AUDIT
negli studi clinici

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Audit

In agenda:

- **cosa sono**
- **a cosa servono**
- **come vengono condotti**
- **riflessioni conclusive**

Cos'è un AUDIT?

- **Controllo sistematico ed indipendente delle attività e dei documenti pertinenti a uno studio clinico per valutare se le attività relative allo studio, la registrazione, l'analisi e la trasmissione dei dati siano state espletate in conformità a:**
  - **Protocollo di studio**
  - **SOP del Promotore**
  - **Good Clinical Practice**
  - **Normative vigenti**

(ICH-GCP Sec 1.6)

Cos'è un' ISPEZIONE?

- **Attività svolta da un ente regolatorio per condurre una revisione ufficiale dei documenti, delle strutture, della registrazioni e delle risorse inerenti uno studio clinico presso**:
  - **il centro**
  - **la CRO**
  - **altre strutture ritenute rilevanti per lo studio**

(ICH-GCP Sec 1.29)

Auditor e Ispettori

AUDITOR

Dipendenti della stessa aziende che promuove il trial o una CRO, normalmente inseriti in una funzione di Clinical Quality Assurance

Devono assicurare l'avvenuto rispetto del protocollo, GCP, SOP e normative applicabili

ISPETTORI

Funzionari governativi

Devono assicurare il rispetto delle normative inerenti i clinical trials e l'affidabilità dei dati clinici che sottendono all' attività e sicurezza di un farmaco

Audit: classificazione

Audit di Routine

- Audit di uno studio nel Centro di Sperimentazione
- Audit di uno studio presso il Promotore
- Audit di Processi o Sistemi
- Audit di Fornitori Servizi (es. CRO)

Audit Mirati

- For Cause

Audit & Ispezioni : quando?

Audit possono avere luogo:

- In qualsiasi momento durante lo studio
- Dopo che lo studio è stato completato, prima della registrazione di un nuovo prodotto

Le ispezioni possono avere luogo anche dopo la conclusione dello studio e la registrazione del prodotto

Audit & Ispezioni

Garantire la tutela dei diritti e la sicurezza dei soggetti in studio

Assicurare che i dati clinici siano credibili ed affidabili

AUDIT

Audit di un centro sperimentale

Audit di un centro sperimentale

Come viene selezionato un centro?

Audit di routine

- Arruolamento : **Numero di pazienti arruolati. Ci si focalizza sui centri che arruolano di più o più velocemente**
- Mantenimento dei pazienti in studio : **frequenza elevata di screening failure/drop-out**
- Eventi Avversi : **numero di EA/SAE superiore/inferiore alla media dei centri**
- Importanza dello studio : **pivotal per la registrazione**

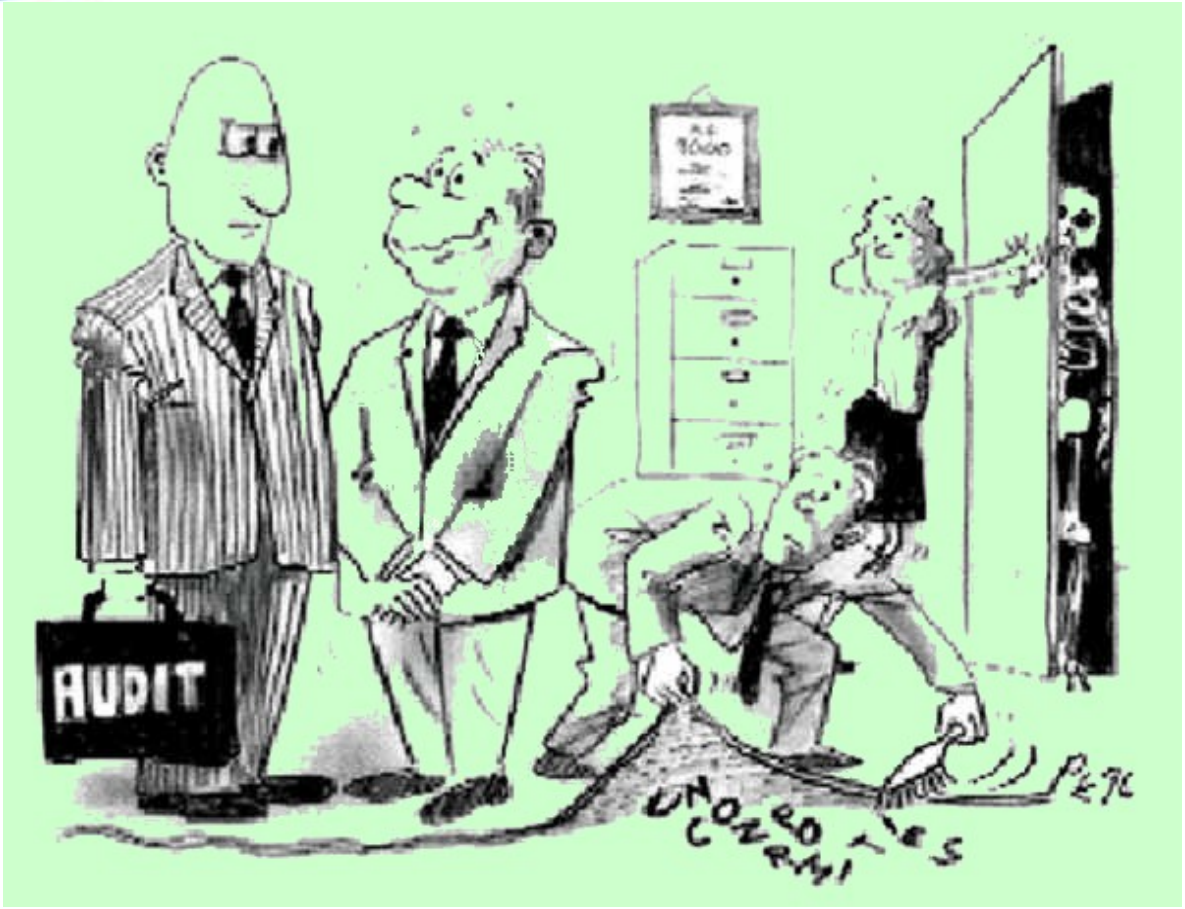
Audit di un centro sperimentale

Come viene selezionato un centro?

Audit For Cause

- Dati di efficacia/sicurezza non in linea con altri centri
- Uniformità dei dati clinici dei pazienti arruolati nel centro
- Apparenti irregolarità nella gestione dei consensi informati
- Arruolamento insolitamente elevato per l'area geografica (epidemiologia)
- Visite/esami di routine condotti in giorni festivi
- Qualsiasi elemento generi sospetto di grave GCP non compliance / frode

Conduzione dell'audit



Preparazione

Esecuzione

Rapporto

Conduzione dell'audit

Il promotore ha generalmente delle SOP che descrivono come deve essere gestito l'audit

Riferimenti

ICH /GCP ENGAGE guidelines (EU forum for GCP Audit Working Party)

International Organization for Standardization

ISO 19011:2002 Guidelines for quality and/or environmental management systems auditing

EFGCP European Forum for Good Clinical Practice Audit Working Party

U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

Compliance Program Guidance Manual For FDA Staff

Conduzione dell'audit

sanofi aventis

QSOP-000378 Audit Preparation, Initiation, Confirmation and Post Audit Letter / Memo

3.1. A pair of auditors is generally assigned to an audit (Lead Auditor and a Co-Auditor). Whenever possible, the entire audit should be performed by the same pair (e.g., in-house and on-site audit).

3.2. For external audits, **whenever possible, the auditor(s) should be accompanied by a sanofi-aventis representative** of the operational team responsible for the audited activity (e.g.,monitoring team member for an investigator site audit).

Conduzione dell'audit

3.4. As a general principle, any audit related information should be sent to the staff directly responsible for the audited activity (i.e., the auditees)

3.4.2. **The audit is confirmed through the confirmation letter/memo** to the staff involved in the audited activity.

3.5. After conducting the audit (which is addressed in specific procedures for different types of audits), **a Post-Audit Letter / Memo will be sent to the auditees.**

On-site Audit

sanofi aventis

WW-QUAL-CQC-SOP-0011 Audit of an Investigator Site

4.3 Conduct of the On-site Audit

1. Carry out the **opening meeting** with the investigator, sub-investigator(s) and/or key staff members participating in the clinical trial**.**

2. Conduct an **interview with the investigator and relevant staff** using, as needed, the questionnaire finalized during the audit preparation

On-site Audit

3. Review the **Investigator Study File (ISF)** for adequacy, completeness and consistency

STUDY PROGRESS

CORRESPONDENCE

PROTOCOL AND INFORMED CONSENT

REGULATORY / ETHICS COMMITTEE / IRB

INVESTIGATIONAL PRODUCTS

CASE REPORT FORM (CRF)

LABORATORY / PK

SAFETY

STUDY SITE / INVESTIGATORS / CONTACTS

MEETING /TRAINING

CLINICAL TRIAL TEAM

STATISTICS / RANDOMIZATION

INVESTIGATOR'S BROCHURE

On-site Audit

4. Review all the **Informed Consent Forms** (ICF) of the patients participating in the study. If the number of patients is higher than 100, a minimum of 100 ICFs should be checked, covering all the different versions used since the beginning of patient inclusion.

5. Compare **CRF data of the patients selected for SDV with the source data** for completeness, accuracy, coherence and consistency.

6. Check the **IP accountability** for the selected patients.

On-site Audit

.**7.** Visit the investigator site facilities:

- General state of the facility
- Specific equipment necessary to meet the requirements of the protocol and related maintenance records
- Pharmacy and/or IP storage/preparation area
- Laboratory services (if applicable)
- Filing of the documentation and archiving
- Other department(s) or satellite sites (when relevant).

8. Review and exchange observations and recommendations made during the audit in order to prepare for the closing meeting.

9. Conduct a closing meeting with the investigator's team

On-site Audit

4.4 Follow-up of the Investigator Site Audit

1. Send a letter to the principal investigator,
2. Calculate the error rates from SDV performed on site
3. Write and distribute the initial audit report (after appropriate peer review).
4. Assess responses and hold a debriefing meeting if necessary to reach agreement on the adequacy of responses.
5. Prepare and distribute the final audit report
6. Close the audit by issuing a closure memo.
7. Check and ensure archiving of all key audit documents.
8. Continually update the audit database when necessary.

GRADINGS OF FINDINGS

- Critical
- Major
- Minor

GRADINGS OF FINDINGS

Critical

- Conditions, practices or processes that adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

Critical observations are considered totally unacceptable.

- **Possible consequences**: **rejection of data and/or legal action required**

- **Remark: Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents. Fraud belongs to this group.**

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm

GRADINGS OF FINDINGS

Major:

- Conditions, practices or processes that might adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data.

Major observations are serious deficiencies and are direct violations of GCP principles

- **Possible consequences**: data may be rejected and/or legal action required
- **Remark:** Observations classified as major, may include a pattern of deviations and/or numerous minor

Minor:

- Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

- **Possible consequences**: Observations classified as minor, indicate the need for improvement of conditions, practises and processes.
- **Remark**: Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

Critical audit findings management

- **Expedited Reporting.**
  - About 65% of the companies report critical findings in an expedited manner. (i.e., during the audit conduct) or within up to 5 working days by phone, email, or meeting.
- **Clinical study reports.**
  - About 60% of the companies report critical audit findings and/or corresponding corrective actions in their final clinical study report.
- **IRBs/IECs and agencies.**
  - Only 17% of the companies report critical audit findings and/or corresponding corrective actions directly to IRBs/IECs and agencies.
- **Recommendations/requests for corrective actions.**
  - About 65% of the audit reports contain recommendations or requests for corrective actions for either critical findings or major findings. About half of the audit reports contain recommendations or requests for corrective actions for minor findings..

U.Streicher-Saied, H. Gertzen et al “Investigator Site Audit Performance” Applied Clinical Trials; Jun 1, 2006

CQA benchmark survey

Main Categories Used for Audit Findings

Figure 2: Categories used to assign audit findings.

U.Streicher-Saied, H. Gertzen et al "Investigator Site Audit Performance" Applied Clinical Trials; Jun 1, 2006

Conclusioni (1)

Il modo migliore per affrontare un audit / ispezione è prepararsi dal momento in cui si attiva lo studio nel centro NON dal momento in cui si riceva la notifica

Conclusioni (2)

La Qualità si costruisce con un costante impegno nel tempo e NON in risposta ai findings di un audit

L'audit da solo non è sufficiente a garantire la Qualità, ma va inserito in un ciclo di continuo miglioramento

L’impegno costante PREMIA