

# Audit and Inspection



## DIPLOMA COURSE

*on*

## Research & Development of Products for Public Health Needs

Thammasat University, Thailand  
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# Agenda

- **GCP Audit & Inspection Processes**
  - Requirements & provisions
  - Inspectorates in the Asia Pacific Region
  - Overseas Inspectorates  
(with focus on FDA Foreign Inspections)
- **How to Treat Auditors / Inspectors**
  - The do's and don'ts
  - Preparation for audits / inspections
- **Learning from Audits / Inspections**
  - FDA changing approach

# GCP Requirements for Audits

§ 5.19 of the ICH GCP:

“**If** or **when** sponsors perform audits, as part of implementing quality assurance, they should consider:

## 5.19.1 *Purpose*

The purpose of a sponsor’s audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.”

# Provisions for Regulatory GCP Inspections

- To be found in applicable regulations for each individual country / region
- Purpose:
  - To establish whether or not the data collected (for an NDA\*) can be considered to be **reliable** in the decision-making process and to assess regulatory **risk** (safe for given populations)

# Active Inspectorates in Asia Pacific

- **Chinese Taipei / Taiwan**
  - **China** (inspects the institution – Clinical Trial Base – qualifications, resources, informed consent process & facilities – not sponsor studies (yet))
  - **Indonesia**
  - **Japan** (incl. foreign inspections)
  - **South Korea**
- + (Overseas Inspectorates)

# Active Inspectorates in Asia Pacific – cont'd

- **Chinese Taipei / Taiwan :**
  - Started July 1997
  - Focus on NDAs
    - One or more clinical trial centres (CTC) per NDA (no sponsor inspection, but sponsor representative asked to participate and submit documents)
    - Check of document availability (no Source Date Verification {SDV})
    - 3 – 7 inspectors for ½ day / CTC
    - 30 – 50 inspections / year (domestic only)

# Active Inspectorates in Asia Pacific – cont'd

## Impact of GCP Inspection [the Taiwan perspective \*]

- Quality Control of CT guaranteed by RA
- All CTs have good CRO / CRA monitoring
- All PIs receive GCP Training Certificate as requested by JIRB / some IRBs
- More CRO / SMO business and experience
- Future plan: Formal Certification Criteria and Incentives for PIs, IRBs and GCP Inspectors, Regional Network

\* From Presentation by Dr. Chern, CDE, at DIA, Washington, DC, June 2004, Session #384

# Active Inspectorates in Asia Pacific – cont'd

- **Japan** (by PMDA):
  - Started (according to “new” GCP) 1999 – 2000
  - Focus on NDAs
    - 2 – 3 CTCs per NDA & sponsor
    - 100% check of document availability (no SDV)
    - 2 inspectors for ½ day (domestic)
    - 1 day / CTC (foreign and / or sponsor)
  - **Foreign inspections: 5 – 6 per year**



# Active Inspectorates in Asia Pacific – cont'd

- **South Korea** (by the KFDA):
  - Focus on NDAs
  - Data driven as the US FDA (statistics not available)
- **Overseas Inspectorates:**
  - US FDA (see following slides) [now also PhV inspections]
  - EMEA (European Union)
    - Recently started inspect outside the EU (e.g. China)
    - Quality **system** focused
    - Submission triggered and In-process inspections

# Inspectorates in Asia Pacific “Under Construction”

- **Singapore** \*
- **Thailand** \*
- **Hong Kong** \*
- **Australia** (TGA has indicated start in 2008, however no signs of this yet)

\* Initiative under APEC to train future inspectors ongoing - 1. workshop in March 08, and 2. planned in March 09. In addition WHO/TDR has conducted workshops. (Also ‘future’ inspectors have participated as observers and trainees during Roche CTC audits).

# The (US) FDA and Foreign Inspections

The following slides are from a presentation by:

**David A. Lepay**, MD PhD  
Senior Advisor for Clinical Science  
Director, GCP Programs  
Office of the Commissioner, FDA

On 5 August, 2004, Sydney

OBS: The FDA often use *inspections* and *audit* interchangeably and FDA *Inspectors* are sometimes also called *auditors* and even *investigators* !

# ***FDA and Clinical Research Outside of the U.S.***

- *FDA has authority to set conditions for accepting non-U.S. data that will be used in support of research (IND) or marketing (NDA) permits in the U.S.*
  
- *FDA can accept this non-U.S. data in two ways:*
  - *If the non-U.S. studies / sites voluntarily operate under a U.S. IND as designated by the sponsor*
  - *Under FDA regulations for accepting non-U.S., non-IND studies*

# *The IND and Non-U.S. Studies / Sites – 1 -*

- *There is **no requirement** for non-U.S. studies / sites to operate under a U.S. IND*
  - *The IND is one mechanism for shipping U.S. – manufactured investigational products to trial sites outside of the U.S.*
  - *Some sponsors prefer to voluntarily operate their non-U.S. studies / sites under a U.S. IND ... for purposes of quality and consistency*

## *The IND and Non-U.S. Studies / Sites - 2 -*

- *If a sponsor voluntarily indicates that a non- U.S. study / site is operating under a U.S. IND, then it is expected that all U.S. IND regulations will be followed*
  - *This includes submission of a signed FDA Form 1572 from each CI to the sponsor*
  - *This includes review by an IRB / IEC that is in compliance with FDA IRB regulations*

# ***Accepting Non-U.S., Non- IND Studies***

- *FDA will accept non-U.S., non-IND studies FOR PURPOSES OF REVIEW in support of an application (NDA) for marketing in the U.S.*
  - *Provided criteria specified in FDA regulations are met*
- *Once accepted for review, such studies are reviewed to the same scientific and data integrity standards as studies conducted in the U.S.*

# **Criteria for accepting Non-U.S, Non-IND Studies – 1 -**

- *On June 10, 2004, FDA issued a proposed rule that, if / when finalized, will change these criteria*
  - **Update:** on 27 October, 2008, the revision to 21 CFR 312.120 “Foreign Clinical Studies not conducted under an IND” became effective



## **Criteria for accepting Non-U.S., Non-IND Studies – 2 -**

- *In the meantime , FDA regulations require that:*
  - *Trials are applicable to the U.S. population*
  - *Well-designed and well-conducted*
  - *Performed by qualified investigators*
  - *Conducted according to world ethical principles*
  - ***Subject to FDA Inspection***

# *Authority to Inspect*

- *FDA has regulatory authority to inspect studies conducted under a U.S. IND / IDE (research permit)*
  - *Addressed as an element of informed consent*
- *FDA's ability to inspect is also a criterion for accepting non-U.S. non-IND studies in support of a U.S. IND / IDE or NDA (New Drug application for marketing in the U.S.)*

# ***Inspectional Activity***

- *FDA conducts approximately 1100 GCP inspections per year*
  - *Clinical Investigators (600 – 700 / year)*
  - *IRBs / Ethics Committees (250 – 300 / year)*
  - *Sponsors / Monitors / CROs (50 – 100 / year)*
  - *Bioequivalence facilities (50 – 100 / year)*
- ***Approximately 30 – 50 of these investigator inspections (per year) are outside of the U.S.***

## FDA CI International Inspections\*

Algeria**	1	France	44	Peru	6
Argentina	13	Gabon	1	<b>Philippines</b>	<b>2</b>
Australia	8	Germany	43	Poland	12
Austria	5	Greece	2	Portugal	2
Bahamas	1	Guatemala	2	Romania	1
Belgium	19	<b>Hong Kong</b>	<b>5</b>	Russia	17
Brazil	10	Hungary	8	Slovenia	1
Canada	126	<b>India</b>	<b>2</b>	South Africa	22
Chile	5	Ireland	1	Spain	15
<b>China</b>	<b>2</b>	Israel	4	Sweden	26
<b>Chinese Taipei</b>	<b>2</b>	Italy	31	Switzerland	2
Colombia	1	<b>Japan</b>	<b>3</b>	<b>Thailand</b>	<b>2</b>
Costa Rica	7	Kenya	1	Turkey	2
Czech Republic	7	Latvia	3	U. K.	85
Croatia	3	Lithuania	1	Venezuela	2
Denmark	8	Malawi	1	Yugoslavia	2
Dominican Rep.	1	Mexico	13	Zambia	1
Ecuador	1	Netherlands	23		
Egypt	1	New Zealand	3		
Estonia	2	Nigeria**	1		
Finland	14	Norway	5		
		Panama	2		

\*Conducted for FDA/CDER  
from 1980 through 09/30/05;  
total: 636

\*\*data reviewed in U.S.

# FDA CI (Clinical Investigator) International Inspections in the region\*

## Number of FDA Inspections:

- Australia: 9
- **China: 5**
- Hong Kong: 5
- India: 3
- Malaysia: 4
- New Zealand: 5
- Philippines: 2
- Singapore: 1
- South Africa: 23
- Taiwan: 3
- Thailand: 4

*\*Region: Asia-Pacific, India & S. Africa; Data from FDA Website as of Mar-2007*

*Link to website: <http://www.accessdata.fda.gov/scripts/cder/CLIL/index.cfm?fuseaction=Browse.Home>*

# FDA CI International Inspections

## Classifications of Findings

- Australia: 9 (6 VAI, 3 NAI)
- **China: 5 (5 VAI)**
- Hong Kong: 5 (4 VAI, 1 NAI)
- India: 3 (3 VAI)
- Malaysia: 4 (3 VAI, 1 NAI)
- New Zealand: 5 (1 **OAI**, 1 VAI, 3 NAI)
- Philippines: 2 (1 VAI, 1 NAI)
- Singapore: 1 (NAI)
- South Africa: 23 (1 **OAI**, 11 VAI, 11 NAI)
- Taiwan 3 (1 VAI, 2 NAI)
- Thailand: 4 (2 VAI, 2 NAI)

# *Focus of GCP Inspections*

- *The focus of GCP inspections at investigator and sponsor sites is the **data** audit*
  - *Co-ordinated closely with FDA's application review and review divisions*
  - *Targeted at primary data, not summary reports*
  - *Developed from information submitted to the application*
  - *Designed to address questions posed by the FDA review division*

and as they also put it ....



**IN GOD WE TRUST**  
**- from all others we want documentation!"**



# Selecting Sites for FDA GCP Inspections

- *Most inspections will occur for studies supporting FDA marketing applications*
  - *Usually after the study is completed (submission triggered)*
- *But parties may be inspected at any time*
- *U.S. IRB's are periodically inspected*
  - *Non-U.S. IEC'S have not traditionally been inspected --- but **can be** as a condition of FDA'S accepting data*

# Selecting Sites for FDA GCP Inspection

- *International inspections have focused on the CI*
- *Selection of clinical investigator sites is based on “impact”*
  - *Size of site*
  - *Contribution to treatment effect or statistical significance of that effect*
  - *Contribution to FDA’s approval process*
- *Sites may also be selected based on complaints received by FDA or issues raised by FDA reviewers*

# **International Studies and Site Selection**

- *Non-U.S. Investigator sites may be inspected*
  - **IF** *there are only non-U.S. data to support an application (i.e., there are insufficient or no adequate and well-controlled U.S. studies)*
    - OR -
  - **IF** *U.S. and non-U.S. data show conflicting results pertinent to decision making*
    - OR -
  - **IF** *there is a serious issue to resolve (e.g., suspicion of fraud, significant subject protection concerns / violations)*

# ***FDA GCP Inspections Outside of the U.S.***

- *Inspections must address the specific questions and needs of FDA's review team for that specific application and clinical trial as well as assure overall compliance with GCP*
- *The procedures for inspecting are the same whether for a U.S. or non-U.S. site*
  - *Procedures are described in FDA's Compliance Programs, which are publicly accessible*

# *What is FDA Looking For ?*

- *Who is doing what at the site ?*
- *Is the investigator personally conducting or supervising all aspects of the investigation ?*
  - *What is the Clinical Investigator's workload ?*
- *Is there an understanding of GCP by the CI and site staff ? How was GCP training accomplished ?*

## *What is FDA Looking For ? – cont'd*

- *Who is administering Informed Consent ?  
(Qualifications ? Training ? Supervision ?)*
- *How is subject recruitment handled ?  
(Incentives ? Problems ?)*
- *Are IEC approvals, queries, and continuing review  
appropriately handled and documented ?*

## *What is FDA Looking For ? – cont'd*

- *Were there exceptions to inclusion / exclusion criteria ?  
(Were all appropriate parties notified, including the IEC ?)*
- *Were there changes to or deviations from the protocol ? How were these handled ?*
- *Is there consistency between information provided by the sponsor, the CI and the site staff ?*

## ***What is FDA Looking For ? – cont'd***

- *Is there an understanding of the basic elements of data quality (ALCOA) ?*
  - *Attributable*
  - *Legible*
  - *Contemporaneous*
  - *Original*
  - *Accurate*
  
- *Is there any evidence of falsification or scientific misconduct ?*

[SDV often conducted in  $\geq 50\%$  of patients]



# Purpose of a Sponsor Audit

- Assess **compliance** with international GCP guidelines / regulations, company SOPs and local regulations (as per ICH GCP § 5.19.1)
- Assure data is **accurate** and **reliable**
- Ensure that patients' **rights** and **safety** are protected

With focus on systems and **documentation**

*Furthermore:*

- Hands-on **training** of site staff and monitor
- Provide **feedback** to management on quality issues

# Clinical Trials Matrix

## CLINICAL TRIAL CENTRES

	Site 1	Site 2	Site 3	Site n	
SYSTEMS	Study Management	●			
	Monitoring	●			
	Clin. Trials Supplies	●			
	Informed Consent	●	●	●	●
	Essential Documents	●			
	CRF Handling	●			
	Central Lab Proc	●			
	etc	●			

[however, a CTC is also a small “system”]

# Sponsor Audit Approach

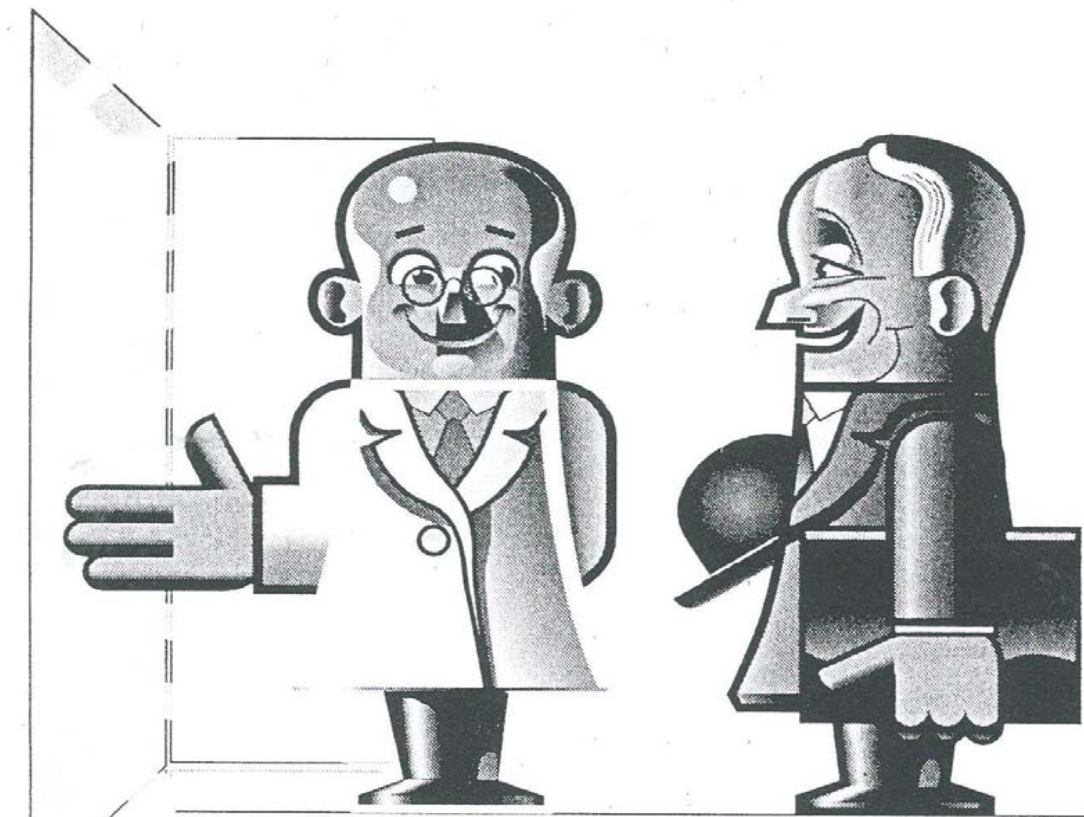
- Both quality **systems & data**
  - **Early in-process** (but not too early):
    - Detect “areas of improvement” in the quality **systems** within and / or between sponsor / CRO / site / IEC / central lab / other, **and** ensure the quality & integrity of the **data**
  - **Later on:**
    - focus on **high recruiters** and quality of documentation and data
  - **Pre-inspection visits:**
    - prepare site for inspections (mentally & physically)

# (As Investigator)

## How to Treat the Auditor / Inspector

1. **Devote** sufficient time for opening meeting & interview, during any questions and closing meeting
2. Be **open & honest** !  
(same question put to various involved site & sponsor staff)
3. **Demonstrate** that you know your responsibilities  
(and the protocol !)
4. **Prepare** the applicable facilities (and staff involved) for visits (e.g., pharmacy, labs, IEC, central archives)

[please remember that auditors / inspectors are not necessarily professionals in the medical science of a study]



**Audit us – anytime.**

...That's the spirit

# And not like this



# FDA Inspectors Trained to Scrutinize Behaviours, Postures, Gestures for Signs of Deception

## BEHAVIORS

- ◆ Overly anxious or polite
- ◆ Defensive
- ◆ Evasive
- ◆ Guarded
- ◆ Rationalizing
- ◆ Apologetic
- ◆ Quiet

## POSTURES

- ◆ Slouching
- ◆ Very rigid
- ◆ Erratic and rapid changes in posture
- ◆ No frontal alignment

## GESTURES

- ◆ Rubbing or wringing of hands
- ◆ Scratching, stroking, picking or pinching
- ◆ Pulling of nose or ear lobes
- ◆ Hair straightening, pulling or twisting
- ◆ Licking of lips, difficulty swallowing
- ◆ Clearing of throat, coughing or sniffing
- ◆ Sighs and yawns
- ◆ Nail inspection, biting or chewing
- ◆ Wiping sweat from brow or neck
- ◆ Knuckle popping or finger drumming
- ◆ Leg bouncing
- ◆ Winding of watch, adjustment of jewelry

Source: Quintiles Consulting

# Preparation for Audit / Inspection

“You should always be prepared ! ?”

- Sponsor to assist site staff
  - The “mechanics” of the inspection / audit (for sponsor audits also stated in the announcement letter to the PI)
  - “FDA questions for investigators” available through the “FDA Compliance Program Guidance Manual for Clinical Investigators” and guidance booklets
  - All essential documents available
  - Applicable facilities incl. pharmacy, labs, IEC / IRB, also prepared and available



# Preparation for Audit / Inspection

“You should always be prepared ! ?”

## Essential Documents / Records / Files

- Check completeness and order, but  
**DO NOT RECREATE / BACKDATE etc**

*[You would tidy up your home before receiving guests, but you would not refurbish / paint / redecorate, would you ?]*

Audit findings if: a number of Notes to File prepared just before an audit and / or numerous monitoring visits after the audit announcement  
(other sites neglected ?)

# Learning from Audits / Inspections – cont'd

- It is furthermore a **LEARNING EXPERIENCE** for all involved – in this spirit, sponsor audits are performed and this is how they should be / are received
- Even the FDA has applied a more pragmatic approach  
- no longer only “policemen”

Again, from Dr. Lepay’s presentation:

# *The Solution: Working Together*

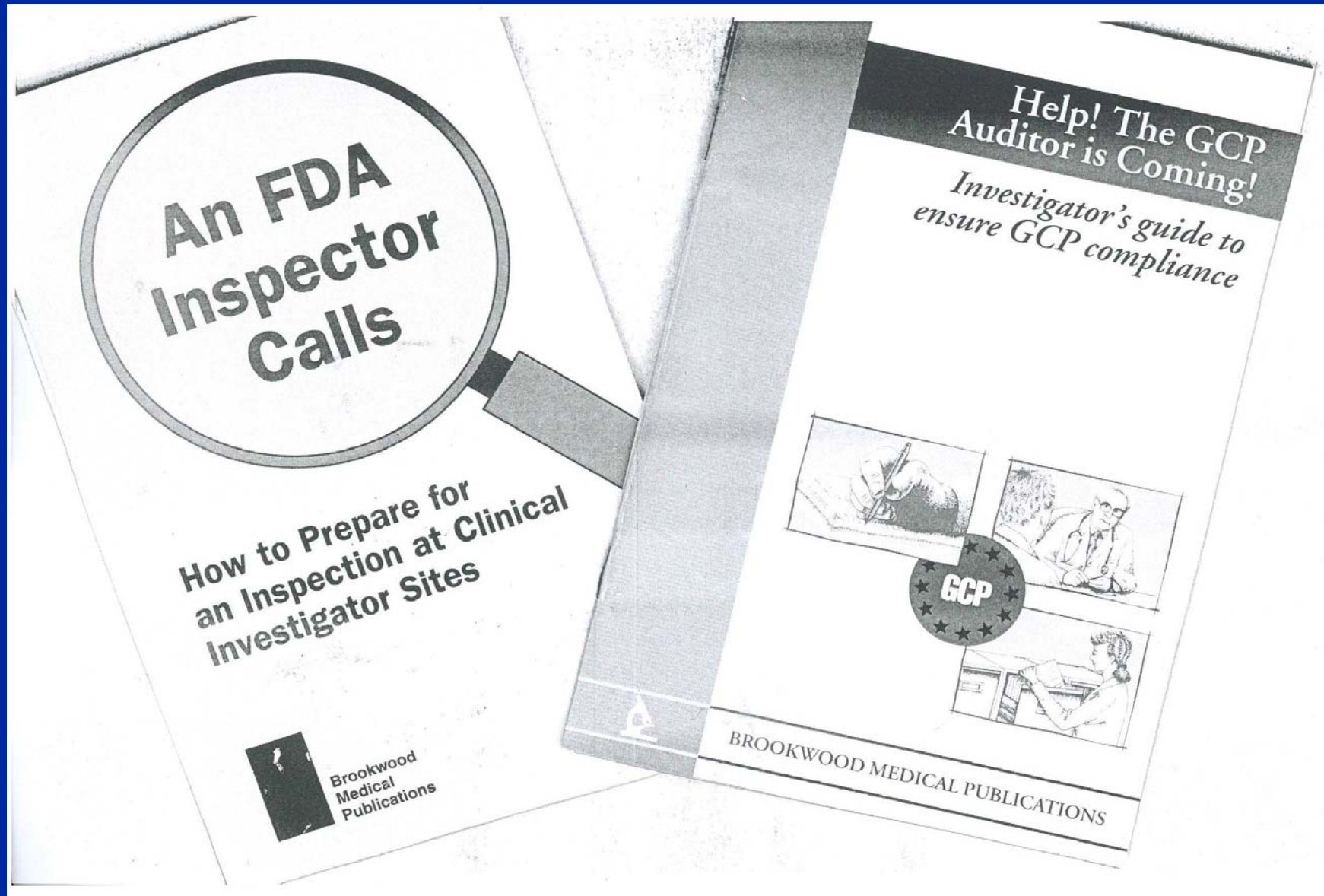
## *Educating* and setting standards

- *Building capacity*
- *Responding to problems / complaints*
- *Keeping involved*
- *Being there, and doing it well !!!*

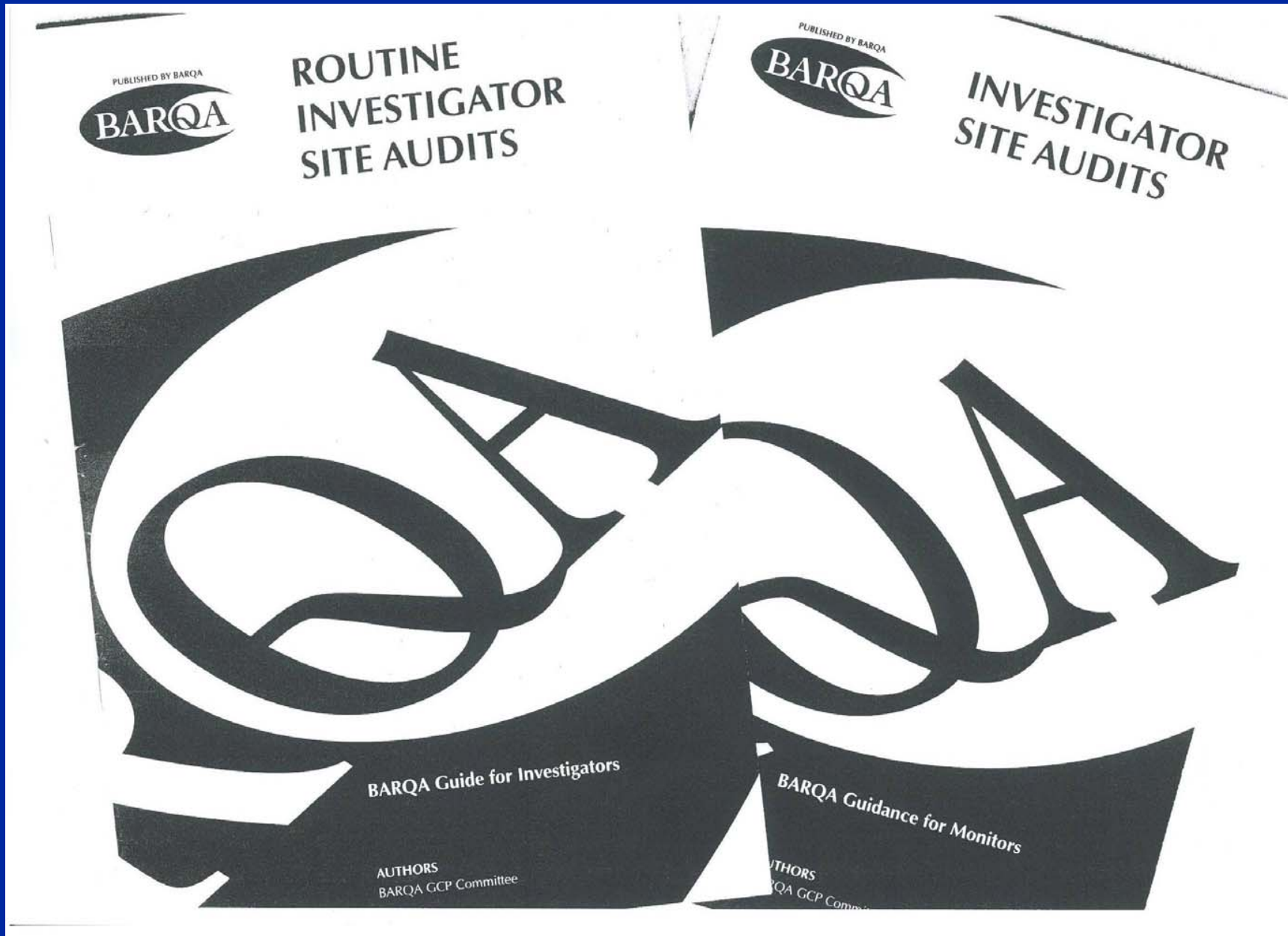
*[GCP Questions Mailbox:  
[gcpquestions@oc.fda.gov](mailto:gcpquestions@oc.fda.gov)*

*Website: [www.fda.gov/oc/gcp](http://www.fda.gov/oc/gcp)*

# Guidance Booklets - 1



# Guidance Booklets - 2



# Reviewing IRB Management during a sponsor GCP Audit

- Disclaimer :
- Pharma Sponsor Auditors do **not** and **cannot** “audit” IRBs, we have no “jurisdiction” to do so, but we can:
  - Review documentation related to the specific trial
  - Ask to visit the IRB in order to interview relevant / available members

# WHY ? Regulatory Framework (1)

According to ICH GCP 5.1.1. (Sponsor Section)

“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 generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.”

## WHY ? Regulatory Framework (2)

And Quality Assurance is defined as:

ICH GCP 1.46 (Glossary):

“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 GCP and the applicable regulatory requirements.”



# WHY ? Purpose of an Investigator Site Audit (1)

- Assess **compliance** with international GCP guidelines / regulations, company SOPs and local regulations [*incl. IRB requirements*]
- Ensure that patients' **rights** and **safety** are protected [*also main purpose of IRB oversight*]
- Ensure data is **accurate** and **reliable** [confidence in the data for regulatory submission]

## WHY ? Purpose of an Investigator Site Audit (2)

In addition:

- Provide **feedback** to management on quality issues (if any)
- Hands-on **training** of site staff and monitor

And finally:

- When **visit to IRB**, always fruitful discussions, exchange of “better practices” and a chance to point out “areas of improvement”

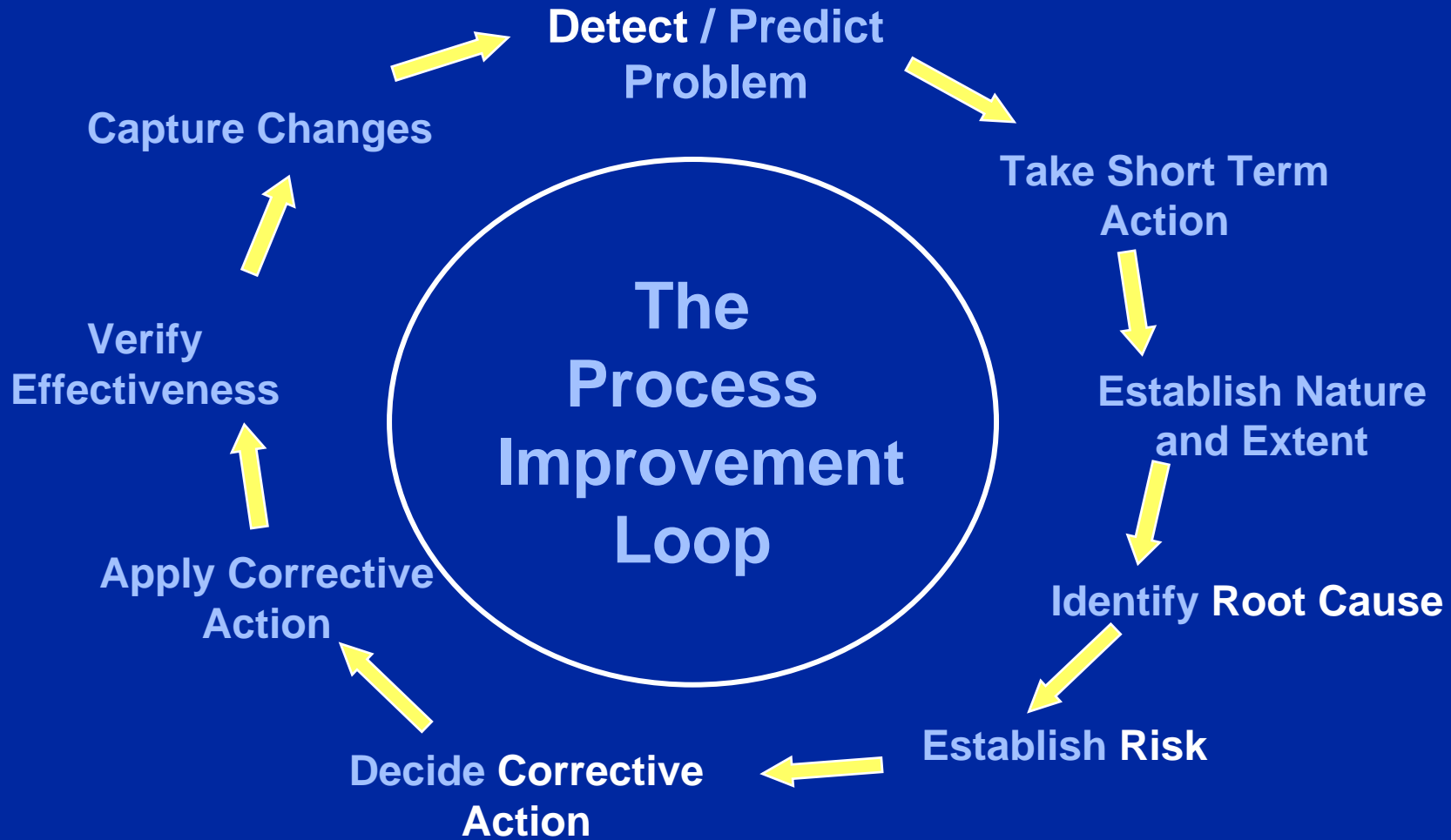
# WHY ? Capacity Building

Learning from audits / surveys / inspections:

The ISO 9001:2000 approach can be applied

**“The Process Improvement Loop”**

# The Process Improvement Loop



# HOW ? Our SOP on Investigator Site Audit (1)

D 14 ...

“Assess the “central” / local IRB / IEC procedures for approval of the protocol and protocol modifications, submission of safety and progress reports and archiving procedures. If necessary \*, ask for an interview with members (eg. the secretary, the chairman) of the IRB / IEC”.

\* in this region we always visit the IRB (if at all possible)

# HOW ? Our SOP on Investigator Site Audit (2)

D 16 ...

“Review relevant documentation to determine whether the IRB / IEC and investigator have received the latest IDB \* and have been informed of any new safety findings in accordance with international, local and IRB / IEC requirements”.

\* Investigational Drug Brochure

# HOW ? Our Questionnaire for IRB Interviews

## 3. Continuing and safety review

How do you deal with protocol amendments ?

What are the IEC requirements in terms of safety reporting and related reports ?

Do you require an annual report ?

Do you re-approve the study annually ?

Do you require a final report ?

## 4. Archiving

What are your archiving provisions and retention period ?

## 2. Ethics submission and initial review

What documents do you require to be submitted ?

How is the review process structured ?

Do you consider:

- The qualifications of the investigator ?
- Payments to patients ?
- Indemnity / insurance issues ?

Are the decisions made in a meeting ?

Do you keep minutes of your meetings ?

How do you communicate the decision to the investigator ?

Do you provide the composition of the committee that approved the protocol ?

Do you have a template for the patient information sheet and informed consent form ?

Do you review the consent form against the requirements of ICH / FDA ?

Is a witness required to sign the consent form ?

What is witnessed - the patient's signature or the whole process ?

What are the requirements for foreign-speaking patients ?

CLINICAL TRIAL CENTRE AUDIT # rnn

Investigator Name, City - Protocol #

ETHICS COMMITTEE INTERVIEW

Interview Date:

Personnel Interviewed (Name and Function)

- 
- 

### 1 General

Are there any specific standards and/or regulations that the Ethics Committee has to comply with ?

Is there a registration or accreditation scheme for ethics committees in your country ?  
If yes, do you participate in the relevant scheme ?

Are you aware of ICH / FDA requirements ?

What is the composition of the Committee and how are members selected ?

Is any member of the study team part of the Ethics Committee ?

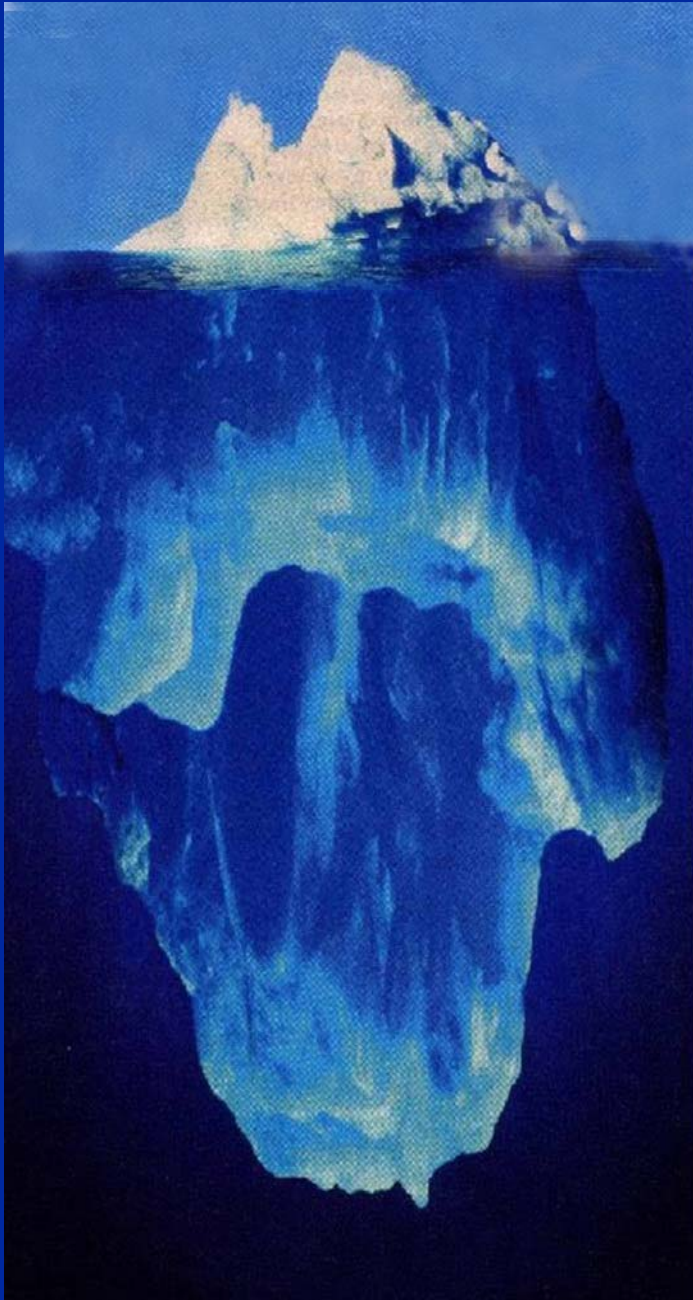
Do you have written procedures ?

How often do you meet ?

Do you have a minimum quorum for meetings ?

Can anything be approved outside a full committee meeting (Chairman's approval) ?

Is this defined in your procedures ?



**Sponsor GCP Site Audit  
(one trial, one sponsor, one protocol)**

**SIDCER / FERCAP  
IEC SURVEY  
multiple protocols  
multiple sponsors  
multiple researchers**



# Questions

