

CLINICAL TRIALS

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What is clinical trials?

Clinical trials are a form of medical research, which follow a defined protocol that has been developed carefully to answer a specific patient care questions.

Clinical trials may investigate the effectiveness of new drug treatments, new combinations of drugs, surgical procedures, or behavioral and lifestyle modifications.

Clinical trials

OUTLINES

- Developing clinical trial protocols
- Institutional review board/ independent ethics committee formulation and working procedure
- Informed consent process and procedure
- HIPAA-new (Health Insurance Portability and Accountability Act)
- Requirement to clinical study process
- Pharmacovigilance safety monitoring in clinical trials

Rationale for Clinical Trials

Need....

- “If you don’t want to practice medicine 10 years from now the same way we do it today then clinical research must be a priority.” *(MH Jan 2013)*

Approach....

- Animal studies are of limited value in determining the full spectrum of toxicities and predicting effectiveness of treatments in humans

Developing clinical trial protocols

- The protocol is a document that turns a research question into a study which allows you to answer that question.
- Clinical trial protocol is a complete written description and scientific rationale for a research activity involving human subjects.
- Protocol writing contains the objectives, design and methodology.
- It is important that a protocol is thorough enough to fully instruct the research team in
 - ✓ how to run the study
 - ✓ to ensure that the outcome of the trial is the 'right' answer (i.e. is reliable)
 - ✓ that the outcome has been obtained ethically and safely.

Purpose of a Clinical Trial Protocols

- Describe the objectives, design, methods, data analysis, and how to perform the specific trial.
- Provide the background/reason for conducting a study, research questions, and ethical concerns.
- Trial protocols must meet GCP/Ethical standards so they are used for review.
- A ton of stakeholders benefit from the protocol even after the end of the trial.

As per the ICH-GCP guidelines, a clinical trial protocol must include the following parts

- Title page (general information)
- Signature page
- Content page
- List of abbreviations
- Background information
- Rationale of the study
- Aim/objective/purpose
- Study design
- Exclusion and inclusion criteria
- Treatment of subjects
- Assessment of efficacy
- Assessment of safety
- Adverse events
- Discontinuation of study
- Statistics
- Quality control and assurance
- Ethics
- Data handling and record keeping
- Publication policy
- Flow chart/project time table
- References
- Supplements

Title page (general information)

- This page introduce the document, its title, precise number, sponsor and author to the reader.
- Also contain the protocol no. and date with if any amendment no.
- Descriptive title identifying the study design, population, interventions.

Title page should contains:

- ✓ Full title should include summary of study design, nature of treatment of medicinal product, in-patient or out-patient, randomized double blind trial
- ✓ Name, title, telephone number and address of the sponsor, sponsored medical experts, qualified physician, clinical laboratory or any involved institutions along with the list of responsibilities

- **Signature page** of all healthcare professionals involves in the trial including contact details of participating sites
- **Content page** help navigation through the documents.
- **List of abbreviation** must be included.
- **Background information** should be not more than 3-5 pages. Information about the study intervention, summary of the non-clinical data and clinical data, and a review of the literature to all part of this section.

This section (background information) should include:

- A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance.
- A summary of relevant clinical research and any history of human use or exposure to the study intervention, including use in other countries, and clinical pharmacology studies.
- Discussion of important literature and data that are relevant to the trial and that provide background for the trials.
- Applicable clinical, epidemiological, or public health background or context of the clinical trial.
- Importance of the clinical trial and any relevant treatment issues or controversies.

- **Study rationale** state the problem or question (e.g., describe the population, disease, current standard of care, if one exists, and limitations of knowledge or available therapy) and the reason for conducting the clinical trial
- The study **objectives/ aims** should be broken down into primary and secondary objectives.
- Objectives need to be specific to the intervention. For a drug, they should specify the dosage level, route, frequency and duration of administration and in a defined population.
- The primary objective is to determine (or evaluate) the... (efficacy, pharmacokinetics, safety, etc.)... of the study intervention...
- The primary objective serves as the basis of the sample size.
- Secondary objectives may be exploratory or hypothesis generating and the study may not be powered to achieve these objectives.
- Each objective has a corresponding endpoint and a corresponding analysis plan.

- **Exclusion and inclusion criteria** are the conditions that must be met in order to participate in a clinical trial. It includes age, sex, type, stage of disease , other medical conditions, treatment history.
- Eligibility criteria should kept minimum and clearly defined which is verified by external auditor.
- It should be straight forward and unambiguous. Pregnant and nursing woman are not eligible.

- **Study design** part should contain a stepwise description of all protocol of this study with sufficient information for the participating site. It includes
 - ✓ Initial evaluations
 - ✓ Screening tests
 - ✓ Required lab tests
 - ✓ Detailed treatment procedure
 - ✓ Device specification
 - ✓ Dose schedule and any modification
- **Adverse effect and side effect** are defined as the undesirable effects of any medication on a patient.
- The **safety or adverse event** part includes
 - ✓ Detailed adverse event report to the sponsor and FDA
 - ✓ Unblinding process
 - ✓ List of expected adverse event

Statistics

- Sample Size section should explain the why the study is proposing to enroll the specified number of subjects and not more or fewer.
- When a power calculation is performed the protocol should include the following:
 1. the primary endpoint (outcome)
 2. the values assumed for the outcome in each study group (eg, proportion with event, or mean and standard deviation)
 3. the planned statistical test
 4. alpha (type 1 error) level
 5. power (usually at least 80%)
 6. the calculated sample size per group - both assuming no loss of data and, if relevant, after any inflation for anticipated missing data modified from

- **Human subject protection**

This section includes discussion of:

- ✓ Subject selection and exclusion
 - ✓ Proposed methods of patient requirement
 - ✓ Minority representation
 - ✓ Recruitment of special subjects
 - ✓ Lists of risks and benefits including justification for risks
- **Data Collection and Management:** Care in data management is a requirement to assure valid study results.
 - **Regulatory and Ethical Considerations:** Identify the areas of risk to human subjects and how the study will minimize those risks.

Informed consent

- Disclosure of relevant information to prospective research subjects.
- Comprehension of the information provided to the subject.
- Voluntary agreement of the subject.

The protocol's informed consent must

- ✓ Be thorough and complete
- ✓ Be written in simple, non technical language
- ✓ Be carefully worded to avoid complexity

The protocol's informed consent must provide

- ✓ Statement that the study involves research
- ✓ Purpose and length of the research study
- ✓ Risk and benefits
- ✓ Confidentiality policy
- ✓ Compensation for injury
- ✓ Contact for further information
- ✓ Statement of voluntary participation

Publication policy: Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

- Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research.
- Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports.
- All parties should adhere to accepted guidelines for ethical reporting.
- Negative and inconclusive as well as positive results must be published or otherwise made publicly available.
- Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication.
- Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

- **Proofreading of protocol:** The document should be checked by spell checker, grammarly software and be proofread for better writing.
- **Appendices:** Based on the protocol, relevant appendices must be attached.
- **Reference:** This protocol include a list of relevant literature and citation for all publications referenced in the text.

HIPAA-new (Health Insurance Portability and Accountability Act)

- HIPAA is United States legislation that provides [data privacy](#) and security provisions for safeguarding medical information.
- The law has emerged into greater prominence in recent years with the many health [data breaches](#) caused by cyber attacks and [ransomware](#) attacks on health insurers and providers.

Purpose:

- HIPAA, also known as Public Law 104-191, has two main purposes:
 - to provide continuous health insurance coverage for workers who lose or change their job and to ultimately reduce the cost of healthcare by standardizing the electronic transmission of administrative and financial transactions.
 - Other goals include combating abuse, fraud and waste in health insurance and healthcare delivery, and improving access to long-term care services and health insurance.

This act consists of 5 titles

- **Title I:** Protects health insurance coverage for workers and their families that change or lose their jobs. It limits new health plans the ability to deny coverage due to a pre-existing condition.
- **Title II:** Prevents Health Care Fraud and Abuse; Medical Liability Reform; Administrative Simplification that requires the establishment of national standards for electronic health care transactions and national identifiers for providers, employers, and health insurance plans.
- **Title III:** Guidelines for pre-tax medical spending accounts. It provides changes to health insurance law and deductions for medical insurance.
- **Title IV:** Guidelines for group health plans. It provides modifications for health coverage.
- **Title V:** Governs company-owned life insurance policies. Makes provisions for treating people without United States Citizenship and repealed financial institution rule to interest allocation rules.

Questions To Consider

- Why was the Health Insurance Portability and Accountability Act (HIPAA) established?
 - The focus of the statute is to create confidentiality systems within and beyond healthcare facilities.
 - The goal of keeping protected health information private.
- Whom does HIPAA cover?
 - All persons working in a healthcare facility or private office
 - Students
 - Non-patient care employees
 - Health plans (e.g., insurance companies)
 - Billing companies
 - Electronic medical record companies
- What are basic HIPAA goals?
 - To limit the use of protected health information to those with a “need to know.”
 - To penalize those who do not comply with confidentiality regulations.
- What health information is protected?
 - Any health care information with an identifier that links a specific patient to healthcare information (name, social security number, telephone number, email address, street address, among others)

- Differentiate between HIPAA privacy rules, use and disclosure of information?
 - Use: How information is used within a healthcare facility
 - Disclosure: How information is shared outside a health care facility
 - Privacy rules: Patients must give signed consent for the use of their personal information or disclosure
- What are the legal exceptions when health care professionals can breach confidentiality without permission?
 - Gunshot wound
 - Stab wound
 - Injuries sustained in a crime
 - Child/Elderly abuse
 - Infectious, communicable, or reportable diseases
- What types of data does HIPAA protect?
 - Written, paper, spoken, or electronic data
 - Transmission of data within and outside a health care facility
 - Applies to anyone or any institution involved with the use of healthcare-related data
 - Data size does not matter
- What types of electronic devices must facility security systems protect?
 - Both hardware and software
 - Unauthorized access to health care data or devices such as a user attempting to change passwords at defined intervals

- What is the job of a HIPAA security officer?
 - IT background
 - Document and maintain security policies and procedures
 - Audit the systems
 - Risk assessments and compliance with policies/procedures
- What does a security risk assessment entail?
 - Should be undertaken at all healthcare facilities
 - Assess the risk of virus infection and hackers
 - Create safeguards against risks
- What are physical safeguards?
 - Secure printers, fax machines, and computers
 - Locks on computer and record rooms
 - Destroy sensitive information
- What type of employee training for HIPAA is necessary?
 - Ideally under the supervision of the security officer
 - Level of access increases with responsibility
 - Annual HIPAA training with updates mandatory for all employees
- What type of reminder policies should be in place?
 - E-mail alert, posters
 - Log-on, log-off computer notices

- How should a sanctions policy for HIPAA violations be written?
 - Clear, non-ambiguous plain English policy
 - Apply equally to all employees and contractors
 - Sale of information results in termination
 - Repeat offense increases the punishment
- What discussions regarding patient information may be conducted in public locations?
 - None
 - Conversational information is covered by confidentiality/HIPAA
 - Do not talk about patients or protected health information in public locations
- How do you protect electronic information?
 - Point computer screens away from public
 - Use privacy sliding doors at the reception desk
 - Never leave protected health information unattended
 - Log off workstations when leaving an area
- How do you ensure password protection?
 - Do not share the password
 - Do not write down the password
 - Do not verbalize password
 - Do not email your password
- How do you select a safe password?
 - Do not select consecutive digits
 - Do not select information that can be easily guessed
 - Choose something that can be remembered but not guessed

HHS (Health and Human Services) initiated 5 rules to enforce Administrative Simplification:

- Privacy Rule
- Transactions and Code Sets Rule
- Security Rule
- Unique Identifiers Rule
- Enforcement Rule

What is the function of HIPAA?

- In passing the law for HIPAA, Congress required the establishment of Federal standards to guarantee electronic protected health information security to ensure confidentiality, integrity, and availability of health information that ensure the protection of individual's health information while also granting access for health care providers, clearinghouses, and health plans for continued medical care.
 - ✓ Standards for security were needed because of the growth in exchange of protected health information between covered entities and non-covered entities. These standards guarantee availability, integrity, and confidentiality of e-PHI. Also, there are State laws with strict guidelines that apply and overrules Federal security guidelines.
 - ✓ The standards mandated in the Federal Security Rule protect individual's health information while permitting appropriate access to that information by health care providers, clearinghouses, and health insurance plans. The Security Rule establishes Federal standards to ensure the availability, confidentiality, and integrity of electronic protected health information. Also, state laws also provide more stringent standards that apply over and above Federal security standards.
 - ✓ Health care providers, health plans, and business associates have a strong tradition of safeguarding private health information. However, in today's world, the old system of paper records locked in cabinets is not enough anymore. With information broadly held and transmitted electronically, the rule provides clear national standards for the protection of electronic health information.

Clinical Significance:

- HIPAA Privacy and Security Rules have substantially changed the way medical institutions and health providers function. The complex legalities and severe civil and financial penalties, as well as the increase in paperwork and implementation costs, have substantially impacted health care. All health professional must be trained in HIPAA and have an understanding of the potential pitfalls and acts that can lead to a violation.

Clinical Care Effects

- HIPAA, combined with stiff penalties for violation, may result in medical centers and practices withholding life-saving information from those who may have a right to it and need it at a crucial moment. Through the HIPAA Privacy Rule, the US Government Accountability Office found that health care providers were "uncertain about their legal privacy responsibilities and often responded with an overly guarded approach to disclosing information. Ultimately, the solution is the education of all healthcare professionals and their support staff so that they have a full appreciation of when protected health information can be legally released.

Education and Training Effects

- Education and training of healthcare providers and students are needed to implement HIPAA Privacy and Security Acts. Effective training and education must describe the regulatory background and purpose of HIPAA and provide a review of the principles and key provisions of the Privacy Rule.

Research Effects

- HIPAA restrictions on research have affected the ability to perform chart-based retrospective research. This has made it challenging to evaluate patients prospectively for follow-up.
- HIPAA Privacy rules have resulted in as much as a 95% drop in follow-up surveys completed by patients being followed long-term.
- Recruitment of patients for cancer studies has led to more than 70% decrease in patient accrual and a tripling of time spent recruiting patients and mean recruitment costs.
- Significant legal language required for research studies is now extensive due to the need to protect participant's health information. While such information is important, a lengthy legalistic section may make these complex documents less user-friendly for those who are asked to read and sign them.
- Many researchers believe that the HIPAA privacy laws have a negative impact on the cost and quality of medical research.

Costs

- HIPAA Privacy and Security Acts require all medical centers and medical practices to get into and stay in compliance. The costs of developing and revamping systems and practices and an increase in paperwork and staff education time have impacted the finances of medical centers and practices at a time when insurance companies and Medicare reimbursements have decreased. Ultimately, the cost of violating the statutes is so substantial, that scarce resources must be devoted to making sure an institution is compliant, and its employees understand the statutory rules.

Conclusions

- HIPAA is a potential minefield of violations that almost any medical professional can commit. Staff with less education and understanding can easily violate these rules during the normal course of work. While a small percentage of criminal violations involve personal gain or nosy behavior, most violations are momentary lapses that result in costly mistakes. Writing an incorrect address, phone number, email, or text on a form or expressing protected information aloud can jeopardize a practice. HIPAA education and training is crucial, as well as designing and maintaining systems that minimize human mistakes.