CLIN. RESEARCH PRACTICES & DRUG REG. AFFAIRS, 6(3), 147-157 (1988)

THE CLINICAL DATA STORY

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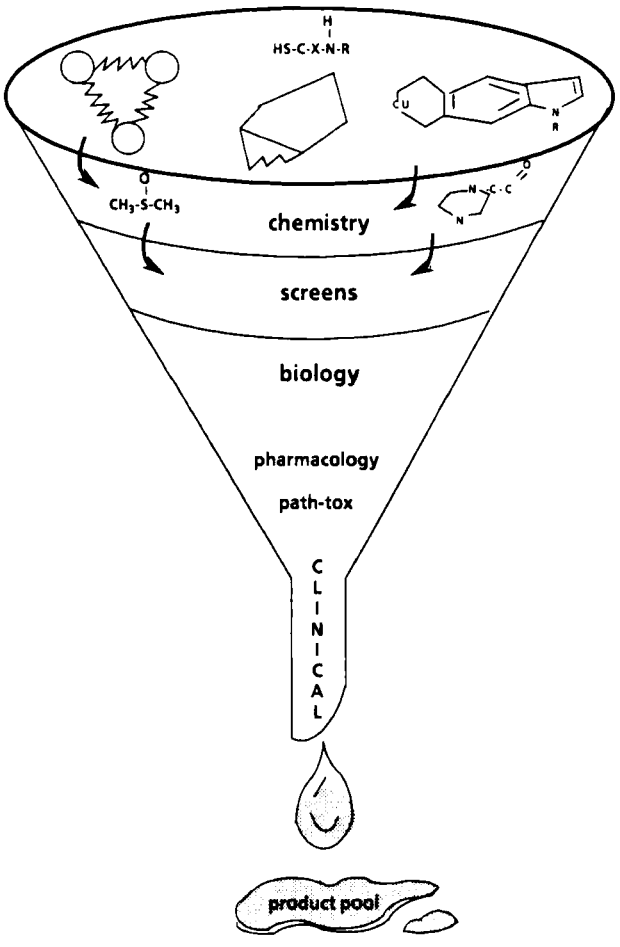
OVERVIEW

To assess the value of a drug in the treatment, prevention, or diagnosis of a disease is a complex process that takes an average of eleven years, at a cost of $90 million. The drug development process has four phases: Drug Discovery, Pre-Clinical Development, Clinical Development, and Regulatory Submission.



The Clinical Data Story looks at the process of developing a drug as a therapeutic article of commerce from the point in time it is launched into clinical investigations until it is submitted to the Food and Drug Administration.

INTRODUCTION

Before walking through "The Clinical Data Story", it is helpful to understand many of the processes that take place as they are defined by the Bureau of Biologics of the Food and Drug Administration.

THE INVESTIGATIONAL NEW DRUG APPLICATION (IND)

Prior to entering clinical investigation, an IND must be filed with the Food and Drug Administration.

The Investigational New Drug application (IND) includes:

- Data on in vivo (animal) and in vitro (test tube) studies that show safety and efficacy.
- Characterization of what a molecule looks like.
- Manufacturing and Control Procedures.
- Protocols explaining how a drug will be tested.
- Qualifications of the investigators that will conduct clinical trials.

Once filing of an IND takes place, the FDA has thirty days to review the application. If there are no problems identified, Phase I Clinical Trials can begin.

PHASE I - CLINICAL PHARMACOLOGY TRIALS

This is the initial introduction of a new therapeutic in man. Normal male volunteers are studied to determine levels of tolerance, as well as preliminary dose-ranges for safety. Between twenty and eighty healthy volunteers, generally male, are subjected to drug therapy.

PHASE II - CLINICAL TRIALS

Phase II studies are designed to demonstrate effectiveness and relative safety of a therapeutic agent in a diseased patient population. One hundred to two hundred patients under tightly controlled protocols are entered into therapy.

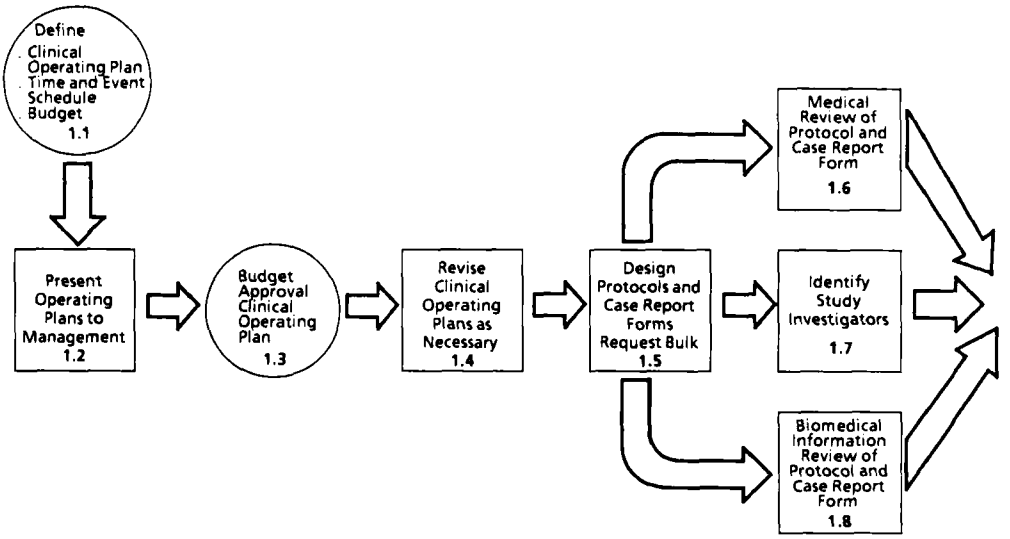


Figure 1
Planning of Clinical Program

PHASE III - CLINICAL TRIALS

Phase III clinical trials consist of studies with and without control groups that are planned to treat thousands of patients. Phase III studies are intended to gather evidence of tolerance, effectiveness, safety, and to identify a profile of adverse drug reactions.

THE NEW DRUG APPLICATION (NDA)

Once a company's clinical and regulatory bodies are confident that a new therapeutic agent is safe and effective, and data is available to support conclusions, an NDA is submitted for approval to market a product.

THE CLINICAL DATA STORY

I. THE CLINICAL PROGRAM

The Clinical Data Story follows a presentation combining a schematic of the clinical development cycle with annotations. Each annotation is preceded by a numeral that references back to a specific activity in the schematic.

In identifying the therapeutic benefit and market potential of a new drug, it is necessary to receive feedback from three sources: Marketing, Management, and Literature. Once input from these sources are melded together, an organization can set the direction for a clinical program.

1.1 Before a clinical program can start, a clinical operating plan must be prepared identifying the activities of development a drug will follow. It is also time to determine the clinical operating budget and time and events schedule.

1.2 Once identified the Clinical Operating Plan (COP), Time and Events Schedule (TES), and budget must be presented to management for approval.

1.3 After sufficient review, management agreement in the form of budget approval will hopefully be received.

1.4 As with any budget, as you proceed forward and receive feedback, revisions are likely to occur.

1.5 We are now ready to put the Clinical Operating Plan into action. Protocols and case report forms are designed for studies identified in the Clinical Operating Plan and requests for bulk materials are initiated so that Pharmacy can begin the process of preparing drug supplies.

While activities in 1.5 are scheduled, three other activities begin:

1.6 The Medical Division performs an extensive review of study protocols and case report forms.

1.7 The Medical Division identifies potential study investigators.

1.8 The Information Handling Division (Biomedical Information) reviews the protocol and case report form and comments on potential concerns.

II. CLINICAL PROGRAM INITIATION

Once the basic structure of an investigational clinical program is determined, clinical studies which are components of the program may start.

2.1 As remaining touches are made to protocol and case report form it is time to identify potential investigators and make appropriate contact for study placement.

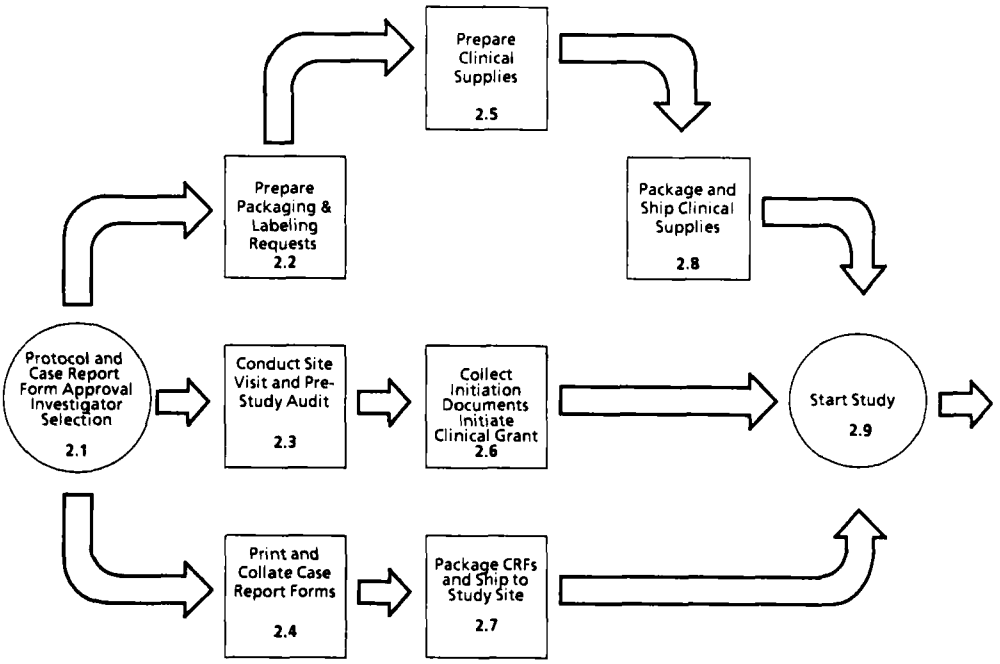


Figure 2
Clinical Program Initiation

As investigators are identified and committed to conduct a study, Steps 2.2 to 2.4 are performed concurrently.

2.2 The pharmacy will receive Packaging and Labeling Requests fron the Medical Department and review specific details so that preparation and distribution of medication will follow on schedule.

2.3 A Clinical Monitor or Clinical Research Associate will visit selected investigators and perform a pre-study site audit. At the same time there will be a review of specific study interaction documents that must be completed prior to study start. These documents are defined in 2.6.

2.4 A case report form that is elegant, professional, and easy to complete is important to smooth study flow. Professional off-set printing is normally utilized for this process.

We have now made final investigator selection and are ready to begin initiating clinical studies.

2.5 The pharmacy will prepare individual unit dosing packages to supply each patient entering the study with the correct amount of medication as specified in the study protocol.

2.6 In Step 2.3 reference to initiation documents that are completed by the study investigator was made. These documents are:

- Investigational Review Board (IRB) Approval
- Patient Informed Consent
- Signed Investigator's Statement
- Investigator's / Co-investigator's Curriculum Vitae
- Budget Estimate

2.7 Under separate package from study medication, case report forms are supplied to investigational sites.

2.8 As stated, shipment of clinical supplies is performed separate from case report form shipment. The reason for this is potential clearance delays with customs of foreign countries.

2.9 We have finally achieved a major milestone in clinical development; the study start.

III. CONDUCT CLINICAL PROGRAM AND BEGIN DATA PROCESSING SET-UP

The clinical program is initiated with the opening of study sites and, with a little luck, patient enrollment is progressing smoothly. In anticipation of receiving case report forms, data processing activities begin.

3.1 A system to expedite the entry of case report forms must be implemented, tested and ready for use when clinical study data is received.

3.2 Having identified in the study protocol study rules and regulations, a database must be designed that will assist the Clinical Monitor and Clinical Research Associate in monitoring progress of a clinical study.

3.3 In the medical writing group, a facsimile or "mock-up" clinical report for the study is produced and reviewed with the Clinical Study Monitor and Study Statistician.

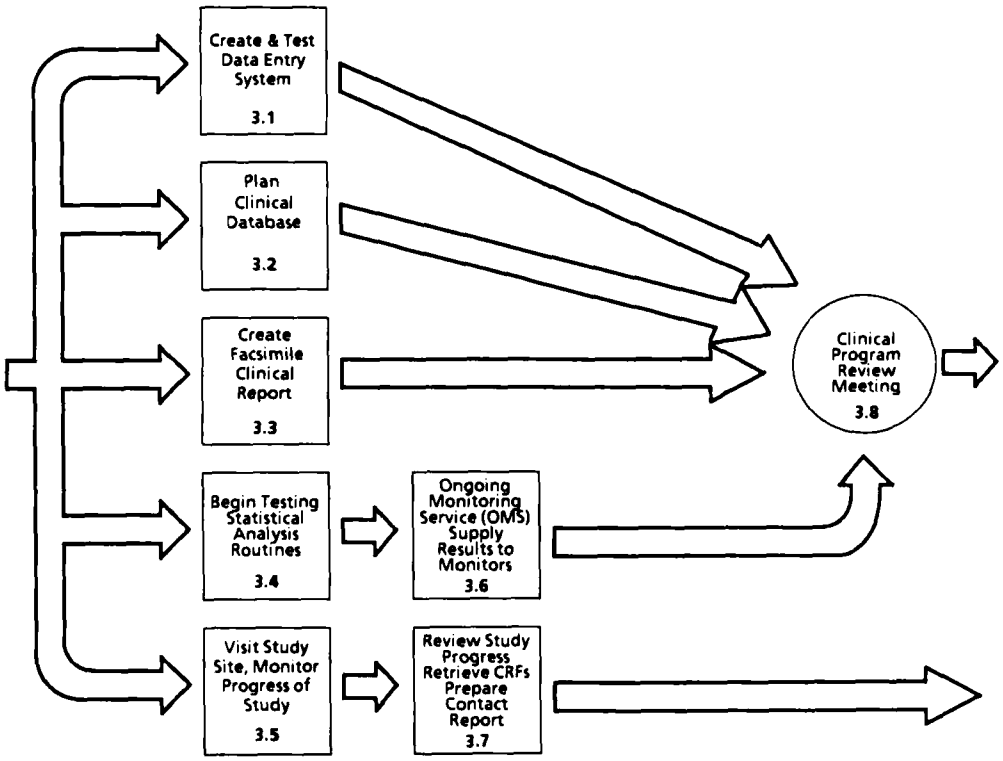


Figure 3
Conduct Clinical Program

3.4 Routines for statistical analysis that were identified in the study protocol are prepared by the Study Statistician in anticipation of the database becoming available. Tabular displays and graphic presentations are also prepared for inclusion in the statistical appendix of the clinical study report.

3.5 Let us not forget the continued activities of the Clinical Monitor and Clinical Research Associate who are overseeing the clinical study as it progresses toward completion.

The study is now in full operation and scheduled activities are performed in preparation of 3.8, the Monthly Clinical Review Meeting.

3.6 The Ongoing Monitoring Service (OMS) is an operation performed by the Study Statistician. OMS tracks the progress of a study, feeding information of potential concern back to the Clinical Monitor and Clinical Research Associate.

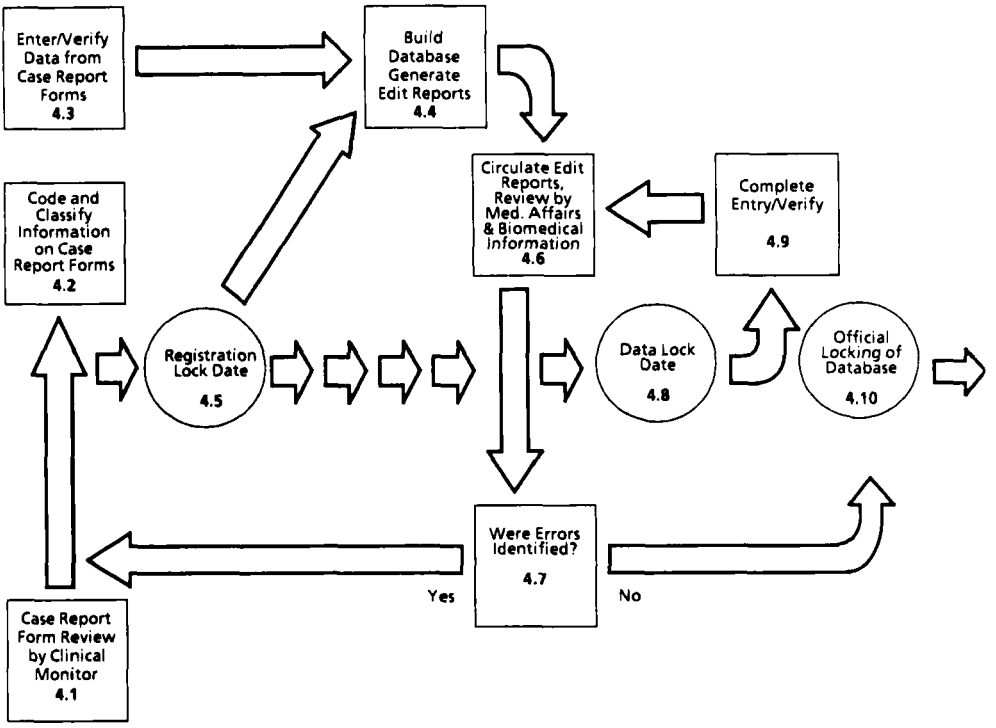


Figure 4
Process Data from Clinical Program

3.7 During periodic visits to the study center, case report forms are retrieved and a Clinical Contact Report is prepared, reporting observations made by the Clinical Research Associate.

3.8 Monthly Clinical Review Meetings are held with management, reviewing clinical program status from a global point of view.

IV. PROCESS DATA FROM CLINICAL PROGRAM

Clinical case report forms are arriving at regular intervals and must be processed and reviewed in a timely manner.

4.1 As clinical case report forms are retrieved from study centers, they are reviewed by the Clinical Monitor and Clinical Research Associate prior to being forwarded to the Clinical Data Processing Group.

4.2 A copy of the original case report form is supplied to the Clinical Data Coder (CDC) for review and classification prior to computer entry. The Clinical Data Coder classifies information on the case report form for consistency in reporting. Information such as clinical side effects and concommitant medications are classified using one of many available classification dictionaries.

4.3 The case report form is keyboard entered and verified prior to transmission to storage in the clinical study database. A screen of edits is imposed on the data prior to database inclusion to avoid "uncleansed" data being combined with "medically cleansed data."

4.4 As data further matures in our process, it is moved into the clinical database for the study.

4.5 The Registration Lock Date (RLD) is another milestone in our process. This is the last day in which a patient may be enrolled for inclusion in the clinical study.

4.6 At predetermined intervals, "intelligent" edits are circulated and reviewed by the Medical Monitor, Statistician, and Medical Writer. Corrections are noted on the edit report and the process continues.

4.7 If errors are identified in the edit reports, reprocessing of Steps 4.2, 4.3, 4.4 and 4.6 will occur. If no errors are identified, Step 4.8 will occur.

4.8 The Data Lock Date (DLD) is a milestone that identifies the last day a case report form will be accepted for inclusion in the clinical study database.

4.9 Final cleanup of the database is taking place and if no errors are identified, the process proceeds to 4.10 database lock.

4.10 The database lock is a milestone in which the Study Monitor, Study Statistician and Medical Writer agree that no further changes to the database will be made.

We are now ready to proceed to the documenting of study results.

V. CLINICAL DOCUMENT PREPARATION

5.1 Final databases are now released for use by all study personnel and the following documents for the New Drug Application are prepared.

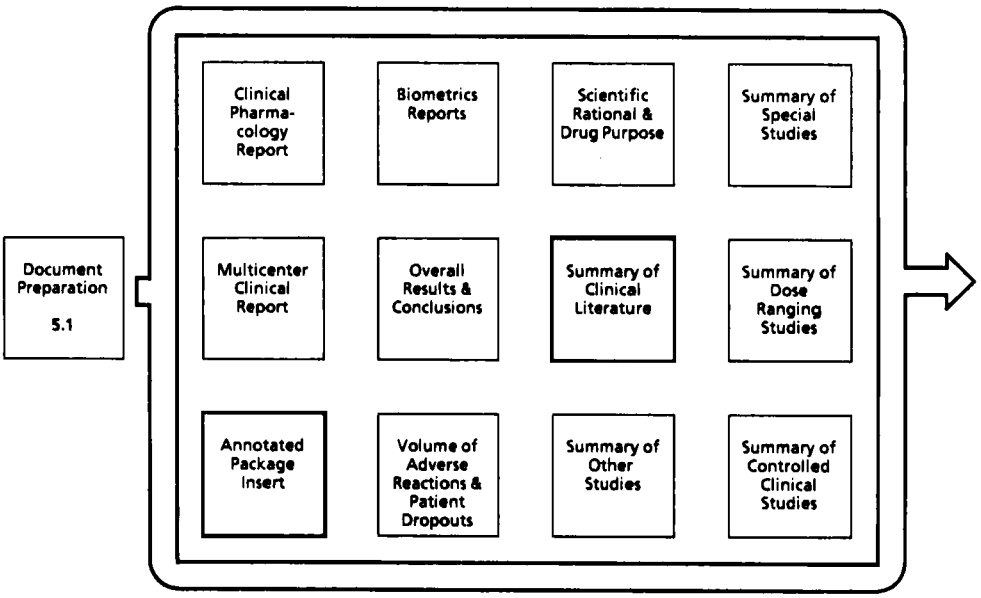


Figure 5
Clinical Document Preparation

VI. REGULATORY SUBMISSION

We are now approaching a series of milestones that are essential to a successful NDA submission to the Food and Drug Administration (FDA). During the processes that follow, meetings are conducted with FDA. These meetings are called pre-NDA meetings.

6.1 As the various components of the NDA are completed, Document Review Meetings are scheduled. Present at review meetings are representatives from Regulatory, Medical, Statistics, and Medical Writing.

6.2 As indicated and agreed to by the Clinical Document Review Committee, revisions are made to clinical documents.

6.3 A further review of the entire NDA is conducted by the Regulatory Affairs Department.

6.4 When all reviews are completed, the NDA receives its final cosmetic touches and is packaged for submission to the FDA. As the FDA reviewer poses questions, they are distributed and answered by the appropriate group in R&D.

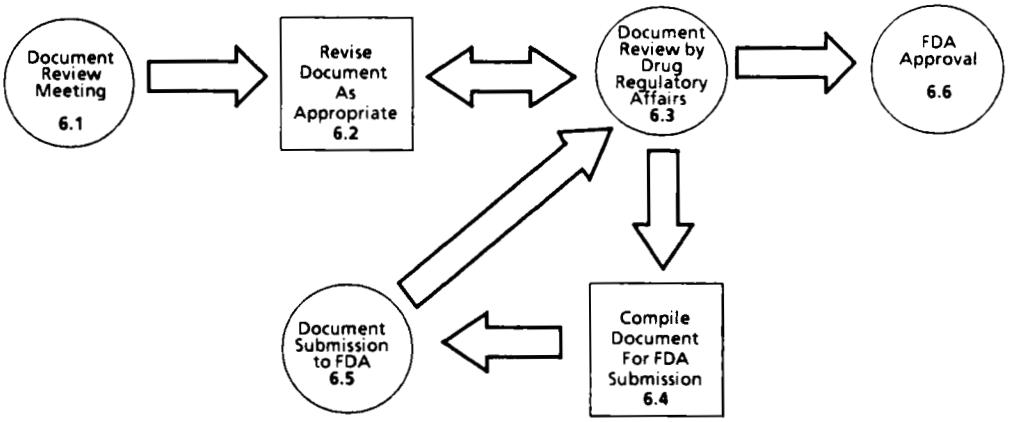


Figure 6
Regulatory Submission

6.5 A banner milestone - the NDA is received at FDA.

6.6 If all things go as planned, in approximately 2½ - 3 years, a company can expect to receive an approval letter from the FDA.

SUMMARY

As in any process, there are "do's and dont's." For the New Drug Application (NDA) they are identified in the federal register. Every company has its own way of planning, initiating, conducting, processing, and documenting the results of a clinical program. No one way is right, and no one way is wrong.

The bottom line for all of us is to bring new therapeutic agents to the marketplace where they can be prescribed for the health care needs of society.