Development and Approval of Drugs and Devices EPI260

Lecture 6: Late Phase Clinical Trials
April 28, 2011
UCSF

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Outline

- Drug Development Process & Overview of Phase 3 Clinical Trials
- Good Clinical Practice
- Protocol Design & Investigators Brochure
- Case Report Forms (CRF) & Guidelines for completion of CRFs
- Ethics in Clinical Trials (EC & IC)
- Pharmacovigilance
- Study Execution:
  - Site initiation, monitoring and closeout
  - Data Management Analysis
  - Report writing
- Regulatory requirements for approval; NDA/BLA and pre-NDA meeting
- Post Marketing Commitments

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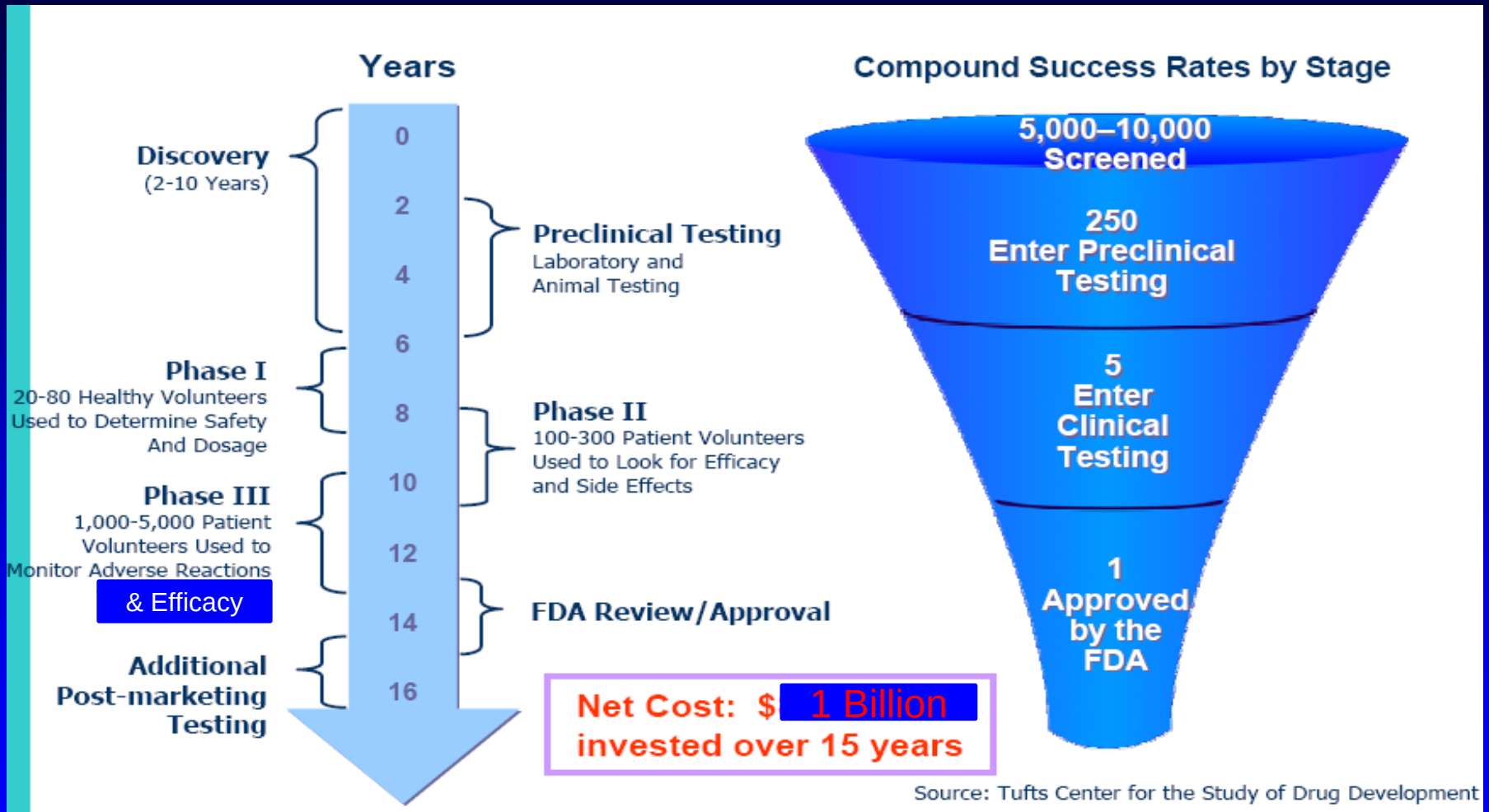
Drug Development Process



Costly, Risky, Time consuming

Summary of Phases I-III

	# Subs.	Length	Purpose	% Drugs Successfully Tested
Phase I	20 – 100	Several months	Mainly Safety	70%
Phase II	Up to several 100	Several months-2 yrs.	Mainly effectiveness; Short term safety	33%
Phase III	100s – several 1000	1-4 yrs.	Efficacy, safety & dosage	25-30%

Late Phase Clinical Trials

- Large multinational trials – typical for Phase 3
- Key steps
  - Design
  - Execution
  - Analysis

AD P3 TRIAL DESIGN

Cognitive Status	Mild AD
MMSE range	18-26
Number of subjects per arm	500-700
Primary outcome measure	ADAS-Cog; CDR-SB
Biomarker outcome	Amyloid β, Tau, MRI
Duration of treatment	18 months
Primary analysis	Change in score/slope of primary outcomes

Late Phase Clinical Trials - Issues

- Issues
  - Logistics
  - Amateur workforce
  - Lack of standardization
- Pitfalls
  - Patient safety jeopardized
  - Poor quality data produced
  - Patient rights violated
  - Laws broken
  - Budget and timelines exceeded

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What is most important in human clinical trials?

- Human Subject protection
- Protect human subjects during a clinical trial
- Protect patients who may take product in the future, once approved

Good Clinical Practice (GCP)

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

Good Clinical Practice

- Subject safety:
  - Study conduct issues related to safety
  - Identification of adverse events
  - Reporting of adverse events
- Study design:
  - Scientifically sound hypothesis
  - Plan for analyzing safety and efficacy data
- Study conduct
  - Oversight and management of the study
- Data Quality
  - Data integrity, data is verifiable

Principles of GCP

- Ethical conduct
- Risk-benefit assessment
- Subjects over science and society
- Adequacy of pre-existing information
- Scientific validity
- Review

Principles of GCP

- Medically qualified care
- Trained and experienced personnel
- Informed consent
- Efficiency of information handling
- Confidentiality
- Drug accountability
- Quality through systems & procedures

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Protocol Design

- Keep it short
- Keep it simple
- Minimize number of procedures
- Minimize data collection (unless you are an academician)
- Keep instructions clear
- Don’t ask for more precision than you need
- Work with a statistician

Key Drivers of Study Design

- Patient population
- Dose
- Endpoint

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Designing Case Report Forms (CRFs) and Guidelines for Completions of CRFs

Case Report Form - CRF

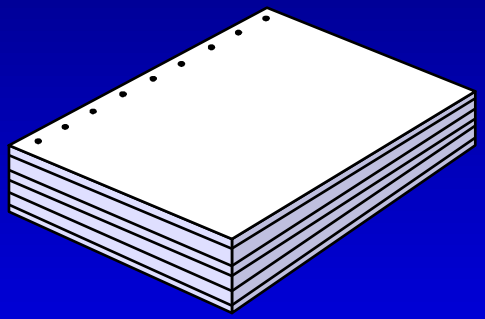
- CRF is the official instrument used in clinical trial to capture data for analysis

- **Modality**
  - Paper
    - Three Part Non-Carbon Forms (NCF)
    - Fax based, Optical Character Resolution
  - Electronic or Web Based
- **Objective – 3Cs**
  - **C**omplete, **C**orrect and **C**onsistent Data

Case Report Form

- CRF

  Official clinical data-recording document or tool used in a clinical study



PAPER

RDC/RDE
(Remote Data Capture,
Remote Data Entry)

CRF Development

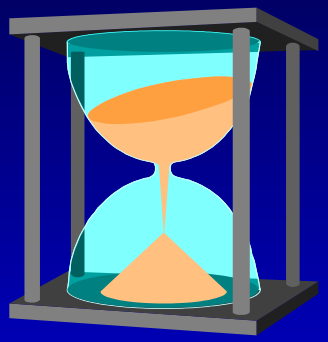
- **CRF and Protocol**
  - Protocol governs what data to be collected on CRF
  - Only collect data that will be analyzed
- **CRF and SAP (Statistical Analysis Plan)**
  - SAP defines how data will be collected on CRF
  - Define critical variables

CRF Development

- **CRF and Standards – Begin with end in mind**
  - CDISC (*Clinical Data Interchange Standards Consortium*)/CDASH (*Clinical Data Acquisition Standards Harmonization*)
  - Facilitates efficient data merging from different vendors for particular study
  - Ensures efficient ISS/ISE (Integrated Summaries of Safety/Efficacy) process across protocols/projects
  - Promotes clinical monitoring and investigator staff efficiency
  - Paves the way for inter-company data exchange

Properly Designed CRF

- Saves time
- Saves money



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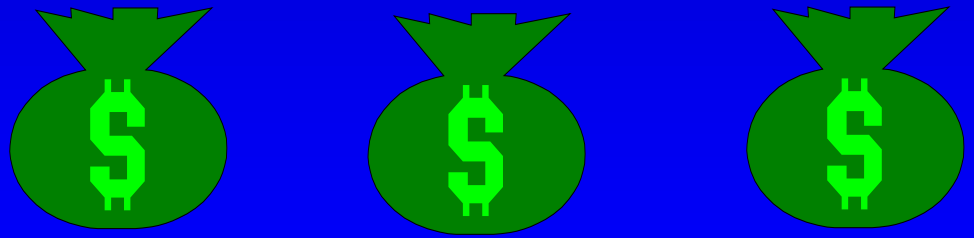


Poorly Designed CRF

- Data not collected
- Database may require modification
- Data Entry process impeded
- Need to edit data
- Target dates are missed
- Collected too much data – *Wasted resources in collection and processing*

Example of Poorly Designed CRF

- An example of poor CRF may contain fields for inputting white blood cell counts, where the field look like this:
  - Neutrophils.....Lymphocytes.....
- In contrast, a high quality CRF will include the unit and the field look like this:
  - Neutrophils (cell/ml blood).....Lymphocyte (cells/ml blood)

CRFs: How do we use it?

- Collect data from the investigational sites
- Helps project team and study site team
  - Reminder to investigator to perform specific evaluation
  - CRA uses to verify protocol is being followed and compare with source documents
  - Biometrics uses it to build database structures, develop edit checks and programming specs

CRFs: How do we use it?

- Data collected is the basis for making decisions about the drug, its benefits, risks, and potential marketability.
  - Subject tracking
  - Data analysis and reporting
  - Reports to FDA on subject safety
  - Promotional materials
  - New Drug Application submissions
  - Support of labeling claims
  - Articles in medical journals

CRF Components

- **Header: Key Identifying Information**
  - Protocol/study identifier
  - Site/investigator identifier
  - Subject identifier
  - Unique subject identifier (an amalgamation of multiple identifiers)

CRF Components

- **Safety Modules**
  - Demographic (DM)
  - Vital Signs (VS)
  - Medical History (MH)
  - Adverse Events (AE)
  - Concomitant Medications (CM)
  - Subject Disposition (DS)
  - Focus on safety analysis
  - Standards are strongly recommended

CRF Components

- **Efficacy Modules**
  - Therapeutic area focused “unique” modules
  - Focus on protocol efficacy end points
  - Develop therapeutic specific CRF library
  - Define diagnostics required – MRI, ECG, lab, etc.
  - Ensure baseline measurements collected appropriately
  - Repeat same battery of tests collected within SAP defined window

CRF Development Guidelines

- **CRF Development Guidelines** – *sophisticated enough to be simple*
  - Compliant with regulatory requirement
  - Collect data defined in the protocol and for analysis purpose only
  - CRF is NOT clinical monitoring tool
  - Avoid duplication to minimize reconciliation
  - Avoid free text response whenever possible
  - Avoid unsolicited comment at all cost

CRF Development Guidelines

- **CRF Development Guidelines** – *sophisticated enough to be simple*
  - Avoid collecting anything can be derived: age, BMI, CrCl, etc.
  - Take advantage of the instruments dynamic function
  - Provide units for numeric value to ensure consistent data
  - Use “None”, “Not Done” and “Not Applicable”

CRF Development Guidelines

- **CRF Development Guidelines** – *sophisticated enough to be simple*
  - Provide precise digits and appropriate decimal points for numeric values, i.e., Temperature XXX.x
  - Provide UAT (user acceptance test) for eCRF
  - Streamline CRF development with edit check process
  - Ensure all CRF are finalized and available before subject enrollment
  - Provide CRF completion guideline

Overview of CRF Development Process

- Drafts CRF from protocol

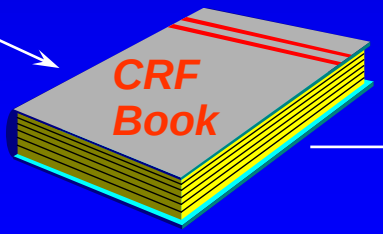
CRF Designer

- CRF Review Meeting
- Comments back to designer

Reviewers

CRF Designer

- Updates CRF to incl. comments
- Review and Sign off
- Coordinate printing and distribution



Site

CRF Development Process

- Review Team (example)
  - Project Clinician
  - Lead CRA
  - Lead Statistician
  - Lead Programmer
  - Lead Data Manager
  - Others
- Database Development, Dictionary Coding, Standards
- CRF review meeting: Collect comments based on draft CRF
- Establish CRF library for future studies

CRF Development Process

- **CRF Development Process**
  - CRF design process:
    - Draft CRF to capture data required by the protocol and used for analysis. Include all safety and efficacy endpoints using standards.
    - Hold CRF review meeting to collect comments from multi-disciplinary team.
    - Incorporate comments to finalize CRF
    - Final review and sign off CRF by the multi-disciplinary team

CRF Development Process

- Interdisciplinary Review is Necessary
  - Each organization has its own process for review/sign-off
  - Should include relevant members of the project team involved in conduct, analysis and reporting of the trial
- Begins
  - As soon in the study prep process as possible

CRF Completion Guideline

- CRF questions should be as self-explanatory as possible
- All instructions should be concise
- Instructions should be standardized along with the CRF as much as possible
- Include clear definition of visit window
- Include definition of subject disposition: screen failure, randomized, early discontinued and completed

CRF Completion Guideline

- Clarify treatment completion vs. study completion, if applicable
- Explain philosophy on AE collection: diagnosis vs. symptom
- Instruction on clear, unambiguous AE verbatim collection: “Chest Congestion”, not just “Congestion
- Date/time format: 00:00 vs. 24:00, etc.

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Ethics in Biomedical Research

Right of the human subject to understand:

- ✓ the nature of research,
- ✓ risks & benefits involved
- ✓ to agree or not agree to participate.

Ethics Committee

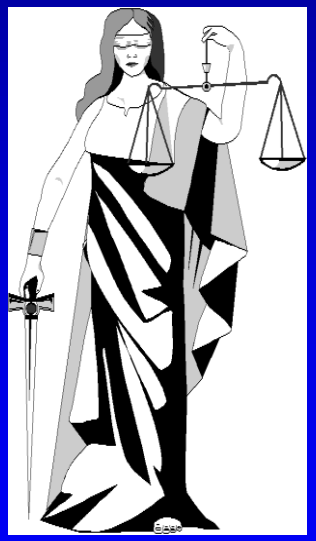
A board or a committee formally designated by an institution to

- ✓ review,
- ✓ approve the initiation
- ✓ conduct periodic review

of biomedical research involving humans

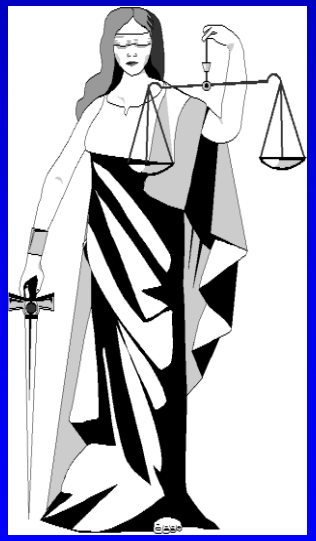
EC: Role in Clinical Research

- Before the study begins:
  - ✓ Submission of research proposal
  - ✓ Review of proposal
  - ✓ Decision making process
  - ✓ Issuing an approval
  - ✓ Record keeping



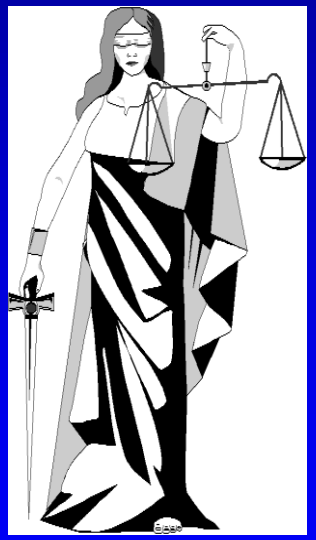
EC: Role in Clinical Research

- During the study:
  - ✓ Review of amendments (Protocol, ICD)
  - ✓ Review of Serious Adverse Events
  - ✓ Protocol deviations
  - ✓ Progress (study status)
  - ✓ Record keeping



EC: Role in Clinical Research

- After the study:
  - ✓ Study report,
  - ✓ Post trial management
  - ✓ Publishing
  - ✓ Record keeping



Informed Consent

CIOMS definition:

"Informed Consent is a decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subject to coercion, undue influence or inducement, or Intimidation"

5 Components of Informed Consent

INFORMATION component and **CONSENT** components

1) Competence: legal and mental
2) Disclosure: complete/partial
3) Understanding: comprehension of what is disclosed
4) Voluntariness: voluntary decision
5) Consent: an authorization to proceed

Barriers to Informed Consent Process

- Distrust in signing documents
- Gender based issues
- Inadequate time
- Pressure for early/fast recruitment

Who is responsible for the content of the Informed Consent Form?

Who is Responsible?

- The IRB is responsible to review and ensure:
  - Required elements are addressed
  - No exculpatory language is used
  - Language is understandable to all subjects

Common ICF Deficiencies

- Identification of person to contact regarding research, rights, & injury
- Incomplete description of alternative procedures
- Inadequate confidentiality statement
- Incomplete description of research procedures
- Incomplete description of compensation and treatment of research-related injury

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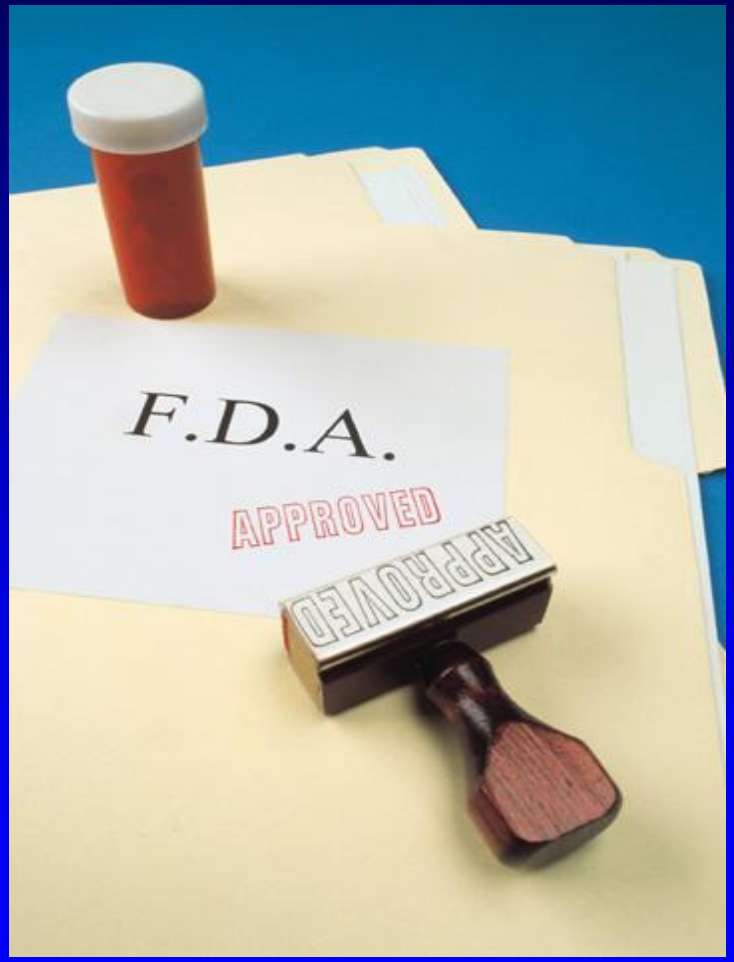
Pharmacovigilance

Pharmacovigilance is the science and activities relating to the Detection, Assessment, Understanding and Prevention of adverse drug reactions or any other possible drug related problems'

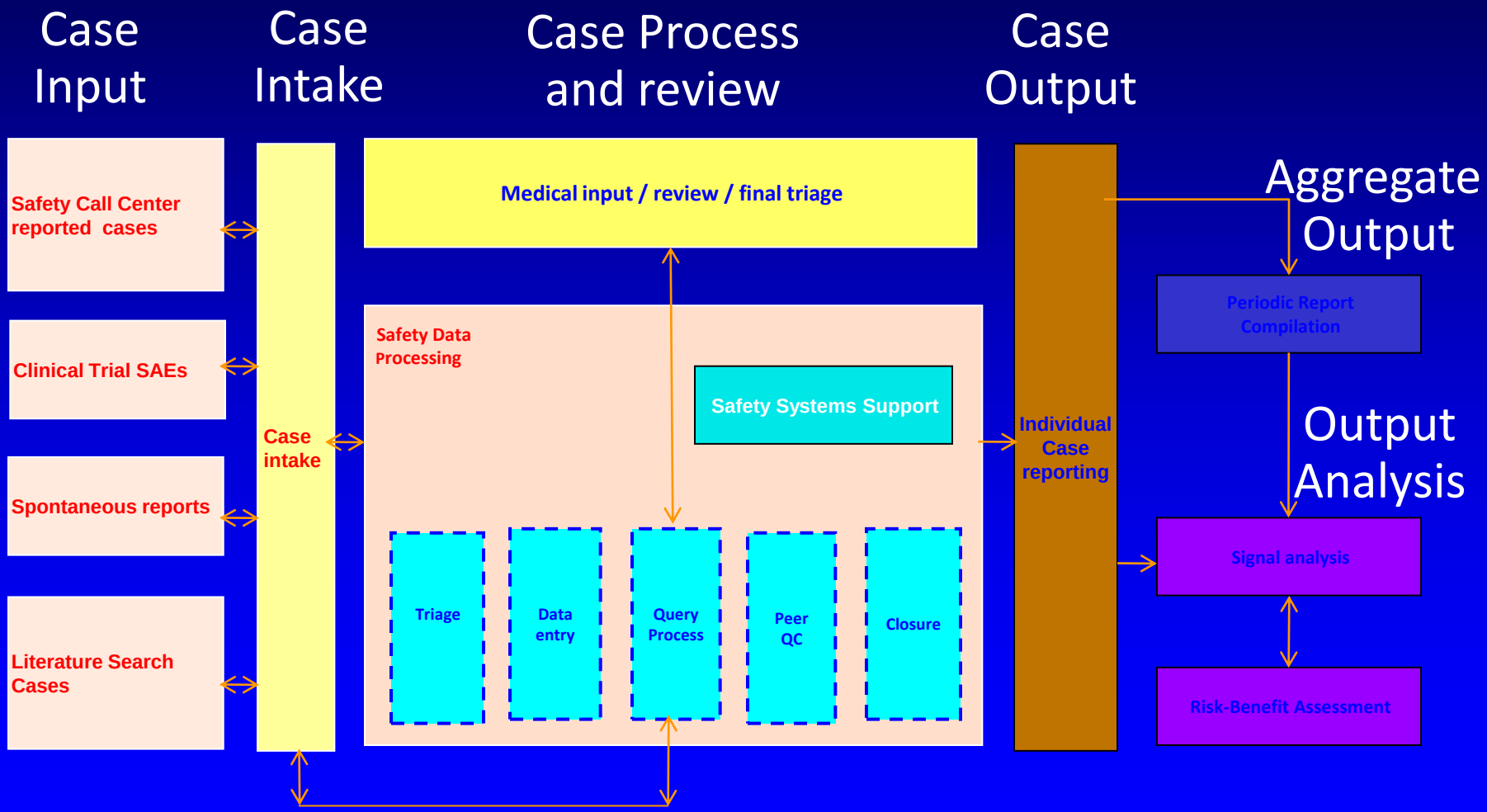
WHO 2002

FDA Office of Drug Safety



- Charged with responsibility for safety of FDA-approved drugs
- Limited (antagonistic?) relationship with drug approval units
- Very limited resources/budget

Summary of the Major Activities Associated with Pharmacovigilance



Sources of Reports

- Voluntary/spontaneous reporting
  - Health care professionals, consumers/ patients, or others
- Manufacturers: Required for postmarketing reporting (>90%)
  - All adverse drug experience information obtained or otherwise received from any source, foreign or domestic

Manufacturer Reporting Requirements

- Within 15 calendar days if Serious and Unexpected adverse drug experience (ADE)
- Periodic reports (quarterly and annual) for:
  - serious and expected ADEs
  - non-serious ADEs
- Manufacturer has duty to follow-up on all serious adverse effects with initial reporter and convey any additional information to FDA

Regulatory Definition of Serious

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Persistent or significant disability
- Congenital anomaly/birth defect
- Intervention required to prevent permanent impairment or damage

Unexpected Adverse Drug Experience

- Not listed in current labeling, or
- Listed in labeling but greater specificity or severity
  - e.g., renal impairment listed, patient experiences renal failure

FDA MedWatch Program

- Objective: User friendly system for communication of adverse effects reports from health care professionals and consumers to FDA
- Also provides for warnings from FDA to health professionals and consumers

http://www.fda.gov/medwatch

MedWatch Program

- Launched in 1993 by FDA Commissioner David Kessler
- Applies to:
  - Drugs [Rx and OTC]
  - Biologics
  - Medical devices
  - Dietary supplements and herbal products
- Intended to only cover “serious” adverse effects
- No causation finding necessary for reporting
- Over 85,000 voluntary reports received to date

Adverse Event Reporting System (AERS)

- FDA database that stores and compiles all adverse effect data for pharmaceuticals collected from manufacturers and through MedWatch
- Standardized formats and definitions employed to facilitate comparisons and aggregation of data
- 375,000 reports per year

AERS Data Follow-Up

- Objective of AERS is to identify a “signal” of potential problem
- Logical follow-up when potential problem identified is a pharmacoepidemiologic study
- Problems:
  - FDA cannot compel post-approval testing
  - Office of Drug Safety has very limited funding for its own studies
  - Epidemiology studies have many limitations (e.g., confounding, ability to detect only relatively large increases, etc)

Factors Affecting Reporting

- Nature of the adverse event
  - very common health conditions (e.g., heart attacks) may be "lost in the noise" and under-reported
- Type of drug product and indication
- Rx or OTC drug status
- Length of time on market
  - reporting most frequent in 2nd year on market
- Public or media attention
  - notoriety increases reporting
- Extent and quality of manufacturer's surveillance system

Limitations of Spontaneous Reports

- Passive surveillance
  - Underreporting (~10%) occurs and is variable from drug to drug and over time
- Quality of the reports is variable and often incomplete
- Industry bias against disclosing adverse data
- Cannot reliably estimate rates of events
  - Numerator uncertain
  - Denominator can only be projected
- Uncertainty about causation

Possible Responses to New Risk Information

- Labeling changes
  - Warnings, Contraindications, Boxes
- Education
- Dear Health Practitioner Letters
- Restricted Distribution
- Withdrawal
- Litigation
  - evidence of adverse effects
  - evidence of manufacturer knowledge of adverse effect

Safety Reporting

- Adverse event reporting
- Adverse event monitoring
- Pharmacovigilance systems
- Reconciling with clinical database
- Breaking the blind

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Sites initiation & monitoring

- Project management
- Multinational studies
- Key personnel
  - Medical director
  - Clinical operations
  - Statistician
  - Data manager
  - Programmer
  - Project leader
  - Project manager
  - Regulatory
  - Safety
  - CMC
  - Pharmacology
  - Pharmacoeconomics
  - Quality
  - Compliance
  - Contracts
  - Finance

Site Initiation & Monitoring

- Feasibility study
- Site identification
- Site qualification
- Site initiation
- Investigators meeting
- Monitoring visits
  - Drug storage
  - ICF
  - Adverse events
- Audits
- Site closeout visits
  - Drug accountability

Operations

- Budget
  - $10,000 - $200,000 per patient
  - Per patient costs increase with smaller study size, longer duration, more procedures, certain specialties, number of sites, number of countries
- Timeline
  - 12 months or more for Phase 1
  - 18 months or more for Phase 2 or 3
  - Key drivers for timeline: drug labeling, IRB approval, regulatory approval, contracts, enrollment, follow-up

Data Management and Analysis

- Case report form
- Statistical Analysis Plan
- Data Quality Plan
  - % target query resolution
- Maintaining the blind
  - DSMB
  - Adaptive design
  - Administrative looks
  - Safety unblinding
- Electronic Data Capture
- Double data entry
- Query generation and resolution

Data Management

- Validation
  - IT system and CFR Part 11
  - Program installation
  - Data listings and tables
    - Double programming
    - Dummy data
  - Sensitivity analysis
    - Imputations for missing data
- Data management costs are about 25% of trial costs

Report Writing

- Clinical Study Reports
- Integrated summary of efficacy and safety
- Tables, Listing, Graphs
- Trial Conduct Report

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Regulatory Requirements for Approval

- Requirements
  - Risk/Benefit
  - Accelerated approval
- Pre-NDA/BLA meeting
- MAA

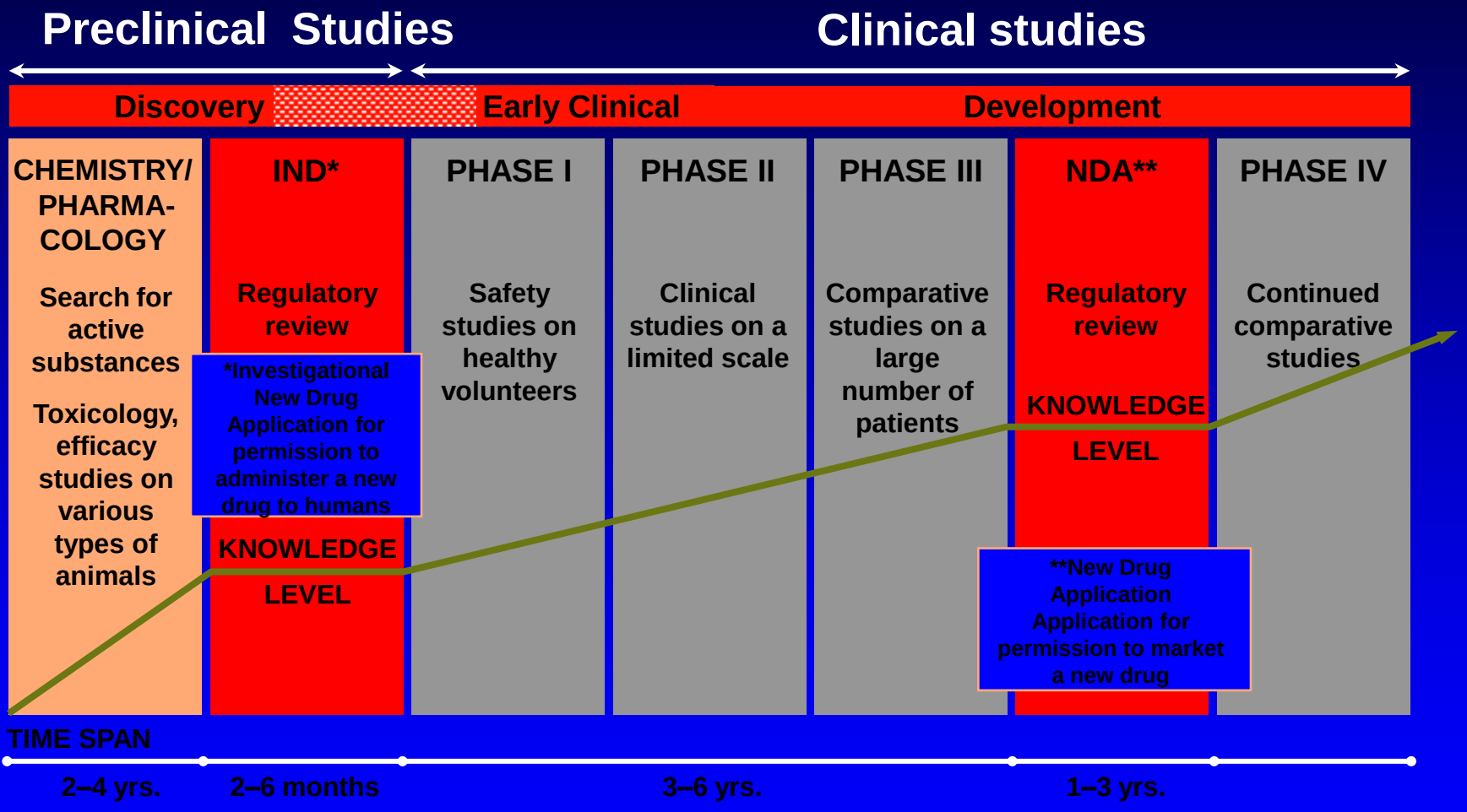
Regulatory Requirements for Approval

- Common Technical Document Format
  - Administrative and prescribing information
  - Overview and summary of modules 3 to 5
  - Quality (pharmaceutical documentation)
  - Safety (toxicology studies)
  - Efficacy (clinical studies)
- REMS
- Filing
  - Rolling submission
- Acceptance of filing

Regulatory Requirements for Approval

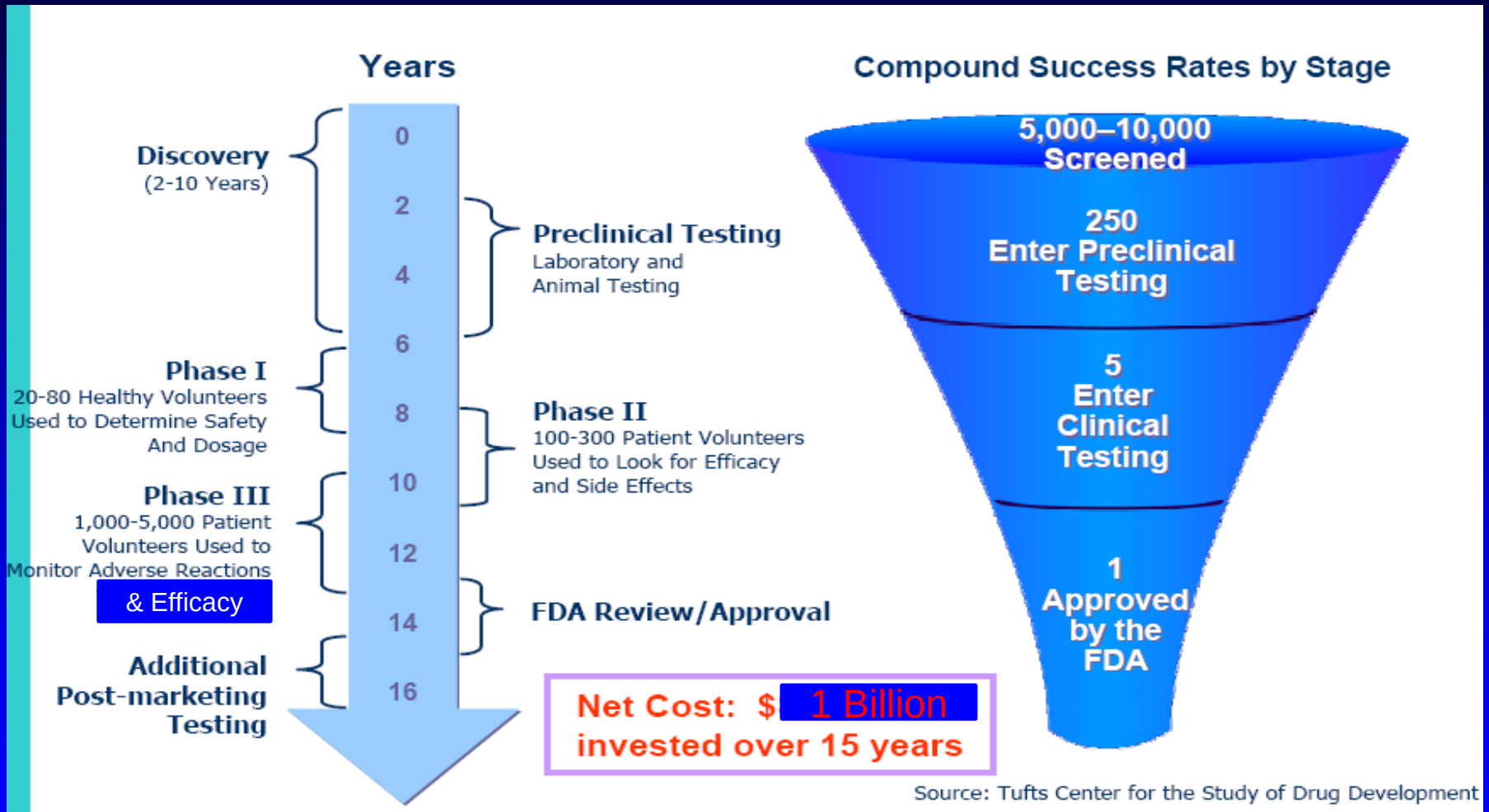
- PDUFA requirements
- Major amendment
- Advisory Committee Meeting
- Approval vs. Complete Response

The R&D Process



Approximately 10-15 years from idea to marketable drug

Drug Development Process



Costly, Risky, Time consuming

Thank you