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Programmer's Perspective: Step into Awareness Regarding Clinical Study Deliverables and their Impact on Trials

Lyma Faroz, Seagen Inc., Bothell WA

Jinit Mistry, Seagen Inc., Bothell WA

ABSTRACT

There are a variety of deliverables that statistical programmers work through in their careers. Those include producing data sets, tables, listings, figures, patient narratives, and patient profiles, among many others. There is often a natural tendency for programmers to focus on generating such outputs without taking a step back and understand why those outputs have been requested in the first place and how they help the clinical study teams in decision making and assessing trial outcomes. When a programmer understands the bigger picture behind why specific analytical output is requested, how it is used to gauge trial outcomes, and how it contributes to the overall strategy in getting investigational product to patients in need, such insights can help increase the quality of production and QC output. A wide range of deliverables will be discussed in this paper, such as interim analyses, SMCs, DSURs, PBRERs, CSRs, publications, conferences, EudraCT and ClinicalTrials.gov, that will help programmers gain a holistic understanding of what drives specific analyses throughout the life of a clinical trial.

INTRODUCTION

Conducting a clinical trial is an expensive venture, requiring huge investments and resources from the sponsor companies. Historically, where clinical trials have been unsuccessful, contributing factors included the unique study design and inability to identify risk factors at the right time, leaving sponsor companies and patients in need with huge losses. To avoid these scenarios, nowadays, clinical trials are planned with adaptive designs to identify outcomes in real time and make changes as needed along the way. This has led to effective decision-making which may include closing trials at an early stage or change their course by adjusting the dose or dosing intervals thereby improving results, changing sample size, etc. The purpose of this paper is to share some common deliverables by which statistical programmers can support analysis and reporting and contribute to crucial trial decisions.

TYPES OF ANALYSIS IN A CLINICAL TRIAL

Throughout the lifecycle of a clinical trial, to check its progress, various analysis will be planned in the trial protocol. By getting more familiarity with analysis requirements, it would enable statistical programmer to understand the importance of the clinical data and how it would be reported in various analysis. Eventually that would help programmer to be detail-oriented and mindful to efficiently handle various programming activities. Let us look at some of these analyses and understand why they are important and check some of the reports in such analyses that are often worked on by statistical programmers.

INDEPENDENT DATA MONITORING COMMITTEE (IDMC), OR DATA AND SAFETY MONITORING BOARD (DSMB), OR DATA MONITORING COMMITTEE (DMC)

Clinical trials that evaluate new drugs, biologics or devices generate a huge amount of data that need to be reviewed and monitored. A DMC is a group assembled by the sponsor which reviews the clinical trial data on an ongoing basis. This committee consists of members with varied clinical expertise such as clinicians with relevant experience relevant to the trial and biostatisticians with expertise in statistical methods for clinical trials and sequential analysis of trial data. The committee can also have other members such as scientists, toxicologists, epidemiologists, and clinical pharmacologists for trials which require such expertise to infer these interim results. The main purpose of the DMC is to independently advise the sponsor on the safety of trial participants both enrolled and yet to be recruited, and the trial

validity and scientific merit, which in turn will remove the bias versus if a trial was exclusively monitored by sponsors, trials organizers or investigators.

In the past, large randomized, multicenter trials sponsored by Federal agencies such as the National Institutes of Health (NIH) and the Department of Veterans Affairs (VA) in the U.S. used DMCs to monitor these trials. Their focus was to assess the primary objective for improvement in survival or reduction in the risk of major morbidity. It was in 1967 that the first idea of a formal committee responsible to perform continuous assessment of clinical trial data to check for safety, efficacy and trial conduct was established by an NIH external advisory group. Hence nowadays we see many sponsor companies form DMCs. According to FDA's Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, most clinical trials might not need a DMC (e.g., clinical trials in initial stages of product development, trials which address lesser outcomes such as relief symptoms, and shorter-duration trials), however a general recommendation is to establish a DMC for any controlled trial that compares rates of mortality or major morbidity.

Pre-defined clinical trial safety and critical efficacy endpoints are assessed based on various reports produced by statistical programmers. Based on the data in these reports, the committee makes recommendations whether a trial can be continued or should be terminated, or they may suggest some modifications. The scope of efficacy and safety data review would be specified in the DMC charter based on sponsor, DMC and trial needs. Based on the phase of clinical trial, the scope may include efficacy outputs for phase 3 trial as specified in the charter.

Example outputs for a DMC:

- Safety:
    - Subject disposition
    - Demographics and baseline characteristics
    - Baseline disease characteristics
    - Important protocol violations
    - Duration of treatment and exposure summaries
    - Selected adverse event presentations
        - Overall summary of AEs (Adverse Event)
        - SAEs (Serious Adverse Event)
        - Grade 3 or higher AEs
        - Treatment related AEs
        - AEs leading to dose modification
        - Treatment related SAEs
        - AEs of special interest (if any)
        - Listing of SAEs
    - Selected laboratory and vital sign measurements (if relevant)
    - Summary of primary cause of death
    - Listing of all deaths
- Efficacy:
    - Summary of overall response
    - Summary of duration of response
    - Summary of progression-free survival
    - Kaplan-Meier plot of progression-free survival

INTERIM ANALYSIS (IA)

According to FDA's Adaptive Designs for Clinical Trials of Drugs and Biologics (Guidance for Industry), an interim analysis is any examination of data obtained from subjects in a trial while that trial is ongoing and is not restricted to cases in which there are formal between-group comparisons. The observed data used in the interim analysis can include one or more types, such as baseline, safety outcomes, pharmacokinetics, pharmacodynamics, or other biomarkers, or efficacy outcomes.

An interim analysis can help re-assess several factors in an ongoing clinical trial, such as:

1. Sample size
2. Dose or dosing frequency of the investigation product
3. Trial design
4. Terminating a trial for futility
5. Open or Close enrollment in Trial cohorts

Various reports that are generated by statistical programmers help clinical teams make these decisions. To understand the application of IAs in ongoing clinical trials with respect to the programmer's role, let us consider hypothetical cancer research study XYZ-001 as an example. In the middle of our XYZ-001 trial, a prespecified IA is performed to evaluate the study. The study programmer develops standard AE tables such as" Treatment-Emergent Adverse Events by Preferred Term" which leads the clinical study team to observe that most patients had an adverse event with the preferred term "dry eye." In response, the medical monitor and/or study team suggests prescribing the drug with eye masks that relieve symptoms and make the treatment tolerable to patients.

Some more example from FDA's Adaptive Designs for Clinical Trials of Drugs and Biologics (Guidance for Industry),

PREVAIL II was a clinical trial conducted to evaluate ZMapp plus the current standard of care as compared to the current standard of care alone for treatment of patients with Ebola virus disease (PREVAIL II Writing Group et al. 2016; Dodd et al. 2016). The trial utilized a novel Bayesian adaptive design in which decision rules for concluding effectiveness at interim and final analyses were based on the Bayesian posterior probability that the addition of ZMapp to standard of care reduces 28-day mortality. Interim analyses were planned after every 2 patients completed, with no potential action taken until a minimum number of patients (12 per group) were enrolled. The design also allowed the potential to add Contains Nonbinding Recommendations 6 experimental agents as new treatment arms and the potential to supplement or replace the current standard of care arm with any agents determined to be efficacious during the conduct of the trial.

Example Outputs:

Figures:

1. Treatment-Emergent Adverse Events with Incidence >= 15% by Preferred Term
2. Duration on Study
3. Maximum Sum of Diameters Percent Reduction from Baseline
4. Percent Change in Sum of Diameters from Baseline over Time

Tables:

1. Treatment-Emergent Adverse Events of Special Interest by Preferred Term and Maximum Severity
2. Treatment-Emergent Adverse Events by Preferred Term
3. Treatment-Emergent Serious Adverse Events by Preferred Term
4. Treatment-Emergent Serious Adverse Events Related to (Investigational Drug) by Preferred Term
5. Overall Summary of Treatment-Emergent Adverse Events
6. Reports on concomitant medications, disposition, demographics, exposure, lab shifts, prior therapies
7. Efficacy reports such as 'Best Overall Response,' 'Progression-Free Survival,' 'Disease Control Rate,' 'Objective Response Rate'

Listings:

1. Adverse Events, Discontinuation or Dose Modification, Concomitant Medication, Death.

DEVELOPMENT SAFETY UPDATE REPORT (DSUR)

According to FDA's Guidance for Industry – E2F Development Safety Update Report, it is crucial to conduct periodic analyses of safety information of an investigational drug during its clinical development phase, thereby constantly assessing the risk of the drug to trial subjects. Sharing these analysis results with regulators and interested parties (e.g., ethics committees) at regular intervals is important to inform the evolving safety profile of the drug and actions taken to address safety concerns. According to current laws and regulations of some ICH (International Council for Harmonization) countries and regions, this information is provided to regulatory authorities in the form of a submission of a periodic report. This DSUR's main goal is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation. Please refer to sample example outputs from Appendix B of FDA's Guidance for Industry – Development Safety Update Report that can be submitted along with detailed information on additional clinical trial information that is expected in the package. Some example outputs are shared as follows.

Example Outputs:

Overview of Ongoing Studies [Study Drug]

Study ID	Phase	Country	Study Title	Study design	Dosing regimen	Study population	FVFP†	Planned enrolment	Subject exposure‡

† FVFP = first visit first patient
‡ Based upon total number of patients recruited as of [date] and applied randomization schemes

Overview of Studies Completed During the DSUR Period [Study Drug]

Study ID	Phase	Country	Study Title	Study design	Dosing regimen	Study population	Subject/patient patient exposure per treatment arm (M/F)

Table 1. Status of Ongoing and Completed Clinical Trials

Interval Line Listings of Serious Adverse Reactions

Study ID EudraCT number	Case ID/ Subject number†	Country Gender Age	Serious adverse drug reactions (SARs)	Outcome	Date of onset‡ Time to onset‡	Suspect Drug	Daily dose Route Formulation	Dates of treatment Treatment duration	Comments
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† Study/center/patient

‡ 'Primary' SAR only

Table 2. Example Headings for Interval Line Listings of Serious Adverse Events

Cumulative Summary Tabulation of Serious Adverse Events (SAEs)

System Organ Class	Total up to 31-Dec-09			
Preferred Term	[Study drug]	Blinded	Active comparator	Placebo
Investigations	**18**	**4**	**7**	**2**
Alanine aminotransferase increased	9	2	4	1
Aspartate aminotransferase increased	9	2	3	1
Nervous System Disorder	**2**	**2**	**4**	**7**
Syncope	2	2	4	7

Table 3. Examples of Cumulative Tabulations of Serious Adverse Events

PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER)

According to FDA's Guidance for industry – E2C(R2) Periodic Benefit-Risk Evaluation (PBRER), reporting is performed on marketed products (including approved drugs that are under further study) among the ICH regions. Approval of new medicinal products for marketing relies on an assessment of safety and efficacy based on data from a limited number of patients, studied under controlled conditions of randomized trials. Often, high-risk subgroups of patients are excluded from clinical trials, and long-term treatment data are limited. Patients are also closely monitored for any adverse events. In clinical practice, as monitoring is less intensive and a variety of patients receive the treatment, events that are usually not seen in clinical trials can be observed. Hence it is critical to continuously analyze the safety, efficacy, and effectiveness information of the medicinal product throughout its life cycle which helps inform its ongoing benefit-risk assessment. The main goal of a PBRER is to present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the medicinal product, and on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile. Appendix B of FDA's Guidance for industry – E2C(R2) Periodic Benefit-Risk Evaluation (PBRER) can be referenced for example outputs, some of which are shared as follows.

Example Outputs:

Estimates of cumulative subject exposure, based upon actual exposure data from completed clinical trials and the enrollment/randomization schemes for ongoing trials.

Treatment	Number of subjects
Medicinal product	
Comparator	
Placebo	

Table 4. Estimated Cumulative Subject Exposure from Clinical Trials

	Number of subjects		
Age range	**Male**	**Female**	**Total**

* Data from completed trials as of [date].

Table 5. Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by Age and Sex

Racial group	Number of subjects
Asian	
Black	
Caucasian	
Other	
Unknown	
Total	

* Data from completed studies as of [date].

Table 6. Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by racial Group

PUBLICATIONS AND CONFERENCES

Many conferences within the medical community covering a range of different therapeutic areas help medical professionals stay informed on clinical trials conducted by pharma or biotech companies. This is a great forum to learn about different investigational drugs that treat a variety of indications, cutting-edge research with various innovative technologies such as ADC (antibody-drug conjugate), CRISPR etc. These conferences also introduce new chemical entities (especially if the data is promising) and provide information on competing research in similar indications. The more companies present their data, the faster the possibility of getting better treatment to patients especially in areas of unmet medical need.

Example Outputs For Oncology Studies:

Figures:

1. Duration of Treatment
2. Percent Change from Baseline in Sum of Diameter of Target Lesions per Investigator
3. Time to First Confirmed Response and Duration of Response per Investigator
4. Kaplan-Meier Survival Curves

Tables:

1. Summary of Demographics, Disposition, Baseline Characteristics, Drug Administration
2. Adverse Events
3. Efficacy tables such as Best Overall Response, Duration of Response, Progression-Free Survival, Overall Survival.

CLINICAL STUDY REPORTS (CSR)

According to FDA's Guideline for Industry (Structure and Content of Clinical Study Reports), a CSR is an integrated full report of an individual study of any therapeutic, prophylactic, or diagnostic agent (referred to herein as drug or treatment) conducted in patients, summarizing outcomes to help evaluate the effectiveness of the investigational drug. A CSR consists of detailed information about the study, study design and methodology, technical statistical documentation, investigational drug information, study protocol, sample case report forms, analysis derivations, safety, and efficacy data in the form of reports such as tables, listings, and figures and many other components as detailed in FDA's guidance document. These reports are submitted to regulatory agencies such as FDA, EMA (European Medicines Agency), and Japan's PMDA (Pharmaceuticals and Medical Devices Agency) to gain approval of their product.

Example Outputs:

Safety data reports:

Demographics, Disposition, Exposure, Adverse Events, Number of deaths on study, Laboratory information, Vital signs, ECG (electrocardiogram), Concomitant medications, Prior systemic therapies

Efficacy data reports (taking oncology studies as an example):

Best Overall Response, Overall Survival, Progression-Free Survival, Overall Response Rate, Disease Control Rate, and other efficacy information per study protocol

EUDRACT (EUROPEAN UNION DRUG REGULATING AUTHORIES CLINICAL TRIALS DB)

EudraCT is the European database of all interventional clinical trials of medicinal products conducted in the EU. A unique number is assigned to identify each clinical study which never expires. Usually, the SDTM Trial Summary (TS) domain presents this identifier in the TSVAL variable with TSPARMCD='REGID,' TSPARM='Registry Identifier' and TSVCDREF='EUDRACT.' The TS programmer ensures to put all trial-specific details in this submission data set. Once the clinical trial is registered in EudraCT, a sponsor is required to provide results for corresponding clinical trial based on guidance published by the European commission. The biometrics team works collaboratively with cross-functional teams on the required analysis based on guidance and communication.

CLINICALTRIALS.GOV

For certain clinical trials, sponsors are required to submit scientific, administrative information and results of the trial according to Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801), to the results database of ClinicalTrials.gov in the United States. This process is like the preparation for a publication in a journal. Study statisticians or medical monitors who are familiar with the study design and data analysis help to summarize results as required by ClinicalTrials.gov review criteria. There are four modules through which scientific information is submitted:

- Participant Flow
- Baseline Characteristics
- Outcome Measures and Statistical Analyses
- Adverse Events

Participant Flow Template — ClinicalTrials.gov

Recruitment Details	
[*] Pre-assignment Details	

Period ①

* Period Title	Overall Study ①		
* Arm/Group Title			
*§ Arm/Group Description ②			
	Number of Participants ④	Number of Participants ④	Number of Participants ④
* Started			
[*] Milestone Title ③			
[*] Milestone Title ③			
[*] Milestone Title ③			
* Completed			
Not Completed	*(automatically calculated)*		
Reason Not Completed Type ③			
[*] Adverse Event			
[*] Death			
[*] Lack of Efficacy			
[*] Lost to Follow-up			
[*] Physician Decision			
[*] Pregnancy			
[*] Protocol Violation			
[*] Withdrawal by Subject			
[*] Other Reason			
[*] Other Reason			
[*] Other Reason			

* Required *§ Required if Primary Completion Date is on or after January 18, 2017 [*] Conditionally required

① Complete a Period table for each stage of the study. If only one Period, the Title is "Overall Study". For multiple Periods, include descriptive Titles for each Period.
② Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
③ [Optional] Add as many Milestone Title or Other Reason Not Completed rows as needed. A descriptive title for each row is required.
④ Number and Type of Units Assigned may also be specified.

Table 7. Participant Flow Template **Table 8. Baseline Characteristics Template. This can be generated for (Age), (Sex/Gender), (Race, Ethnicity, Region), (Study-Specific Characteristics)**

Outcome Measure Template — ClinicalTrials.gov

* Outcome Measure Type	(Select One) Primary Secondary Other Pre-specified Post-Hoc
* Outcome Measure Title	
[*] Outcome Measure Description	
* Outcome Measure Time Frame	

* Arm/Group Title							
*§ Arm/Group Description ①							
* Overall Number of Participants Analyzed ②							
[*] Analysis Population Description							
* Measure Type	* Measure of Dispersion/Precision						
(Select One) Count of Participants ③ Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM Number Count of Units ③	(Select One) Not Applicable ④ Standard Deviation Standard Error Inter-Quartile Range Full Range ____ % Confidence Interval Geometric Coefficient of Variation						
[*] Row/Category Title ⑤			③④		③④		③④
[*] Row/Category Title ⑤			③④		③④		③④
* Unit of Measure							

* Required *§ Required if Primary Completion Date is on or after January 18, 2017 [*] Conditionally required

① Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
② Overall Number of Units Analyzed and Type of Units Analyzed may also be specified.
③ If Measure Type is a "count," percentage of participants/units is automatically calculated from Overall Number of Participants/Units Analyzed. The percentage can be hidden (display is optional).
④ Not Applicable should be used only if Measure Type is Number, Count of Participants, or Count of Units. No dispersion/precision value is needed if Measure of Dispersion is Not Applicable.
⑤ [Optional] Add as many Rows/Categories as needed. If more than one is entered, a Row/Category Title and Outcome Measure Data are required for each row. Row/Category Titles are only required if more than one row.

Table 8. Outcomes Measure Template

All-Cause Mortality and Serious Adverse Events Template — *ClinicalTrials.gov*

*§ Time Frame											
[*] Adverse Event Reporting Description											
Source Vocabulary Name for Table Default ①											
*§ Collection Approach for Table Default ①	(Select One) Systematic Non-Systematic										
* Arm/Group Title											
*§ Arm/Group Description ②											
*§ All-Cause Mortality											
	*§ Number Participants Affected	*§ Number Participants at Risk		*§ Number Participants Affected	*§ Number Participants at Risk		*§ Number Participants Affected	*§ Number Participants at Risk			
*§ Total											
* Serious Adverse Events											
	* Number Participants Affected	* Number Participants at Risk	Number Events	* Number Participants Affected	* Number Participants at Risk	Number Events	* Number Participants Affected	* Number Participants at Risk	Number Events		
* Total											
* Adverse Event Term	* Organ System										
	③		④[*]			④[*]			④[*]		
	③		④[*]			④[*]			④[*]		
	③		④[*]			④[*]			④[*]		
	③		④[*]			④[*]			④[*]		
	③		④[*]			④[*]			④[*]		
	③		④[*]			④[*]			④[*]		

* Required *§ Required if Primary Completion Date is on or after January 18, 2017 [*] Conditionally required

① If entered, the table default values apply to all Adverse Event Terms. The values may be changed for any single Adverse Event, if different from the table default.
② Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
③ Organ System must be selected from a pick-list of high-level categories. See the Results Data Element Definitions for details.
④ Number of Participants at Risk for an Adverse Event Term is only required when the value differs from the Total Number of Participants at Risk.

Table 9. All-Cause Mortality and Serious Adverse Events Template

CONCLUSION

Clinical trials are performed to evaluate how a drug can benefit patients and the data collected is invaluable in several ways. We hope that after reviewing details in this paper about the clinical trial stakeholders, data reporting authorities and general analysis requirements, programmers will gain an understanding of the work they do every day, broaden their perspective, and significantly increase the value that programmers can bring to patients.

REFERENCES

Guidance for Clinical Trial Sponsors (Establishment and Operation of Clinical Trial Data Monitoring Committees)
https://www.fda.gov/media/75398/download

Adaptive Designs for Clinical Trials of Drugs and Biologics (Guidance for Industry)
https://www.fda.gov/media/78495/download

Guidance for Industry (E2F Development Safety Update Report)
https://www.fda.gov/media/71255/download

E2C(R2) Periodic Benefit-Risk evaluation Report (PBRER) – Guidance for Industry
https://www.fda.gov/media/83371/download

Guideline for Industry – Structure and Content of Clinical Study Reports
https://www.fda.gov/media/71271/download

European Medicines Agency
https://www.ema.europa.eu/en/news/posting-clinical-trial-summary-results-european-clinical-trials-database-eudract-become-mandatory

ClinicalTrials.gov
https://clinicaltrials.gov/ct2/manage-recs/how-report

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CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Lyma Faroz
Seagen Inc.
21823 30th Drive S.E.
Bothell, WA 98021
lfaroz@seagen.com

Jinit Mistry
Seagen Inc.
21823 30th Drive S.E.
Bothell, WA 98021
jmistry@seagen.com