WHAT is Clinical Research

- Drug Development Overview
- Regulations/GXPs
- Protocol Compliance
- Study Management
- Clinical Trial Monitoring

WHO are the CROs

- CRO Oversight
- Management of 3rd Party Vendors

WHERE does Audit fit in

Q&A
YOUR BACKGROUND
WHO/WHAT IS Clinical?
Clinical Research

- The study of potential new treatments in humans. Two main types:
  - Interventional studies; Observational studies
  - In US: http://clinicaltrials.gov/

Focus on Sponsor Interventional Studies

- An intervention: drug, medical device, food, behavior modality
- A good understanding of drug development and clinical research will assist in discussion on oversight and audit’s role

NOT focusing on:

- Investigator Initiated Research
- Non-Interventional studies; epidemiological Studies; Outcomes research studies
- Compassionate Use programs; expanded access
- Marketing studies
- Patient Support Programs
- Collaborative Research; Co-promotes/Co-development
- Clinical research in animals
- Accelerated approvals; orphan drug law
- Preclinical
- Also, not focusing on financial or healthcare compliance e.g. FCPA or Sunshine Act
Drug Development Overview

PRECLINICAL

Laboratory Animals

CLINICAL

Clinical Trials in Humans

KEY CONSIDERATIONS

TREATMENT: evidence based EFFICACY – and – SAFETY

COUNTRY STRATEGY: each country has a regulatory body that governs approvals
Drug discovery is a complex, lengthy, costly process

1) **Indication** → Disease Selection
2) Pharmaceutical Target Identification & validation
3) Further ID Lead Molecule (compound, not a drug per se)
4) Optimize Lead Molecule
5) **PRE-Clinical (non-clinical)** Trials (Investigational Product-IP) → InVitro (test tube/cells) / InVivo (animal) → **IND**
6) Clinical Trials → Phase I-IV; first in human (FIH) through to increasing levels of complexity e.g. dosing regimes
7) NDA (new drug application) Submission → Approval → **MARKET/Commercialization** → Distribution of Product;
   1) Country Strategy for where to submit first, and in what indication, drives subsequent decisions
8) **Post-Marketing Studies** → **different** indications, different countries/submissions, different patient populations (pediatrics, elderly), different formulations, additional safety requirements, expand labeling, etc

**Preclinical or NonClinical - DISCOVERY**

1. Identify the Disease, **Indication**
2. Identify & validate the Pharmaceutical Product
3. Identify Lead Molecules
4. Optimize Lead Molecules
5. Pre-Clinical (laboratory & animal) **Candidate (CAN)**
6. Clinical Studies

**Clinical**

6. Clinical Trials
7. NDA Application
8. Approval & Circulation

Changes occur throughout any stage in drug development lifecycle, positively and/or negatively impacting development.
Drug Development Overview

**PHASE I**
- First In Humans (FIH)
- Healthy Volunteers *exceptions e.g. Onc/HIV*
- Test SAFETY, tolerability, doses
- Study Duration: days
- Size: 10-100

**PHASE II**
- Proof of Concept (POC), method
- Subjects with specific illness, otherwise healthy; exploratory or pilot
- Test SAFETY, EFFECTIVENESS, dose range (begin considerations market)
- Study Duration: weeks/months
- Size: 100-300

**PHASE III**
- PIVOTAL, COMPARATIVE Studies— to gold standard; often Randomized-pbo controlled; Blinded; Global; Multi-Ctr
- Expand usage; gather add’l information
- Test EFFICACY, SAFETY, benefit/risk,
- Filing & Market Access Strategies
- Study Duration: years
- Size: 1000-2000

**PHASE IV**
- POST Marketing/Approval STUDIES
- Post Marketing Commitments (PMCs), Post Authorization Safety Studies (PASS)
- Broader use of drug in public setting
- Additional data collected on long-term use; EXPAND LABEL
- Study Duration: years
- Size: 1000s (10,000)
Drug Development Overview

Time, Cost, Quality, Marketability

High Risk Undertaking

- **COST**: average/new drug is ~ $802 million (post approval 900m)\(^1\); 1.2 BN\(^2\); 5BN \(^3\)
  - Cost increased 7.4% ANNUALLY over inflation for past 20 years\(^1\); cause multifactorial
  - Increased protocol complexity (local, nat’l, internat’l)
  - Increased regulations / excessive risk averse interpretations of regulations
  - Increased time and pressures on clinicians/investigators
  - USE OF CRPS

- **TIME**: takes ~ 12 years from discovery to market approval

- **SUCCESS**: out of 4000 compounds synthesized, in 1 in 5 tested in humans, reaches the market

- **RETURN**: 1 in 3 drugs reaching the market recaptures development costs

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3. Kramer, Judith M, Schulman, Kevin; 2012; Transforming the Economics of Clinical Trials’. *Institute of Medicine of the National Academies*
4. Herper, Matthew; 2013; The Cost of Creating a New Drug Now $5 Billion, Pushing Big Pharma To Change; *Forbes*
Clinical Research Overview

Key Concepts/Terms

**KEY CONCEPTS**

- **CLINICAL RESEARCH** –
  - a study (controlled clinical investigation) done in humans to investigate a potential new treatment e.g. drug, device
  - The primary groups involved in clinical research are: sponsors, investigators, internal review boards (IRBS) or Ethics Committees (ECs), human subjects and regulatory authorities.
- **SPONSOR**
  - ‘a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual (as defined in 21 C.F.R. 50.3),
- **INVESTIGATOR**
  - the individual who is responsible and accountable for conducting the clinical trial.
  - Lead Investigator is called the Principle Investigator (PI). The PI assumes full responsibility for the treatment/evaluation of human subjects, and for the integrity of the research data and results
- **IRB/EC**
  - A multidisciplinary body composed of a broad spectrum of personnel e.g. MDs, RNs, social workers, clergy, community reps, etc, which addresses the moral and ethical issues of a study
- **Human Subjects**
  - Volunteers, Subjects, Participants, Patients
  - Human Research Participant Protection (HRPP)
KEY CONCEPTS

INVESTIGATIONAL PRODUCT [IP] vs commercial - the compound/drug being studied
- The INTERVENTION, the treatment, experimental treatment.
- Blinded / Unblinded (double-blinded), open/closed label, randomization, treatment groups, comparators including placebo

EFFICACY – how well the treatment works in the clinical trial
- Effectiveness: how well treatment (compound, drug, medication, device) works in practice
- Evidence based: scientific/clinical; BENEFIT:RISK Ratio

SAFETY ↔ Pharmacovigilance
- Evidence that a treatment is safe (BENEFIT:RISK Ratio), adverse events

ENDPOINTS
- an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial, i.e. related to occurrence of a targeted outcome e.g. disease, symptom, lab abnormality.

IND
- Investigational New Drug – filed once you think you have a compound/drug that would be safe and beneficial to test in humans; a request for authorization from the FDA to administer an investigational drug or biological product to humans

NDA
- New Drug Application (MAA/Marketing Authorization) – filed with a regulatory authority once you have evidence that a drug is both safety and beneficial for humans
  - Submission/Filing - Labeling

Regulatory Authorities (Health authorities, Regulators)

Marketing/Launch
A highly regulated area
Increasing Globalization
Constantly evolving
Very Complex
**GXP** - collective term for GCP, GLP, GMP, GPvP

**Framework of Good Clinical Practice**

Many types of regulations apply to the clinical development process. For example:

- GCP (Good Clinical Practice)
- GLP (Good Laboratory Practice)
- GMP (Good Manufacturing Practice)
- GPvP (Good *Pharmacovigilance* Practice)

The essence of each of these has the same intent: to promote good practices, assure data validity, protect the rights and welfare of patients and research subjects, and foster good regulatory decision making.

**Including Quality**

- Quality by Design (QbD)
- Quality Control (QC)
- Quality Assurance (QA)

Good read:

[http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm)
In the US, the FDAs regulations for the conduct of clinical trials, which have been in effect since the 1970s, address both GCP and HSP and are CODIFIED in the ***CODE OF FEDERAL REGULATIONS***

**Define Good Clinical Practice**

According to the International Conference on Harmonization (ICH) – GCP (1.24) Definition, Good Clinical Practice is:

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected.

**Purpose of GCP**

The purpose of GCP is to:

- Protect the rights, safety, and welfare of the research subjects, and
- Ensure the integrity of the clinical data

Compliance with ICH-GCP provides public assurance that the rights, well being, and confidentiality of trial subjects are protected, and that trial data are credible.

**Where Does GCP Apply?**

To all research:

- All sponsors: private, government, university, industry
- All study designs: double blind, open-label, comparator
- All study phases: Phases I to IV
- All investigational products: new drugs, new indications, biomedical device, new methodology, new surgical techniques
1753

- First CONTROLLED Clinical Trial (CT)?
  - *LINDS STUDY* for the *INDICATION* of...
  - Two *TREATMENT* Groups...
  - What was the *OUTCOME* or *RESULTS*...

1948

- First documented randomized controlled CT?
  - *STUDY* for the *INDICATION* of...
  - Two *TREATMENT* Groups...
  - What was the *OUTCOME* or *RESULTS*...

- SCURVY
  - Sea Water (2) vs Limes/Oranges (2)
  - Patients on limes/oranges were cured

- Pulmonary TB
  - RANDOMIZED Streptomycin vs bedrest
  - Streptomycin was effective
Clinical Research

history - ethical conduct

- 1946 - International Standards Organization (ISO) [26000 social responsibility; 9000 quality mgmt]
- 1947 - The Nuremberg Code
  - Prior to this, no generally accepted code of conduct governing the ethical aspects of human research
- 1964 - The Declaration of Helsinki
  - Developed for the medical community by the World Medical Association (WMA); widely regarded as the cornerstone document on human research ethics
- 1979 - The Belmont Report
- 1989 - International Conference on Harmonization (ICH-GCP)
  - Joint regulatory initiative; started in EU

EU Legislation

1970s - CODE OF FEDERAL REGULATIONS (CFR)

Adopted Ethical Principles

- Increased participants (patients)
  - Rights, Well-being, Respect ...privacy
- Minimized clinical research risk

Implemented ethical considerations
  - Protocol Design
  - Informed Consent
  - Voluntary Participation

- Expanded over time from ethical considerations to scientific, medical, regulatory and operations

- Leveraged by regulatory bodies e.g. CFR & IRBs/ECs.
The ‘codification’ of the general & permanent rules/regulations published in the US Federal Register by the executive departments/agencies of the US Federal Government

Supports the implementation of GCP

Divided into 50 titles that represent broad areas subject to federal regulation.

- 21 CFR 11: Electronic Records & Signatures
- 21 CFR 50: Protection of Human Subjects
  - 21 CFR 50.25(c): Informed Consent Elements
- 21 CFR 54: Financial Disclosure by Clinical Investigators
- 21 CFR 56: Institutional Review Boards (IRBs)
- 21 CFR Part 312: Investigational New Drug Application
- 21 CFR 812: Investigational Device Exemptions
- 21 CFR 814: Premarket Approval of Medical Devices

FDA GCP Regs & ICH Guidance: [http://www.fda.gov](http://www.fda.gov)
WHO/WHAT ARE CROs?
**Contract Research Organization (CRO)** means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the FDA.

ICH-GCP E6 1.20 on technical requirements for registration of pharmaceuticals for human use and use of CRO

**Types and Services vary**
- One off service
- Full Service Providers
- Strategic Partnerships
- CROs, Vendors, Contractors, Site Mgmt Organizations (SMOs), Academic Research Organizations (AROs)
More than 1000 CROs globally

- Models - may be large/global or small/niche focused
  - HISTORICAL MODEL -> transactional
    » Project-by-project and/or for a specific function
    - < cost, > flexibility to a degree, ? efficiencies
  - NEWER MODEL -> strategic
    » More integrated in the end-to-end process
    - > oversight/governance, > mutual investment, > alignment & efficiencies

- Largest CROs according to Industry Standard Research,[1] are Quintiles, PAREXEL, Covance, Pharmaceutical Product Development (PPD), ICON, INC Research, InVentive

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TOP 7 CROs

- publically traded CROs ranked by their amount of market capitalization—their number of shares outstanding multiplied by the share price (Oct2013)

1. WUXI PHARMATECH
   - 2013 Market Cap: $8.838 billion (12/31/12: 561,121,002 shares * share price $15.75)

2. QUINTILES
   - 2013 Market Cap: $5.018 billion (7/25: 128,922,047 shares * $38.92 per share)

3. COVANCE
   - 2013 Market Cap: $4.462 billion (8/16: 56,217,133 shares * share price $47.73)

4. PAREXEL
   - 2013 Market Cap: $2.683 billion (8/16: 56,217,133 shares * share price $47.73)

5. CHARLES RIVER
   - 2013 Market Cap: $2.190 billion (7/22: 49,060,865 shares * share price $44.63)

6. ICON
   - 2013 Market Cap: $2.102 billion (6/11: 60,822,488 shares * share price $34.56)

7. PANTHEON

1 http://www.genengnews.com/insight-and-intelligence/top-7-cros/77899911/
CROs in Clinical Research

Discovery | Ph 1 | Phase 2 | Phase 3 | Registration & Approval | Launch & Phase 4

Study Start Up (SSU) | Study Conduct | Study Completion (or interim analysis) | Submission (or publication)

CROs may be used during any of the above phases

CROs may be used for any of the clinical trial steps long the study lifecycle
Clinical and CRO OVERSIGHT
Oversight/audit is considered with each phase and every step in the study lifecycle.

EVERY PHASE OF RESEARCH HAS THE FOLLOWING STEPS:

- **Study Start Up (SSU)**
- **Study Conduct**
- **Study Completion (or interim analysis)**
- **Submission (or publication)**

Every phase and every step in the study lifecycle.
What is the study objective?

- PROTOCOL DESIGN & COMPLIANCE
- SUBMISSION / REGULATORY STRATEGY
- COUNTRY STRATEGY
- INVESTIGATOR SELECTION
- STUDY MANAGEMENT
- DATA MANAGEMENT
- MONITORING

STUDY PLANNING for all phases/stages starts at the beginning with a well designed protocol and understanding of goal. Must include cross-discipline of experts.
Oversight – Clinical Research

Study Start Up
- Protocol Design
- Statistical Analysis Plan
- CRF/Database Design
- Programming
- Country + Investigator FEASIBILITY / Selection
- Financial Disclosure
- Regulatory
- Clinical Supplies
- IT Systems (CTMS)
- Document Management (ICD, translations, TMF)
- TRAINING (GCP, Protocol, Safety, SOPs)

Study Conduct
- Protocol Adherence
- Protocol Deviations
- Protocol Amendments
- Subject Recruitment
- Data Entry (DMC / Benefit-Risk analysis)
- Clinical Supply – dosing
- SOP Adherence
- Investigator Oversight
- Document Mgmt
- MONITORING
- Safety – AE reporting
- Interim Analysis
- CRO Support, monitoring
- QA, QC, Audit

Study Completion
- Protocol DATA Review
- Data, Data, Data
- Site Oversight & Closeout
- Data Reconciliation
- Safety Review
- MONITORING
- Clinical Supply retrieval /destruction
- QA, QC, Audit

Submission
- Benefit / Risk analysis
- Endpoint evaluations
- Data reviews
- More extensive document/data reviews
- Clinical Study reports
- Regulatory requirements – US, local country

Aligned with GXP (local & national) Regulations & company standards: Inspection Ready
21 CFR Part 312 Investigational New Drug Application

.50 ‘General responsibilities of the Sponsor’

.52 ‘Transfer of Obligations to a CRO’

- Transfer of responsibilities must be described in writing; ...must describe each of the responsibilities being assumed by the CRO

Sec. 312.52 Transfer of obligations to a contract research organization.

(a) A sponsor may transfer responsibility for any or all of the obligations set forth in this part to a contract research organization. Any such transfer shall be described in writing. If not all obligations are transferred, the writing is required to describe each of the obligations being assumed by the contract research organization. If all obligations are transferred, a general statement that all obligations have been transferred is acceptable. Any obligation not covered by the written description shall be deemed not to have been transferred.

(b) A contract research organization that assumes any obligation of a sponsor shall comply with the specific regulations in this chapter applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations. Thus, all references to "sponsor" in this part apply to a contract research organization to the extent that it assumes one or more obligations of the sponsor.
WHERE DOES AUDIT FIT IN
Oversight - Audit

1st Line Quality

Functional Unit Audit

Additional Oversight

Governance
Audit Types

- PROCESS AUDITS
- INVESTIGATOR SITE AUDITS
- COUNTRY ORGANIZATION AUDITS
- SUBMISSION DOCUMENT AUDITS
- VENDOR or CRO AUDITS
  - 3rd parties
  - Collaborative partners / Co-development/promote

Risk based and/or cyclical

In coordination with other stakeholders
EVERY PHASE OF RESEARCH HAS THE FOLLOWING STEPS

**Discovery**
- **Study Start Up (SSU)**
  - ✔ Protocol Design
    - ✔ Protocol Adherence
  - ✔ Statistical Analysis Plan
  - ✔ CRF/Database Design
  - ✔ Programming
  - ✔ Country + Investigator FEASIBILITY / Selection
  - ✔ Financial Disclosure
  - ✔ Regulatory
  - ✔ Clinical Supplies
  - ✔ IT Systems (CTMS)
  - ✔ Document Management (ICD, translations, TMF)
  - ✔ TRAINING (GCP, Protocol, Safety, SOPs)

**Phase 1**
- **Study Conduct**
  - ✔ Protocol Adherence
    - ✔ Protocol Deviations
    - ✔ Protocol Amendments
    - ✔ Subject Recruitment
    - ✔ Data Entry (DMC / Benefit-Risk analysis)
    - ✔ Clinical Supply – dosing
    - ✔ SOP Adherence
    - ✔ Investigator Oversight
    - ✔ Document Mgmt
    - ✔ MONITORING
    - ✔ Safety – AE Reporting
    - ✔ Interim Analysis
    - ✔ CRO Support, monitoring
    - ✔ QA, QC, Audit

**Phase 2**
- **Study Completion (or interim analysis)**
  - ✔ Protocol Adherence
    - ✔ Protocol Deviations
    - ✔ Protocol Amendments
    - ✔ Subject Recruitment
    - ✔ Data Entry (DMC / Benefit-Risk analysis)
    - ✔ Clinical Supply – dosing
    - ✔ SOP Adherence
    - ✔ Investigator Oversight
    - ✔ Document Mgmt
    - ✔ MONITORING
    - ✔ Safety – AE Reporting
    - ✔ Interim Analysis
    - ✔ CRO Support, monitoring
    - ✔ QA, QC, Audit

**Phase 3**
- **Study Completion (or interim analysis)**
  - ✔ Protocol Adherence
    - ✔ Protocol Deviations
    - ✔ Protocol Amendments
    - ✔ Subject Recruitment
    - ✔ Data Entry (DMC / Benefit-Risk analysis)
    - ✔ Clinical Supply – dosing
    - ✔ SOP Adherence
    - ✔ Investigator Oversight
    - ✔ Document Mgmt
    - ✔ MONITORING
    - ✔ Safety – AE Reporting
    - ✔ Interim Analysis
    - ✔ CRO Support, monitoring
    - ✔ QA, QC, Audit

**Registration & Approval**
- **Submission (or publication)**
  - ✔ Benefit / Risk analysis
  - ✔ Endpoint evaluations
  - ✔ Data reviews
  - ✔ More extensive document/data reviews
  - ✔ Clinical Study reports
  - ✔ Regulatory requirements – US, local country

**Launch & Phase 4**

AUDIT EVALUATES RISK/CONTROLS ALONG THE R&D CONTINUUM
During every study phase, each study lifecycle step
For each audit type e.g. process audit, vendor audit, document review
Audit against

- Regulations
  - US and Rest of World (ROW)
- Company Standards e.g. Corporate Policies, Standard Operating Procedures (SOPs)
- Clinical Trial Process Quality Standards
  - Metrics
- Universal Standards
- CROs
  - Contractual Obligations
  - Their SOPs/Policies; Bridging documents
AUDIT will be responsible for conducting audits of CROs and/or subcontractors who may be supporting work on behalf of the sponsor.

21 CFR Part 312; Subpart D
- .50 General responsibilities of Sponsors
- .52 Transfer of Obligations to a CRO
OVERSIGHT - AUDIT

❖ REMEDIATION & CAPA
  ➢ CAPA: Corrective and Preventative Actions
  ➢ Track through to completion
  ➢ Robust process

❖ INSPECTION READINESS

❖ SUBMISSION READINESS
Conclusion

- Better Understanding
- Drug Development
- Clinical Research
- Regulatory/GXPs/GCPs
- Clinical/CRO Oversight
- Compliance/Auditing