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BUILDING YOUR EARLY PHASE CLINICAL DATA, FROM PROTOCOL TO REGULATORY SUBMISSION

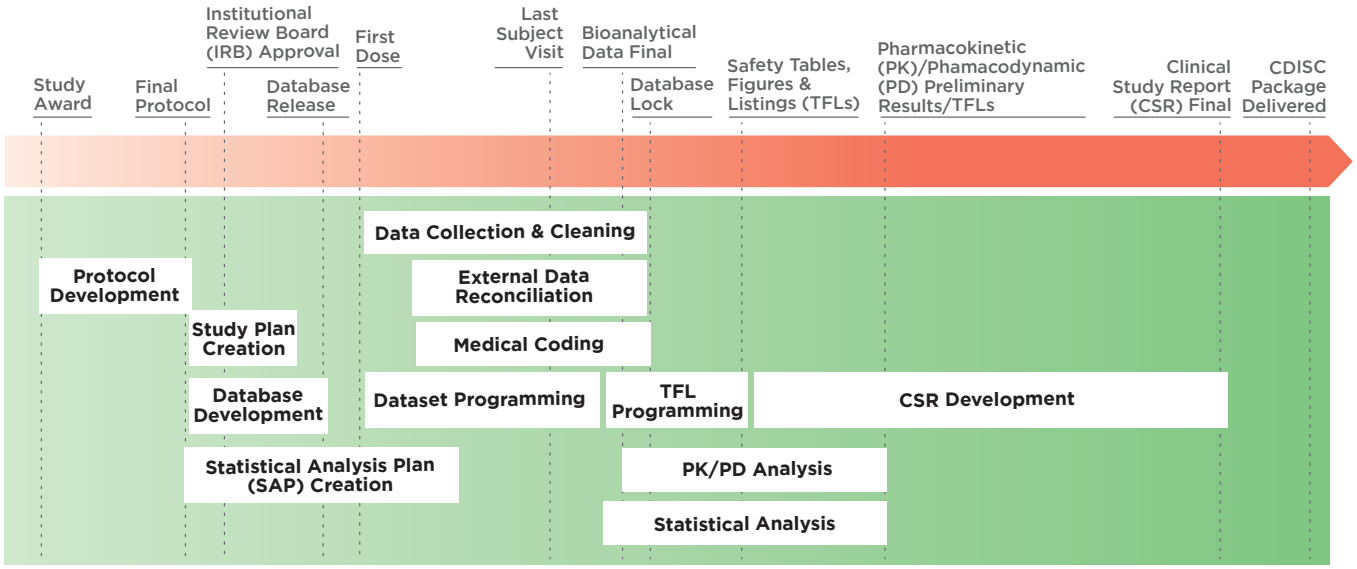
Quality, reliable data is the key to successful drug development. From the initial preclinical data, the plan to bring a drug to market is built upon the foundation of solid, reliable data that demonstrates safety in a human patient population.

In this article, we lead you on the complex, multi-step data journey for Phase I clinical trials, from conceptualization and initial protocol development, collection and analysis, through final regulatory submission. We highlight best practices and approaches to mitigate challenges, and show how integration and collaboration build the strongest datasets for your drug development program.

Figure 1 below graphically demonstrates the many interrelated processes for study planning, data collection, and data analysis, and how they interact/overlap with administrative, clinical, and bioanalytical processes.

Figure 1.

OVERVIEW OF A CLINICAL PROJECT



PROTOCOL DEVELOPMENT

Developing a protocol is the first step in making your study design a concrete, actionable plan to generate data for regulatory submission. Meticulously documented and validated, a well-designed protocol provides the structure for the trial activities that will generate the data to support the study objectives; it is integral to the success of any drug development program.

The necessary contents of the study protocol are detailed in the **ICH E6 Good Clinical Practice Guidelines**.

The credibility of the data from the trial is mainly dependent on the trial design. The trial design in the protocol defines the endpoints and study type (double-masked, placebo-controlled, parallel design), and includes detailed information about the investigational product (IP), the anticipated duration of subject participation, and the sequence and duration of all trial periods, including follow-up. Discontinuation criteria are also key elements for data-driven decision-making during study conduct.

In addition, the protocol includes the description of the analysis and statistical methods to be employed, including timing of any planned interim analyses and quantification of the approach, such as selection criteria for analysis populations (all randomized, all dosed, all eligible, etc.), sample size, calculation of power of the trial, and clinical justification. Finally, the protocol details procedures for reporting any deviations from the original statistical plan, and the use of any excess, missing, or spurious data.

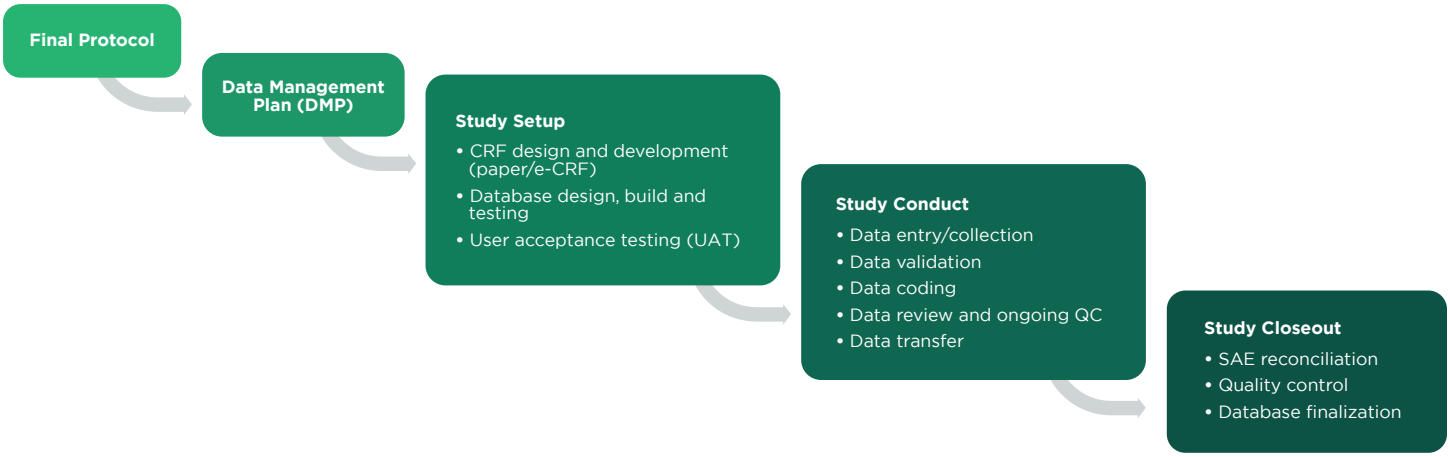
Once the study protocol is final, it becomes the foundation for additional and more detailed study documents, including the Data Management Plan (DMP) and Statistical Analysis Plan (SAP). Here, the first steps of the data journey truly begin.

DATA MANAGEMENT

The DMP, see Figure 2, provides structure and guidance for the data journey, and typically includes details and instructions for data collection, review, storage, protection, archiving, and sharing, to ensure that everything is done according to the protocol and in alignment with all regulatory guidelines.

Figure 2.

PLANNING FOR QUALITY DATA



The DMP is composed of detailed instructions for delivering on the protocol, including standard operating procedures (SOPs), description of processes, responsibilities, and accountabilities, from study start to final data archiving—to anticipate and mitigate any issues. The DMP is thorough, detailed, and forward-looking, with a strategic vision for how the critical processes will be implemented and what the goals are.

The DMP is prepared by the Clinical Data Management (CDM) team, and includes pre-trial study setup activities, data management during clinical study conduct, and study closeout activities, as described below.

Study Setup

- Case Report Form (CRF) design and development (paper/e-CRF)
- Database design, build, and review
- User Acceptance Testing (UAT)

Case Report Form (CRF) Design — The CRF defines all datapoints required by the study protocol for final analysis. The data management, biostatistics, clinic, and pharmacokinetic/pharmacodynamic (PK/PD) teams work together to ensure that all the critical information for end-of-trial activities are appropriately captured.

Database Design and Build — A relational database of subject demographics and protocol-required information is developed for every trial, driven by the format of the CRF. In alignment with Clinical Data Acquisition Standards Harmonisation (CDASH), the database should respect Study Data Tabulation Model (SDTM) standards, published by the Clinical Data Interchange Standards Consortium (CDISC).

Development of Validation Rules — The core of a Data Validation Plan, these rules define how the data will be verified, cleaned, and corroborated.

User Acceptance Testing (UAT) — A thorough library of test cases allows the clinical data management team to validate the structure and functionality of the database and system checks.

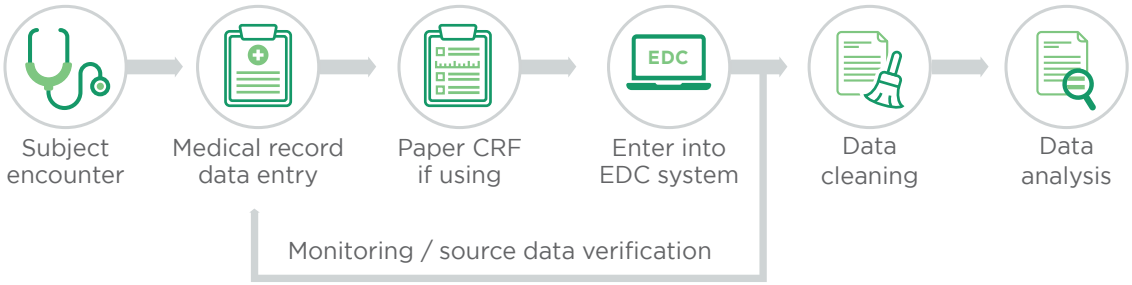
Study Conduct

- Data entry/collection
- Data validation and discrepancy management
- Data coding (MedDRA and WHO DDE dictionaries)
- Data review and ongoing quality control (QC)
- Data transfer

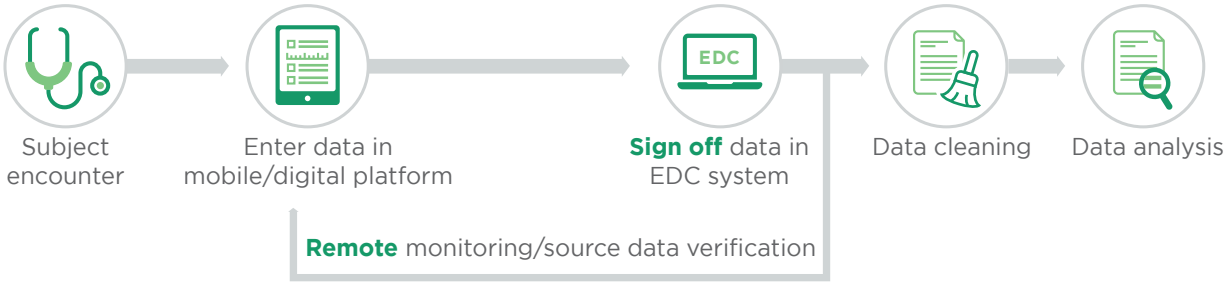
Figure 3 below shows a high-level flow for two common clinical trial approaches, standard and mobile/digital, which can be employed to collect data.

Figure 3.

Standard data collection approach for clinical trials



Mobile/digital data collection approach for clinical trials



Data Entry/Collection — Data are collected directly into an integrated electronic system or entered into the database by well-trained, designated clinical staff with the appropriate, study-specific access and knowledge.

Data Validation and Discrepancy Management — Validation checks run automatically whenever data are saved into the database. Data entries that do not meet validation rules can only be modified by clinical site staff with appropriate access; an audit trail is maintained for any data changes or corrections.

Data Coding — The Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced (WHO DDE) serve as standardized dictionaries for coding of adverse events (AEs), medical history, medical procedure, and concomitant medication data. This allows for the standardization, collation, and summarization of disparate data.

Data Transfer and Reconciliation — Data collected by external parties must be integrated into the final study datasets, verified against the CRF data, and validated. Some examples include central laboratory sites, subject-recorded data for studies where subjects record data outside of the trial location, and other external data, such as cardiac, bioanalytical, or PK/PD assessment data.

Study Closeout

- Serious adverse event (SAE) reconciliation
- Quality control
- Database finalization

SAE Reconciliation and Reporting — The CRF collects data on all AEs reported during the trial. These data are reported to regulatory authorities as required and reconciled against the sponsor's global safety database to ensure accurate SAE data across the drug development program.

Quality Control — The QC process verifies the database content for the essential qualities of accuracy, completeness, and appropriate formatting so that all subsequent data processes can run seamlessly.

Database Finalization — The database is considered final once the above steps are fully completed. Once the database is final, the data are ready for analysis and a database lock is implemented.

STATISTICAL SUPPORT

Statistical support is provided for the data journey during a clinical trial, and includes study design input, study protocol review, sample size calculations, statistical analysis planning, along with mock table, figure, and listing (TFL) shell development, statistical analysis of various data (including PK data, clinical safety data, PD data, and other biomarkers/clinical endpoint data), and preparation of statistical reports for the final clinical study report (CSR).

Statistical Analysis Plan — The content of the SAP varies with the trial, and should include, at a minimum: study endpoint identification and definitions (PK, PD, safety, efficacy in later phases, and other clinical endpoints), analysis population definitions, analysis and statistical methods, guidelines for handling of missing/incomplete data, interim analysis and data safety monitoring, and general information related to data presentation.

Some of the statistical methods are outlined in Table 1. The selection of methods is dependent on the study design and objectives.

Table 1.

Descriptive statistics	T-test	Chi-square test
ANOVA	ANCOVA	Linear regression
Logistic regression	Outlier tests	Wilcoxon signed-rank test
	Wilcoxon rank-sum test	

ANALYSIS AND REPORTING

Safety Analyses

Throughout the drug development life cycle, safety is monitored to evaluate whether a drug is safe in a given population, at a given dose, and for a given duration. Analysis of these data identifies key safety signals and trends guiding drug development and product labeling.

Pharmacokinetic and Pharmacodynamic (PK/PD) Analyses

PK analyses characterize how the body absorbs, metabolizes, and excretes a drug. Depending on the study protocol, PK analyses can be conducted during the study, to help inform ongoing dosing decisions, as well as after the study conduct is complete, to fully characterize the IP.

PD analyses characterize how drugs affect the body. These can include biomarkers, clinical assessments (e.g., vital signs), and subjective measures (e.g., questionnaires, visual analog scales [VAS], or cognitive tests). Parameters may be calculated to quantify response to the drug administered.

Once the necessary analyses have been completed, the data journey for this trial is almost at its end. What remains is to present the data and details of its collection in the final CSR that will be submitted to regulatory authorities, and attach the supporting CDISC-compliant datasets.

Final CSR Generation

The CSR describes the conduct, methods, and results of a clinical study, and provides conclusions to the study objectives. It is developed by the medical writer, in close collaboration with the relevant subject matter experts. The statistical analyses, TFLs, and related information are collected and documented in ICH E3 and electronic common technical document (eCTD) compliant format. Attachments to the CSR include key study documents like the protocol, supporting reports, and analysis. This comprehensive, thorough package represents the final study deliverable, and is the culmination of months to years of rigorous data collection, validation, and analysis. It is a key measure by which regulators can assess the outcome of a clinical study. With the generation of the CSR, the data journey is complete for this clinical trial.

At Altasciences, we take pride in the way we handle your data and facilitate your journey. We have a talented, experienced, and integrated team, whose collaborative efforts ensure that your data is collected and managed with the utmost speed, efficiency, and respect for quality.

Following rigorous processes and standard operating procedures, and leveraging a deep and broad knowledge of CDASH and CDISC guidelines, we ensure that your critical trial data is delivered in regulatory-compliant format. Our PK and PD experts ensure that all analyses are carried out with rigor, in a timely fashion, so that the data is thorough, accurate, and actionable. When you partner with us, you need never be concerned about the quality, security, or accuracy of the data you present in support of your drug development program.

ALTASCIENCES' RESOURCES

Webpages

Scientific and Regulatory Support

Data Management

PK/PD

Biostatistics

Fact Sheet

Research Support Services

The Altascientist

CDISC Data Standards

Blog

Data Management Excellence–What it Takes

Q&A: Setting up Your Clinical Research for Success, with Dr. Nicole Maciolek

Protocol Design Concepts in Phase I Ethnobridging Clinical Trials

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.