Practical Conduct of Clinical Trials

Overview

- Regulation of clinical trials
- SA as a clinical trial destination
- The clinical trial process
- Phases of clinical development
- Different study designs

VXPHARMA

Clinical trials are research studies that test how well new medical approaches work in people.

Each study answers scientific questions and tries to find better ways to prevent, screen for, diagnose, or treat a disease.

Clinical trials may also compare a new treatment to a treatment that is already available

VXPHARMA

Regulation

Declaration of Helsinki

- 1964 - first significant effort of the medical community to regulate research
- The **Declaration of Helsinki** is a set of ethical principles regarding human experimentation developed for the medical community by the World Medical Association (WMA). It is widely regarded as the cornerstone document on human research ethics.

ICH GCP

- The **International Conference on Harmonization, Good Clinical Practice (GCP)** provides a unified standard to facilitate the acceptance of clinical data by regulatory authorities.


The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they have serious doubts about the morality of the ... that it is too ... syphilis in participants.

Doctors in ... they are now ... over other ... they can give ... while the study ... effects continue.

Dr. Merlin K. ... ant Secretary ... tion and Welf... and Scientific ... pressed shock ... the study. He ... making an ... gation.

The experi... Tuskegee Stu... 1932 with about 600 black men.

VXPHARMA

South Africa as a Clinical Trial Destination

SA GCP

- Based on ICH GCP
- More stringent and relevant to local realities
- Scope of Guidelines:
    - Investigator Competence
    - Privacy
    - Ethical review
    - Informed Consent
    - Safety Monitoring

South Africa as a Clinical Trial Destination

Regulated by:

- **MCC**
  - Clinical Trials Committee (CTC)
  - Approval document serves as import permit for Investigational Product (IP)
  - 6 Monthly progress reports required
  - Focus on study design
- **Ethics Committee**
  - Local e.g. Wits
  - Central e.g. Pharma Ethics
  - Continuous safety reporting throughout the study
  - Focus on patient safety
- **DOH** – Export permit for biological samples
- All trials listed on SANCTR (http://www.sanctr.gov.za/)

VXPHARMA

South Africa as a Clinical Trial Destination

- Mature clinical research destination
- Large multinational CROs are strongly represented in South Africa
- Low cost, English-speaking destination with advanced infrastructure
- Research studies well -regulated through Medicines Control Council of South Africa (MCC)
- High standard of private healthcare practice and practitioners
- Public healthcare system has a high number of treatment-naïve patients for chronic lifestyle disorders
- Diverse demographics

VXPHARMA

Clinical Trial Process - Glossary

Sponsor – Pharmaceutical Company/ Funder

Clinical Research Organization (CRO)

- Contracted by sponsor
- International or local
- Provides study management team

Monitor/ Clinical Research Associate (CRA)

- Appointed by CRO to engage with clinical trial sites
- Provide training to the site
- Monitor quality of data generated by the site

Investigator

- Oversee clinical trial site and adherence to protocol and GCP

Clinical Trial Process - Feasibility

- Sponsor/CRO will approach sites locally or internationally depending on patient population and patient numbers required.
- Site assessed for specific requirements:
  - Access to required patient population
  - GCP Trained Staff
    - Principal and sub-investigators (Specialty required?)
    - Study Coordinators (Nurses, counsellors, phlebotomists, lung function technician)
    - Data Capturers
    - Lab Technicians
    - Pharmacist or lisenced dispenser
    - Registered with professional bodies
    - Malpractice insurance available

VXPHARMA

Clinical Trial Process - Feasibility

- Calibrated Equipment e.g.
  - BP machines, ECG
  - Fridges, Freezers (-20˚C and -80˚C)
  - Refrigerated Centrifuges
  - Spirometers
  - Thermometers (Room Temperature, fridges and freezers)
  - Synchronized clocks throughout facility
  - Ice Machine
- Secure Storage Space
- Access Control
- Standard Operating Procedures and Quality Control

VXPHARMA

Clinical Trial Process – Start Up

- MCC Application (3 months)
- Ethics Application (1 month)
- Contract and Budget Negotiation
- Financial Disclosure
- Develop Site Recruitment Action Plan (SRAP)
  - Database
  - Referrals
  - Advertising

VXPHARMA

Clinical Trial Process - Initiation

- Training provided to staff
  - Investigator Meeting
  - Onsite Initiation Visit by CRA
- Site setup
  - Electronic Data Capture (eDC)
  - IWRS/IVRS system for randomization and unblinding
  - Source documents drafted for capture of information
- Investigational Product received (Blinded or Unblinded)
- Lab kits received (Local or central Lab)
- SRAP Initiated

Clinical Trial Process - Recruitment

- Patient Identification
  1. Informed consent process
  2. Screening visit
  3. Randomization onto treatment arm if all inclusion /exclusion criteria met
  4. Follow up visits according to protocol design
- Patient Withdrawal
- Lost to Follow Up

VXPHARMA

Clinical Trial Process - Conduct

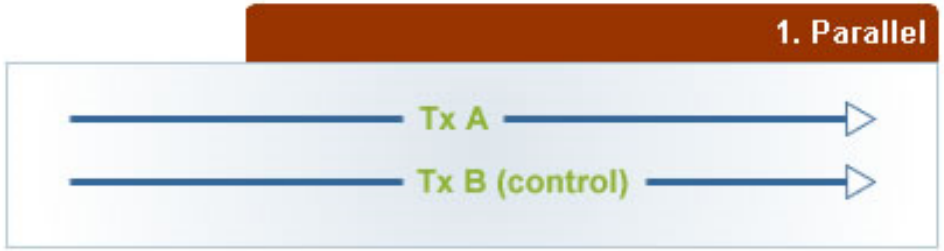
- Complete source notes:
  - All medical notes and tests
  - IP use and compliance
  - Document all concomitant use of medication
  - Monitor primary and secondary endpoints e.g. infection, Cardiovascular event etc
  - Document all adverse events
  - Immediately report all SAEs
- Transfer all data in source notes to eDC system
- Monitor/CRA comes to site to verify source data against eDC system
- Data from all sites entered into eDC used to complete statistical analysis an clinical trial reports used for clinical application to register a medicine

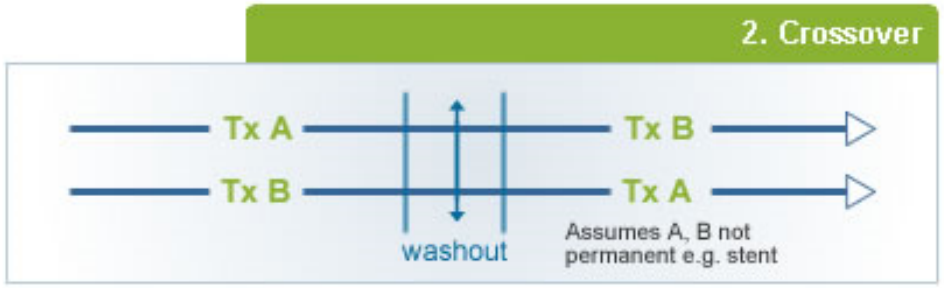
Clinical Trial Methodology

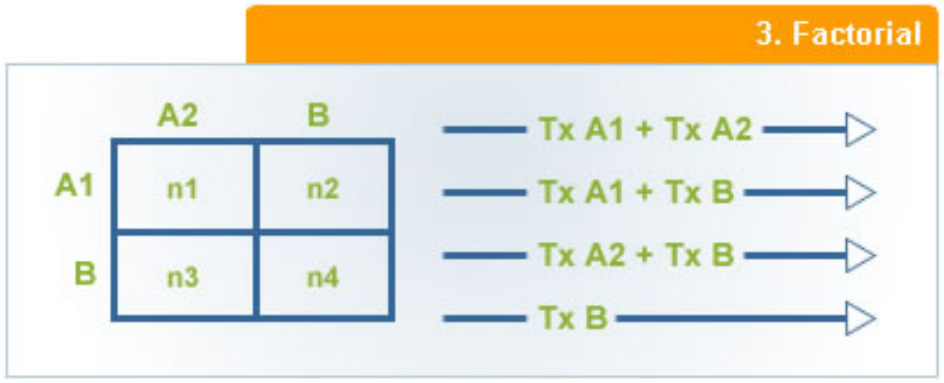
- Innovator Phase of clinical development:
  - Phase I
    - First in human – Human Pharmacology (Identify dose, safety and tolerability)
    - First in patient
  - Phase II – Therapeutic Exploratory (Dosing requirements and efficacy)
  - Phase III – Therapeutic Confirmatory
  - Phase IV – Therapeutic Use (Long term risk benefit)
- Bio- Equivalence
  - Pilot – small, validate analytical methodology, assess variability, optimize sample collection intervals.
  - Pivotal – Full scale

Different Study Designs

- Study design
  - **Parallel**
  - **Cross-Over**
  - **Factorial**
- Dose escalation
  - Different cohorts,
  - Safety review







VXPHARMA

Different Study Designs

Special considerations per study design

- **Parallel**
  - Multiple treatment groups
  - Long term studies
  - Acute illness
- **Cross-Over**
  - Smaller patient group for same statistical relevance
  - Not for drugs with a long half life - carry over effect to next treatment
  - Patient act as own control
  - Only chronic diseases
- **Factorial**
  - High variable drugs
  - Determine interactions

Different Study Designs

Methods to minimise bias

- Randomization
  - Random allocation of treatment
- Blinding
  - **Double-blind**
  - Single-blind
  - Open-label
  - Double dummy

Clinical Trial Methodology

Consideration for individual clinical trials

- Conduct
  - Standardization of study conditions: Food, times
  - Sampling Methods: Blood / Serum / Urine
- Objective
- Design
- Selection of subjects
- Selection of control group
- Number of subjects
- Analysis
- Reporting

Conclusion

Clinical trials are essential to test potential treatments in human volunteers to see whether they should be approved for wider use in the general population.

We need to ensure:

- Patient safety
- Oversight of Investigators
- Regulatory and Ethics compliance
- GCP compliance
- Accurate data management and statistics

SA Clinical Research Association	http://www.sacraza.com/
Educating the public	http://www.medicallegends.co.za/

VXPHARMA