Learning points from Research Audit in Iran: an investigator`s point of view

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History and origin of current guidelines for clinical trials

1938
- **(USA)FOOD&DRUG COSMETIC ACT: SAFETY**

1947
- **Nuremberg Code : emphasized on the voluntary consent**

1962
- **(USA)FOOD&DRUG COSMETIC ACT: EFFICACY**

1964
- **Declaration of Helsinki(18th World Medical Assembly): ethical principles of medical reseach (6 revisions to 2008)**
- **Not legally binding**

Thalidomide Tragedy 1950/60s

1996
- **International Conference on Harmonisation on Good Clinical Practice (ICH GCP) : to develop standards to facilitate the mutual acceptance of clinical data by regulatory authorities in USA,EU,Japan**
  - **Gold standard of clinical research for safety of subjects and credibility of data**

Roles and responsibilities of involved parties in Clinical Trials

- ETHICs:
  - Independent Ethics Committee (IEC) or Institutional Review Board(IRB): to ensure an independent ,objective review of a CT on protection of the right, health and safety of participants
- INVESTIGATOR:
  - Qualified and well trained and educated team
  - With Ethical, Scientific and Administrative responsibility
  - Should be aware and comply with GCP
- SPONSOR:
  - An individual, company, institution, or organization which takes responsibility for initiation investigator selection, study design, submission of protocols and Documents to EC , management, compensations ,and /or financing of CT (ICH-GCP 1.53)
  - Sponsor can transfer some or all of responsibilities to a Contract Research Organization(CRO)
  - Quality always remains the ultimate responsibility of sponsor
- Regulatory Authority:
  - CT should be submitted to RA prior to start for review, acceptance and/or permission which is dated with clear protocol identification

TRIAL	SPONSOR	CRO	IEC/IRB	National Regulatory Authority (NRA)
SIPPET	*Fondazione Angelo Bianchi Bonomi, Milan - Italy*	SINTESI RESEARCH	• SBMU • National EC	Clinical Trial Committee (CTC) of FDO
3WINTER-IPS	*Fondazione Angelo Bianchi Bonomi, Milan - Italy*	SINTESI RESEARCH	• PCHD-RC • SBMU • National EC	Clinical Trial Committee (CTC) of FDO
SMART-7	*NOVO NORDISK A/S DENMARK*	-	• PCHD-RC • SBMU • National EC	Clinical Trial Committee (CTC) of FDO
کار ازمایی بالینی اسورال	*IPHOS/ OSVEH ph.company*	-	• SBMU • National EC	Clinical Trial Committee (CTC) of FDO
کار ازمایی بالینی سه سویه کور مقایسه ای دسفوناک و دسفرال	*MCTSD / RONAK ph. company*	-	• PCHD-RC • SBMU • National EC	Clinical Trial Committee (CTC) of FDO
کار آزمایی بالینی نوترکیب هفت فعال	*IPHOS/ ARYOGEN ph. company*	-	• PCHD-RC • SBMU • National EC	Clinical Trial Committee (CTC) of FDO
کار ازمایی بالینی نوترکیب هشت	*SAMEN DAROU ph.company*	-	• PCHD-RC • SBMU	Clinical Trial Committee (CTC) of FDO

DEFINITION

- Monitoring: نظارت مستمر
- Audit: بازبینی
- Inspection: بازرسی

Benfits and outcome:

- Safety of trial subjects
- Credibility of data
- Assess resourcing(manpower,equipment,time,etc)
- Improve systems: study procedures/records design/methodology
- Notification of serious and persistent Non-compliance to terminate the investigator`s participation and notification of regulatory authorities

Audit vs. Monitoring:

(ICH-GCP 5.18;5.19)

AUDIT

- Retrospective(like a photograph) during or after the trial
- Expert and qualified individuals, who are independent of the clinical trials/systems
- Quality Assurance (QA) : To be performed and data generated and reported according to GCP
- Written procedure should define what to ,how to, and when to audit
- Site visits may be just one BIG visit
- Appointment is rule (it is not unexpected visit!)
- To be provided when required by local law

MONITORING

- Prospective controls of trial by representative of sponsor during trial (like a camera recording)
- Not independent procedure
- Multiple visit
- Quality Control(QC): techniques to verify that the requirements for quality have been performed or not

Audit:
common areas of audit findings

- Protocol adherence:
  - Enrolment : *inclusion/exclusion criteria*
  - Deviation of trial procedures and methods: *dosage;visit times,etc*
  - Delegation of tasks
  - Dates: approval-ICF-blood sampling-treatment with trial product-data collections
  - Amendments vs administrative changes
  - Monitoring frequency

Audit:
common areas of audit findings

- Informed consent forms:
  - The most important Doc. Of trial!!
  - Cultural respect; illiterate subjects; site personel on behalf of subject
  - Corrections, whiteouts ;date overwritten; different pen by one person; etc..
  - Investigator`s unfamiliarity of the concept of signed ICF prior to participation in trial: Date of signature must be before any trial activity
- Ethic committee constitution &approval:
  - Validity of membership : *investigator should not be /sign as an EC member/chairman*
  - Clear instructions on submission requirement: version of protocol ,brochures, CRFs and reporting AEs
  - Contract , financial and payment agreements before trial initiation

Audit:
common areas of audit findings

- Laboratory /equipment/trial supplies &DOC. :
  - Accreditation of lab
  - Normal ranges for lab values
  - Your equipment should:
    - Be certificated
    - Have SOP documents
  - Freezer for samples(-40) , refrigerators for drugs (+4), etc. : *thermometer alarm certificate*
  - Temperature log
  - Drug accountability and Security of storage area : *used/unused drugs ; locked rooms; Separation of trial drugs ; Appropriate destruction of returned stock;Stock sheet*

Audit:
common areas of audit findings

- Quality of source documents:
  - Trial Doc.(CRFs) and patient files and original patients` Doc. (CBC,biochemistry,CT,etc.) should be adjusted
  - Inadequate documentation: *reason for screen failure and withdrawals; dates of activities; AEs ; concomitant illnesses and medications*
  - Corrections should be explained ,signed and dated by investigator accordingly : *NO White-outs ; NO non-signed raw data in DOCs*

Audit:
common areas of audit findings

- SAE reporting: unclear about
  - definition of AE and SAE vs ADR
  - Forms to be completed
  - Timelines for reporting : delay should result a warning letter to sponsor /company by FDO
  - Local regulations and laws

- Monitoring files

- Indemnity and payment issues:
  - Investigator fee
  - Patient fee: Only for travel costs(home to hospital),Meals(long visits,etc.)
  - ANY PAYMENT FOR ENTERING STUDY IS PROHIBITED

Inspection
(ICH GCP1.29)

- By regulatory Health Authority (FDO in Iran)
- In Iran it is defined as FDO audit
- The act of official review of documents ,facilities, records, and any other resources related to CT that may be located:
  - At the investigator site
  - Sponsor`s and/or CRO`s facilities
  - Any other establishments deemed by FDO
- Can be routine OR for cause

Inspection
(ICH GCP1.29)

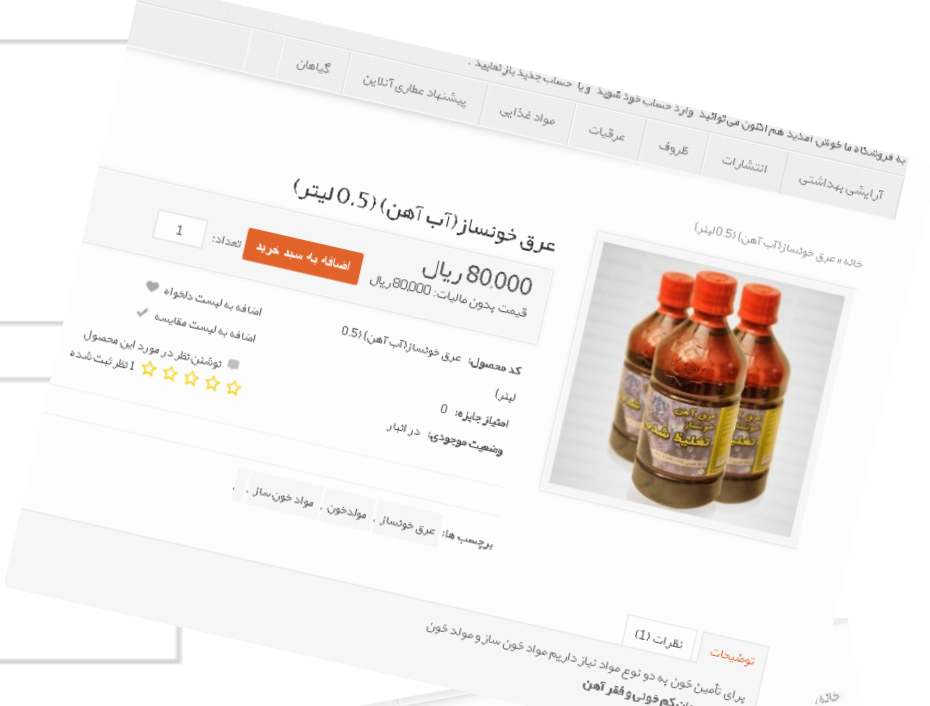
- Inspection type:
  - Surveillance /routine: periodically ; usually due to pending application for market approval
  - FOR-CAUSE: any suspicion on
    - High volume of bioresearch at site
    - Research out of field of site
    - Toxicity results abnormally low
    - Efficacy results too good
    - Very rapid enrollment
    - Too similar results to other sites
    - Sponsor complaint
    - Public importance

Inspection
(ICH GCP1.29)

- Inspection by international regular authorities (FDA/EMA/etc) on multicentric and international studies:
  - Protocol adherence :
    - inclusion /exclusion criteria; randomization; efficacy tests; unauthorized changes by sponsor; deviation
  - Maintain adequate records:
    - Destroyed or missing; non-signed or dated; on behalf signed without explanation; etc.
    - AE /SAE and key data reporting failure
  - Obtain proper ICF: verbal; short; after admission
  - Drug accountability/concomitant medication
  - Fraud (fabrication/alteration and omission of data)OR Carelessness(wrong observation,assumption or analysis)

Challenges in implementing GCP in IRAN

1. Non-familiarity of investigators with GCP:
   - Conduct of CT
   - Inadequate or inaccurate records
   - Failure to adhere to protocol
   - Drug accountability
   - ICF
   - Reporting AEs
2. Resistance to regulations by companies/ sponsors and investigators
3. No OR ineffective and formal Audits and Inspections
   - No active , expert and credited CRO (GCP trained) in IRAN
   - Non-adherence to regulations by government:
     - Shortages of medicines; sanctions; socioeconomic and political issues
     - Cultural and issues (TEB-E-SONNATI)



طب سنتی فعلی: هر گونه مداخله دارویی

و درمانی که اصولا نیازی به کار آزمایی بالینی

(آزمون پذیری علمی/تکرار پذیری نتایج) نداشته و مبتنی بر ادعای نقل

ها یا تجربیات گذشتگان و مصون