計畫書遵從、文件與資料保存

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PI之角色與責任

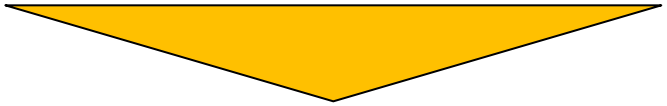
- 認知
  - 角色及責任
  - Qualification/Training
  - 授權
  - Regulation/Institutional approval
  - HRPP
    - Resources
    - Management如藥物、device之管理
    - Rules
  - IRB
  - COI
  - Quality/Efficiency
    - 依計畫書執行與記錄
    - 未依計畫書執行之通報與處置
    - 依規定保存資料
- 經驗
  - 執行計畫
  - 受試者族群/approach/vulnerable issues
  - IC/ICD/ICF
  - AE/SAE/SUSAR/NC/UAP通報
  - 資料/檢體保存與再使用

文件與資料保存

- Good Documentation Practice, GDP
  - 什麼文件需管理
    - Raw data (GLP)
      - GLP Term – In short, it's a record of an original observation (e.g. rash on neck 10 min post dose)
        - Pen hits paper and you document
        - Instruments capture electronic data
      - 何處有Raw data
        - Pharmacy dose preparations(weigh out)
        - Recording vitals, body weight, etc.
        - Actual dose time(11:57am)
        - Actual blood draw time(pre, 0.5 hr, 1.0hr, etc.)
        - Centrifuge speed, temperature, and duration
        - ECG recordings
        - Freezer sample logs (log-in/log-out)
        - Where else?
    - Transcribed data
    - Source data(ICH)
    - Source documents(ICH)

Transcribed Data – Limit This

- Transcribed data – copy data(e.g. raw) from one record into another record(e.g., tables)：
  - Manual entry after visual review
  - Electronically (software, Excel copy-n-paste)



  - Body weights in a CRF transcribed to a report table
  - WinNonLin PK results transcribed to a report table

Phoenix® WinNonlin® is the industry standard for non-compartmental analysis (NCA), PK/PD, and toxicokinetic (TK) modeling

- High error potentials – Assess QC needs!

Source data：ICH E6 1.51

- All information in *original* records and *certified copies* of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)

Source Documents：ICH E6 1.52

- Original documents, data and records
  - e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial
- This definition describes the various types of documents which collectively form the source documents

Good Documentation Practices (GDP)

- GDP is one of the most common inspection findings in a GCP clinic or at the Sponsor
  - Lack reliable, accurate and adequate source documentation
  - Lack understanding of basic GCP principles which can have a negative impact on the quality of the study
  - The importance of GDP must be emphasized to investigator sites
  - GDP can ensure credible and valid data study results

What is the purpose of source documentation

- Reconstructs the trial as it happened
- Enables independent observer to reconfirm data
- Provides audit trail to permit investigation
- Source documentation is the medical record of the subject before, during and after the trial
- The tool to confirm subject eligibility criteria
  Documents progress of the subject from consent until subject completes study

What is the purpose of source documentation

- Records accountability of investigational product dispensed, consumed and returned by subject
- Serves as complete medical record of the subject to the treating physician at any point of time
- Forms a strong foundation for the data that gets transcribed into CRF, which gets translated into a clinical study report
- Irrespective of clinical trial, accurate documentation supports the fundamental principle of protecting subject's rights, safety and well-being

GDP principles

- 未記錄，未執行

  If it was not documented, it did not happen!
- Document what is done (as well as what is not done)
- Roots of good documentation principles are in ICH-GCP, where the terms *source data* and *source document* are first defined

GDP principles

- Key attributes by USFDA
- ALCOA:
  - Attributable
  - Legible
  - Contemporaneous
  - Original
  - Accurate
- Adapted by WHO and further evolved by EMA (particularly for electronic documentation)

GDP principles

- **Attributable**: It should be clear who has documented the data
- **Legible**: Readable and signatures identifiable.
- **Contemporaneous**: The information should be documented **in the correct time frame** along with the flow of events. If a clinical observation cannot be entered when made, chronology should be recorded. Acceptable amount of delay should be defined and justified.

NO BACKDATING OR PRE-DATING RECORDS… EVER!!!

- **Original**: The first record made by the appropriate person. The investigator should have the original source document. If not original should be exact copy.
- **Accurate**: Accurate, consistent and real representation of facts.

常見Source documentation疑義 -USFDA 2010

- 未適當與正確保存文件

  Failure to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation

- 未依規定年限保存

  At one investigator site source documents were not available because the computer *'crashed'*. So in the absence of availability, adequacy of the records could not be evaluated. The investigator was warned for failure to retain records required to be maintained for the required timeframe per regulations

  - 研究結束後3年/研究產品上市後2年

- 無法確認是否符合納入標準

  Eligibility criteria could not be confirmed

常見Source documentation疑義-USFDA 2010

- 相同時間點之相同記錄有不同數值

  Multiple records for *same data* points making it unable to determine which served as the accurate source record

  - e.g., multiple versions of visual analog scales completed for same visit with different values

- 無法確知以何紀錄判定療效指標

  Discrepancies in records to confirm primary efficacy endpoint of the study

  - e.g., the total administered dose of morphine, as reflected in hospital records, was different from the CRF. The primary efficacy endpoint of the protocol was to measure the reduction in the requirement for morphine use in the 24 hours following surgery measured by total morphine usage compared to placebo

常見Source documentation疑義-USFDA 2010

- 超標值未記錄於檢驗報告，或與source documentation不符

  Clinical significance for out of range lab values not documented on the lab reports or conflicting information found in the source documentation,

  - e.g., significant high glucose value marked as clinically nonsignificant on the lab report although the subject was referred to primary physician for further follow-up

- 受試者資料缺漏、未註明為何修正、不正確之受試者資料、編號或檢驗日期

  Missing pages from subject interview scales, numerous unexplained corrections months after the initial entries and conflicting information; incorrect subject identifiers, incorrect date

  - e.g., same date on screening visit, visit week 1 and week 4

常見Source documentation疑義-USFDA 2010

- 未依規定通報或延遲記錄

  Numerous AEs not reported in CRFs, delays in transcribing data in CRFs, discrepancies between source and the CRF. Lack of timely reporting of AEs in eCRFs jeopardizes subject safety and reliability and integrity of data captured at the site

- 未記錄試驗產品實際用量與日期

  Incorrect/incomplete documentation regarding the disposition of drugs-dates, quantity and use by subjects

常見Source documentation疑義 -USFDA 2010

- Issues may appear minor
- Discrepancies in source and CRF and unexplained corrections point toward a lack of understanding
- Source docs fail to provide confidence and assurance of data quality and safety of the subjects.
- Data may be deemed unfit for use. All trial efforts could be wasted (Sponsor, subject, investigator, staff, etc)

其他文件與資料保存建議

- 註明
  - 研究期間
  - 退出時
  - 研究結束後，已收集資料如何處理，包含
    - 由誰管理
    - 保存於何處
    - 安全機制
      - 隱私/保密
    - 保存期限
      - 國內共識：20年
      - 永久保存，必要性為何，如何持續保存與管理
    - 何時及如何銷毀

Lights! Camera! Action!

Your data is like a “video clip” in time and records should be documented as each procedure is completed

GDP

- Someone else needs to be able to follow and possibly defend your work
- Ask for help when you are not sure what to do
- Get it right the first time
  - Educate yourself and your peers
  - You'll save time, money, and stress
- Humans make mistakes – just don't make big ones
- Get your work reviewed!!
  - Ensure Quality Control processes

Stop, Check, Enter

Stop – 第一次輸入就正確

- 專注：避免干擾，輸入時想清楚需要記錄什麼
  Focus：Avoid interruptions and think about what you need to document
- Know what's going on (i.e., protocol, SOPs, training)
- Use good judgement and proper resources

Stop, Check, Enter

Check – 需要記錄什麼

What do I need to document?

- Probably a simple “follow the prompt” entry
- Signature/date or initials/date
- Is my entry clear or do I need more info?
- I know what I did, but can a reviewer tell what I did/decide?
- If you’re not sure, ask a knowledgeable peer/boss

Stop, Check, Enter

Enter - Document, document, document

- Procedure entries (e.g., CRF, form prompts)
- 適時修正誤值處Fix errors with timely corrections
- 加註說明Add clarifications if an entry is not clear
- Add cross-references, as helpful
- Other?
- Sign/date or initial/date, as required
  - What's the date? What's the year? What's my name?!!
  - Signature in delegation form

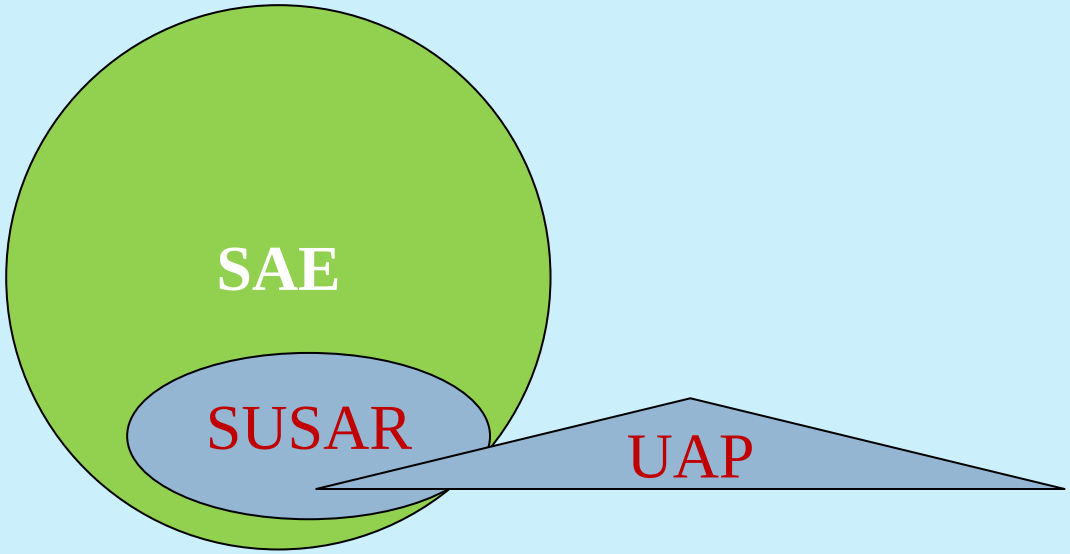
REVIEW

REVIEW

REVIEW

不遵從(Non-compliance, NC)/非預期問題(Unanticipated Problem, UAP)通報與處理

Non-compliance



不遵從(Non-Compliance)/非預期問題 (UnAnticipated Problem)

- UAP
  - 未預期unexpected
  - 相關或可能相關Related or possibly related
  - 造成更大風險或傷害Places the subject or others at greater risk of harm that was previously known OR results in the subject or others actually incurring harm
- 類似SUSAR但範圍更廣

Thank you for your attention

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