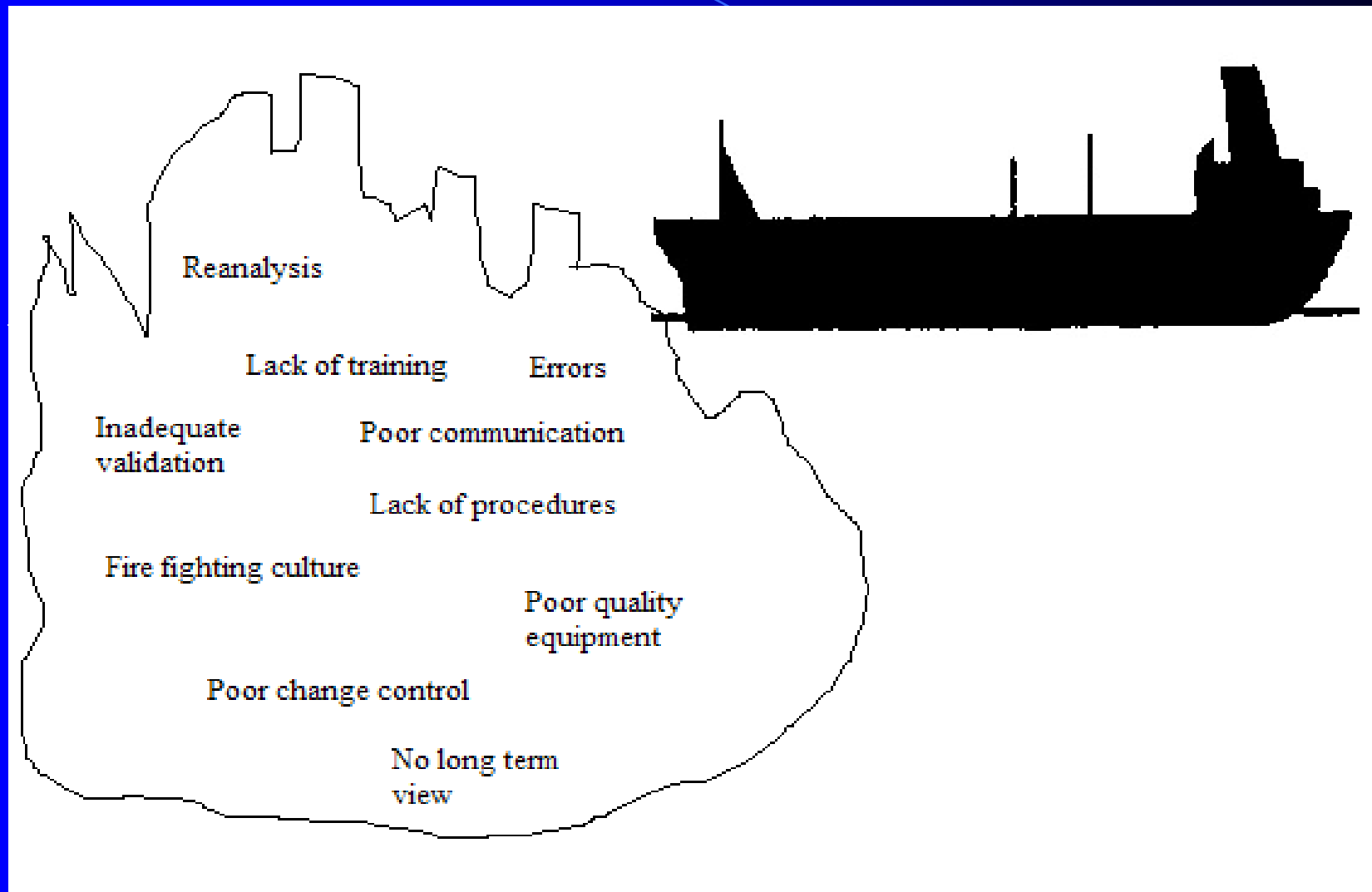
Quality and Standards

Quality can be defined as:

1. A standard of excellence
2. Having or showing excellence
3. Superiority in performance
4. Suitability of intended purpose

A more tangible definition would be
ADHERENCE TO STANDARDS

PROBLEM ICEBERG



Quality Management

Essential basic elements

1. The importance must be clearly stated and drive should come from management
2. Required standards, guidelines understood and properly followed
3. System must be capable of preventing errors, emphasis on prevention (DON'T ACT LIKE TRAFFIC POLICEMAN)
4. Independent assessment of compliance (measure the trend)
5. Flexible system (many regulations to follow)
6. State individual responsibilities clearly in quality management

Five Basic Variables

1. Man
2. Materials
3. Methods
4. Equipment
5. Environment

Bioequivalence study

TWO PHASE'S

CLINICAL

Clinical conduct

ANALYTICAL

Analysis (samples)

Regulatory Requirements :

GCP

- ICH
- FDA
- Countries regulations

GLP

FDA
OECD
UK

Definitions

Good Clinical Practice (GCP)

A standard for design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial subjects are protected.

[1.24, ICH Topic E6, GCP]

Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

[1.47, ICH Topic E6, GCP]



GCP DEFINITION

Quality Assurance

All those planned and systematic actions that are **established** to ensure that the trial is performed and the data are **generated, documented (recorded), and reported** in compliance with **Good Clinical Practice (GCP)** and the applicable regulatory requirement(s).



GLP DEFINITION

Quality Assurance

A **defined system**, including personnel, which is independent of study conduct and is designed to assure test facility management of compliance with these Principles of Good Laboratory Practice”

Audit

“A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed and accurately reported, according to the protocol, sponsor’s SOP, GCP and the applicable regulatory requirement(s).”

ICH-GCP 1.6

Regulatory Requirements

Quality Assurance Unit

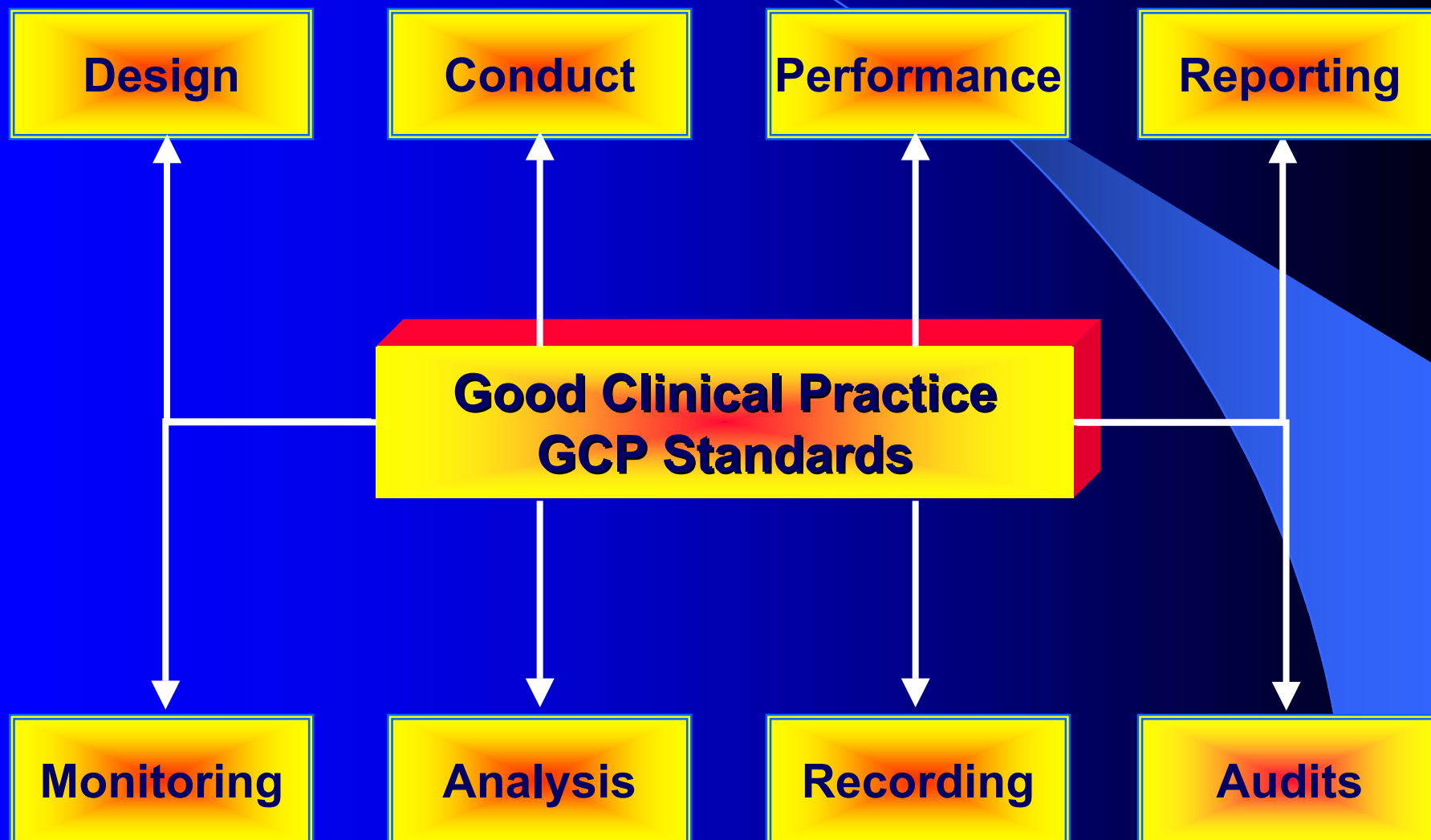
“A testing facility shall have a quality assurance unit which shall be responsible for monitoring of each study to assure management that the facilities, equipment, personnel, methods, practices, records and controls are in conformance with the regulations in this part”

***58.35, sub-part B – Organization & personnel
21 CFR part 58 – Good Laboratory Practice for
Non-Clinical Laboratory studies***

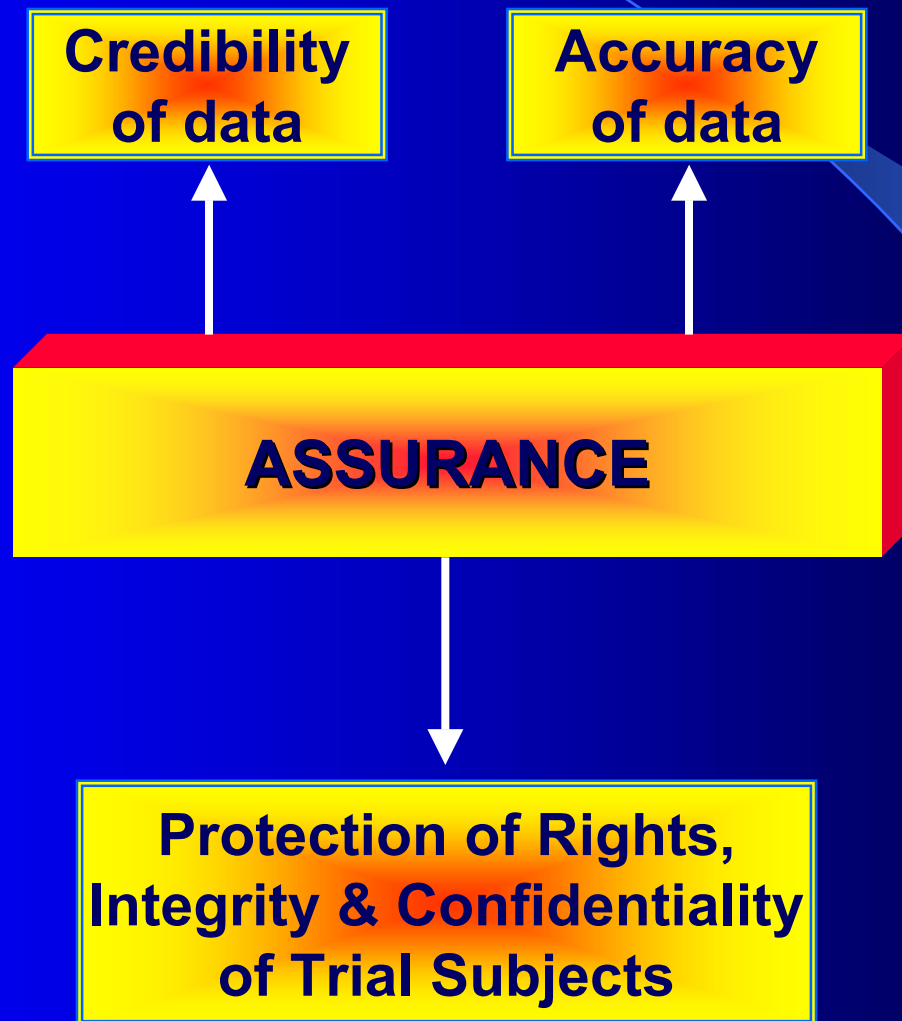
The Role of QA Function

- Confirm GCP compliance
- Act as a catalyst for quality improvement
- Provide advice on GCP matters
- Provide help with training clinical research staff
- To help establish a quality and compliance based culture

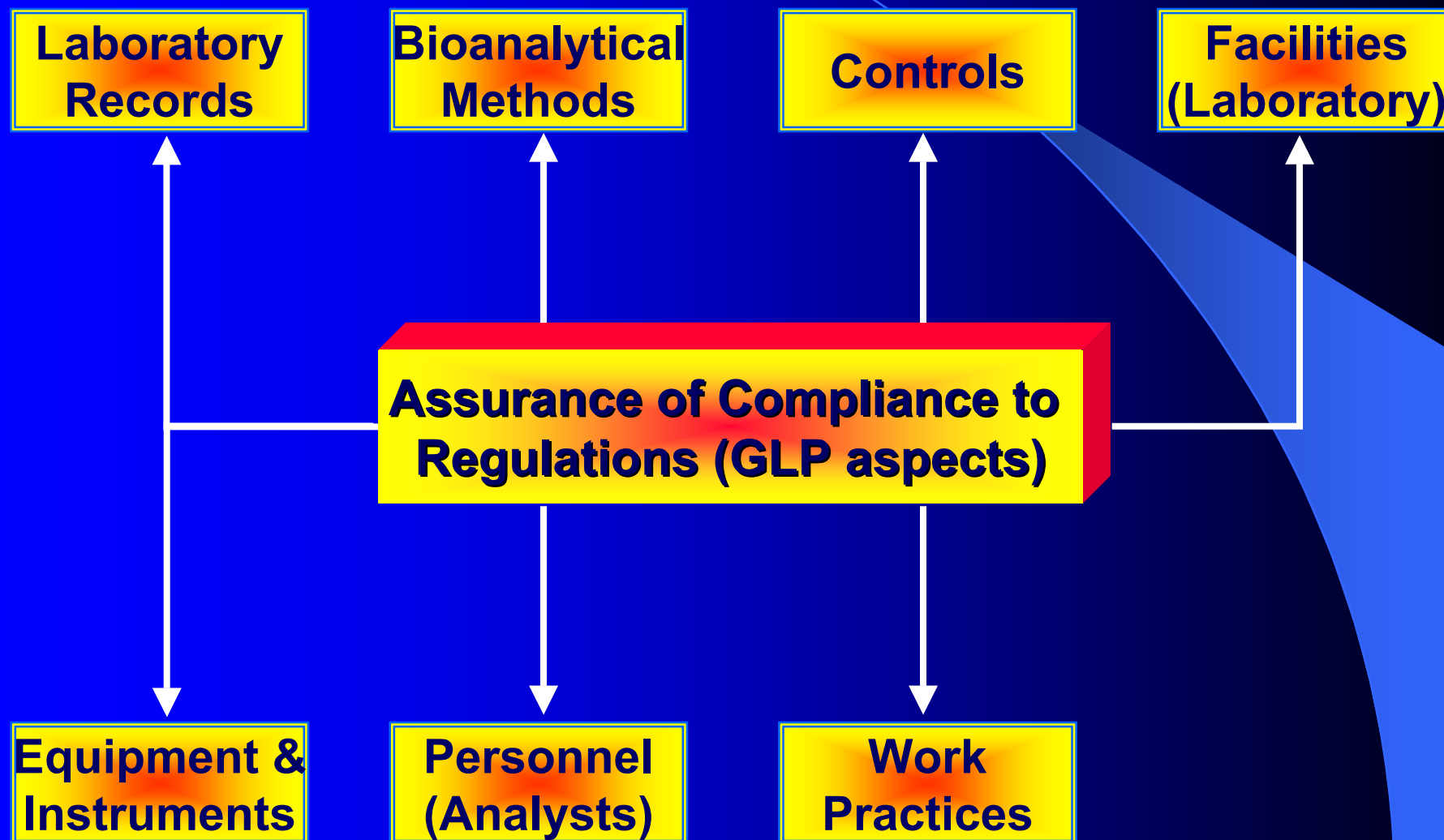
Clinical Trials – GCP Aspects



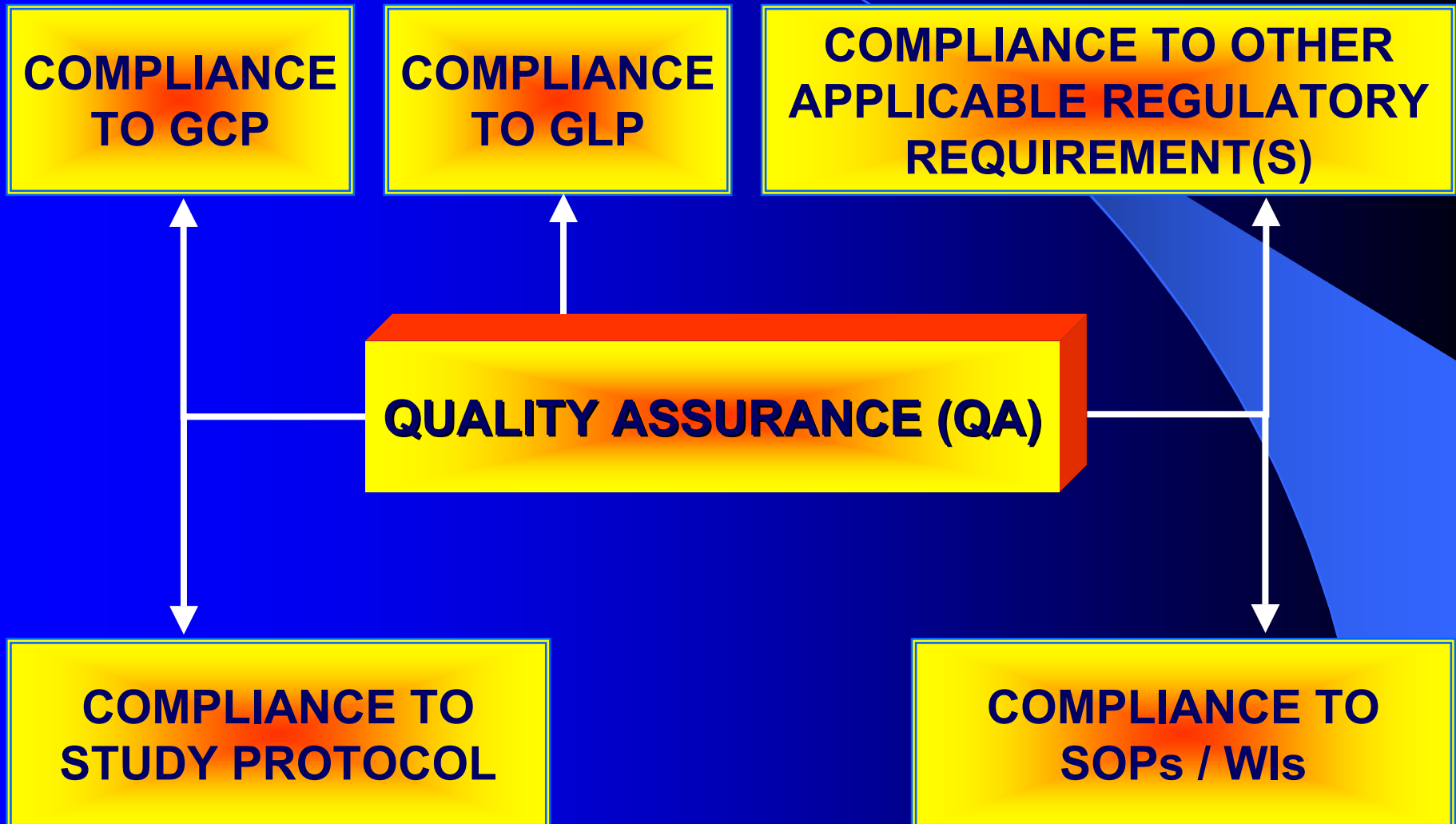
Assurance by GCP



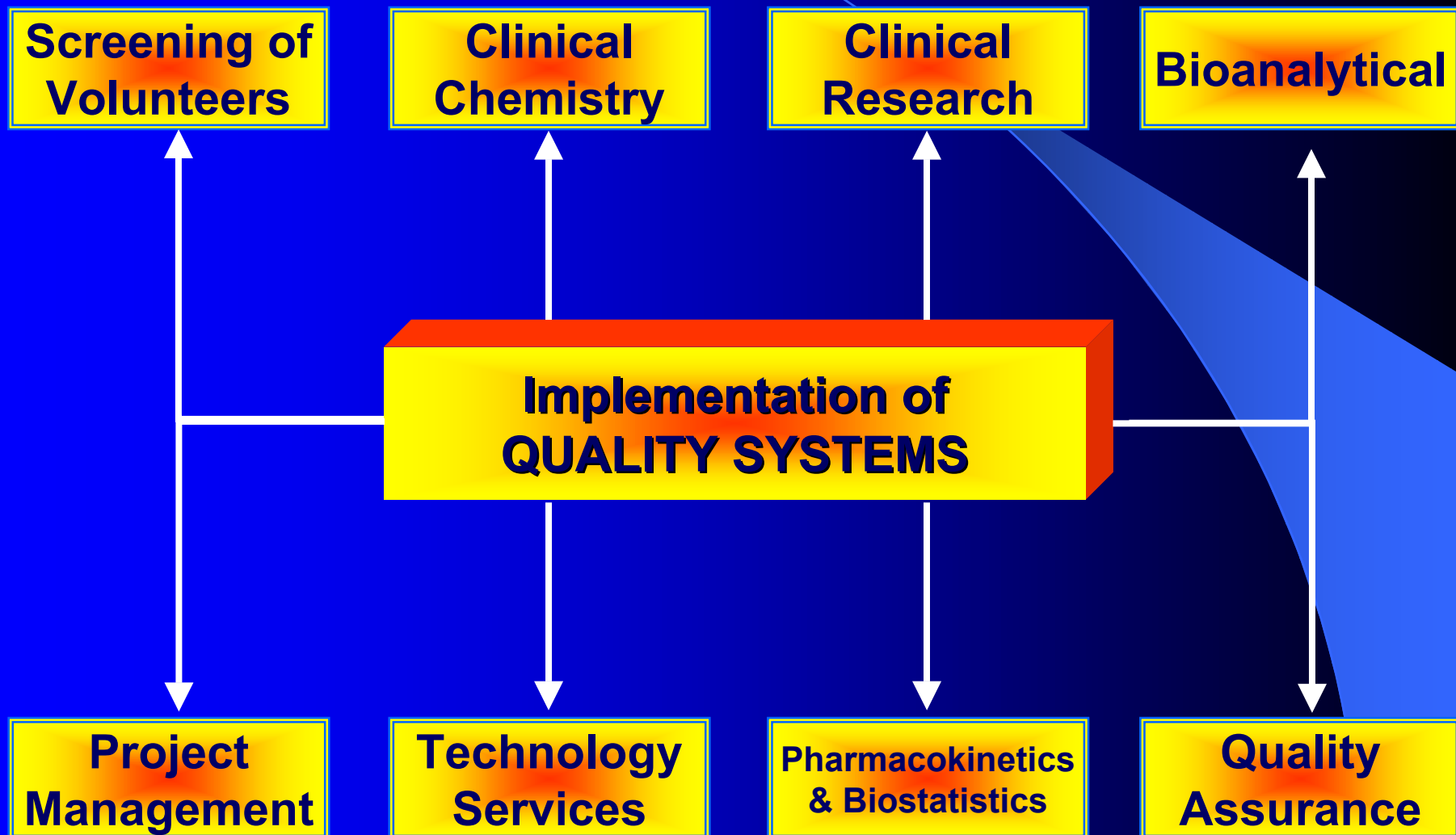
Clinical Trials – GLP aspects



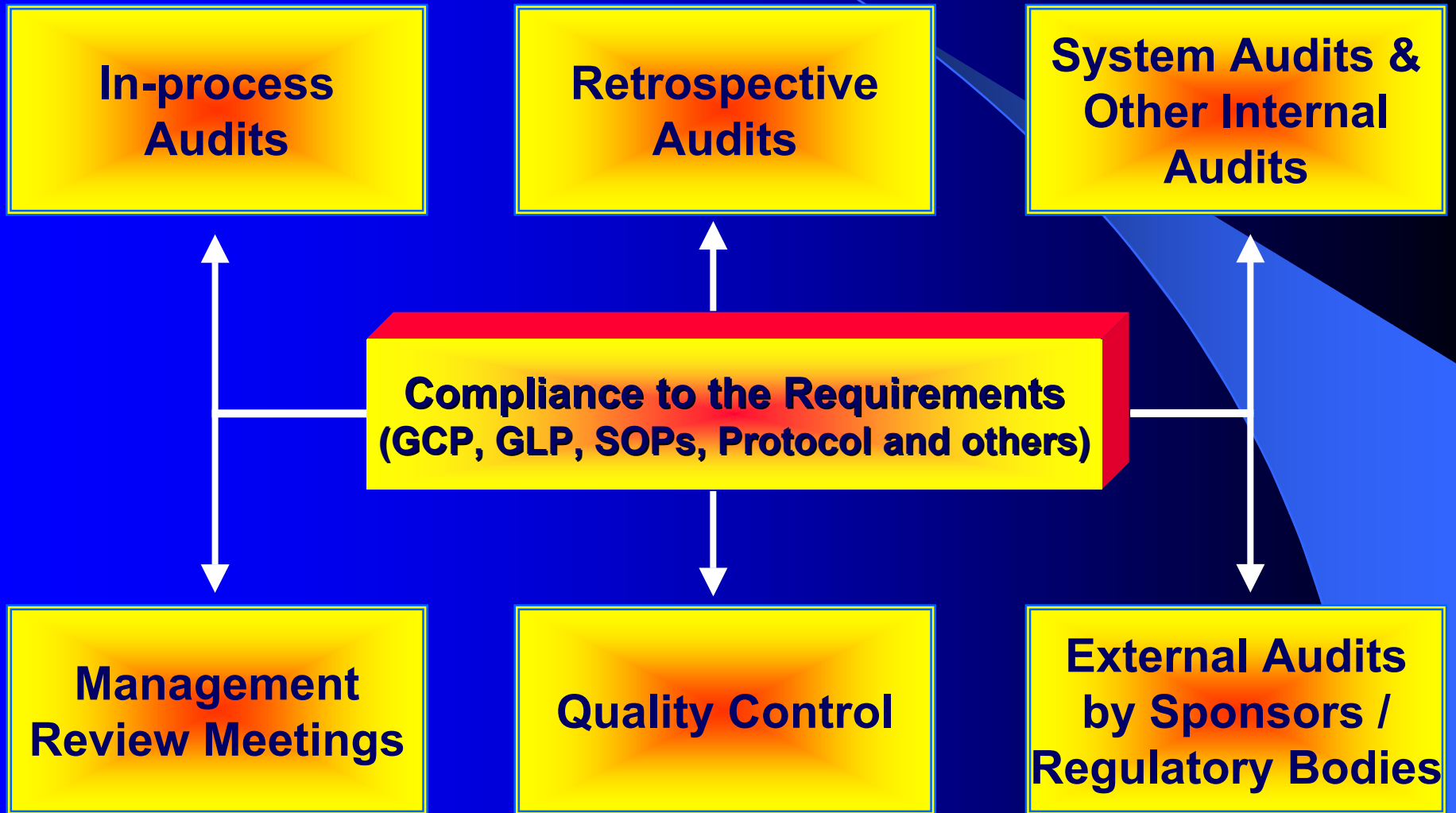
Role of Quality Assurance



How is it ensured ?



How is it measured / ensured ?



Clinical Audit Policy

- Independence of QA
- Agreement and commitment of all
- Application to clinical trial process as well as data
- Application of audits during as well as after trial
- Use of sampling systems
- Applied to each part of clinical development process

SYSTEMS AUDITS

- Adverse event handling and reporting
- Staff training records
- Standard Operating Procedures
- Equipment records
- Facilities
- Procedural inspections
- Archiving

Adverse Event Handling

- All staff aware of reporting AE procedure
- SOPs available for reporting AEs
- Documentation to demonstrate timely and satisfactory handling of AEs
- Regulatory reporting requirements fulfilled

Staff Training

- Job description must be created for each member of staff
- A CV
- Training records
- Organizational chart of the company
- Procedures and SOPs

Standard Operating Procedures

Ensure that they are consistent with:

- Relevant international regulations
- Local requirements eg DCGI
- Guidelines such as ICH-GCP
- Company policies and procedures

Equipment Records

- An SOP describing the use of the equipment
- The service and maintenance requirements of the equipment
- Records to illustrate that the use, service and maintenance of the equipment occurred in accordance with requirements

Facilities

Certain in-house facilities, for example , for human volunteer studies, may need to comply with specific standards. QA need to verify for compliance.

Eg. ABPI guidelines on standards for the facilities in which studies on non-patient volunteers are conducted.

Archiving

- A dedicated facility
- An individual responsible
- An index of the archive contents
- Records of entry and data examined
- Data should be logged into the archive within a reasonable period of time
- Appropriate data protection measures
- SOPs

MASTER SCHEDULE

- Aware of planned studies and must have a copy
- Plans audits necessary to support the study
- Maintains its own audit plans study by study

Preparation and conduct of audit

- SOPs for audit should be prepared for :
Performing, documenting and reporting (Writing, approval, distribution and archiving of audit reports)
- List of studies planned and in progress (necessary for planning QA activities)
- Checklist established formally and updated may be used as a memory aide

Preparation and conduct of audit

Auditor should prepare for audit by

- Reviewing protocol, applicable SOPs and past audit report beforehand
- Must allow sufficient time for audit
- Document observations and findings
- At close of audit before report is generated discuss problems with the staff inspected

Internal QAU inspections and audits target events and organization, not people. The more problems uncovered and resolved the better the level of quality.

QA Audit Report

- Detailed to enable the audit to be reconstructed
- Types of audits, phase(s) of study inspected, dates of audit, auditor conducting the audit
 - Comments should be clear and specific
 - Comments should be constructive
- Distributed to Management
- Valuable if important findings are picked up, reported accurately and discussed and acted on.

Not normally available to regulatory authorities encourage the QAU to report findings honestly, without tactical fears that the facility will be damaged in the eyes of the outside world.

Audit Reports

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graph TD; AR[Audit Reports] --> S[Summary]; AR --> MB[Main Body of the report]; S --> SRP[Responsible person<br/>Manager<br/>Senior Manager]; MB --> MRP[Responsible person<br/>Manager]; SRP --> RTR[Response to recommendations indicating:]; RTR --> RTR_L[Agreement or not<br/>Actions to be taken and when<br/>Who is responsible];
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Summary

- Significant findings
- Recommendations
- Agreed with responsible person

- Responsible person
- Manager
- Senior Manager

Response to recommendations indicating:

- Agreement or not
- Actions to be taken and when
- Who is responsible

Main Body of the report

- Detailed findings
- Response made to each finding
- Responses discussed and agreed

- Responsible person
- Manager

Reporting of Findings of an Audit

Final report/ Raw Data Audit

- Review raw data during experimental phases, process inspection, audit of final report
- Audit with reference to protocol, SOPs and raw data
- Enough data should be audited
- Look for evidence of authenticity and GLP/GCP compliance
- Cover the following during the report audit

- Contents.
- Data completeness.
- Protocol compliance.
- GLP/GCP compliance.
- Test item QC/accountability.
- Dose preparation/dosing/QC records.

- Individual tables versus raw data (sample basis).
- Summary tables.
- Appendices.
- Conclusions.

QUALITY ASSURANCE STATEMENT

- Provides the dates of study audits
- IT IS NOT THE GCP/GLP COMPLIANCE STATEMENT
- Should indicate study report reflects the study data
- IT assures that study report is complete
- Study was performed to GLP/GCP
- All audits comments are satisfactorily resolved

Responsibilities of QA Personnel

- Maintain all approved protocol and SOP's and have access to up-to-date master schedule
- Verify Protocol
- Conduct audits – Study based, facility, processed (record to be retained)
- Audit records and final reports
- Training organizational personnel in regulatory requirements

Responsibilities of QA Personnel

- Report inspection report to management/study director/ principal investigator
- Prepare and sign a QA statement
- Acting as the laboratory contact point for regulatory and other inspections
- Maintaining record of quality assurance

Requirements for Functioning

❑ Written SOPs

Representative list

- Quality assurance units aims, scope and organization
- Selection and training of QAU SOPs
- Conducting study phase inspection
- Conducting study data inspection
- Conducting process inspection
- Final report audit
- Preparing QA statement

Requirements for Functioning

- ❑ Documented training program
 - Encompassing all aspects of QA work
 - Where ever possible include on-the-job experience
 - Training in communication techniques and conflict handling(advisable)
 - Training documented and evaluated

Qualification of QA Personnel

- Training, expertise and experience
- Familiar with test procedures, standards and systems
- Understand the basic concepts underlying the activities being monitored

Quality Systems



Organizational Structure

- Well defined functional departments and organograms
- Clearly identified and written job responsibilities of employees
- Continuous training to the employees

Quality Systems



Operational Procedures

- Quality manual of the Organization
- Study specific Protocols
- Department wise SOPs and Working Instructions for conduct of study related activities
- Review of SOPs & Working Instructions periodically
- Design of study specific Protocols
- Evaluation of technical changes through Change Control system
- SOPs / Protocol deviations handling procedure

Quality Systems

- ✓ Qualification & Validation of new major equipment & instruments prior to its routine use (IQ, OQ and PQ)
- ✓ Validation of analytical methods
- ✓ Periodical Calibration and Services of equipment & instruments
- ✓ Preventive maintenance of building & facilities
- ✓ Standardization of vendors who supply us equipment, instruments, accessories & consumables etc.
- ✓ Document and Data Control
- ✓ Archiving of Documents

Need for QA in changing Clinical Trial Landscape

- ✓ More studies, more sites, greater volume
- ✓ New players in the role (CROs)
- ✓ New technologies (Electronic Records, Electronic CTD of dossiers)
- ✓ Stringent regulatory requirements (EC Directives – 2001/20/EC)
- ✓ Increasing inspections by Regulatory Authorities (WHO, USFDA, MHRA-UK etc.)
- ✓ More participation by vulnerable subjects
- ✓ Global expansion

Quality Systems

- ✓ **Internal audits by Quality Assurance**
 - In-process Audits
 - Retrospective Audits of raw data generated during study / reports / documents
 - System Audits
 - Pre-inspection audit
 - Follow up audit
 - For cause (Investigational)

What does QA do ?

QA Assures:

- ✓ Readiness of site for any external audit
- ✓ Internal processes are effectively implemented
- ✓ Data generated is valid & verified
- ✓ Study personnel are compliant
- ✓ Avoid reworks !!

QA Policies and Procedures

QA SOPs

- Review of clinical study protocols
- Audit of clinical study reports
- Audit of clinical study data bases
- Investigator site audit
- Filing and archiving of QA records
- Training of QA staff
- Review of SOPs
- Inspection of clinical study files
- Review of data handling procedures
- Inspection of CROs
- Review of computer systems
- Handling of fraud
- Systems inspection

THE ROLE OF QA IN COMPUTER SYSTEMS

Check for Minimum Documentation to demonstrate:

- System is clearly defined including objectives
- A formal validation policy and master plan exists
- Systems and its functions are adequately tested (test protocols, records of testing, lists of tests performed)
- Procedures for making any changes
- Security of the system
- Electronic archiving of the data and related SOPs
- Necessary documentation and SOPs exists in the production area

Effective Quality Management

1. **Anticipate errors**
 - Look for all the ways a process could fail and then make improvements to ensure that it doesn't
2. **Procedures**
 - Develop clear systems and procedures
3. **Train**
 - Ensure that staff are trained for the tasks they perform
4. **Validate**

All operations must be validated
5. **Avoid short-cuts**
 - Follow SOPs
6. **Control change**
 - Uncontrolled change can cause non-compliance
7. **Challenge what you do**
 - Regularly check that systems meet applicable standards

THANK YOU

The image features the words "THANK YOU" in a bold, 3D, gold-colored font. The letters are arranged in a slightly curved line across the center. The background is a gradient of blue, transitioning from a lighter blue at the top to a darker blue at the bottom. A thin, white, curved line arcs across the upper portion of the image, starting from the left and ending on the right. The overall composition is clean and modern.