Paper PP18

Milestones Matter – Understanding Key Milestones in Clinical Trials

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ABSTRACT

As statistical programmers within the pharmaceutical industry, we primarily work on analysis datasets, tables, listings, and graphs that contribute to a wide variety of milestones in the journey of clinical trials. These milestones are critical for making important decisions about the study, from inception to final analysis, spanning phases from First-in-Human trials to the drug's market release, including post-marketing analysis.

This poster/paper will provide an overview of the diverse milestones we contribute to, highlighting the purpose and scope of analyses, key deliverables, stakeholders, timelines, and important decisions or outcomes associated with each milestone.

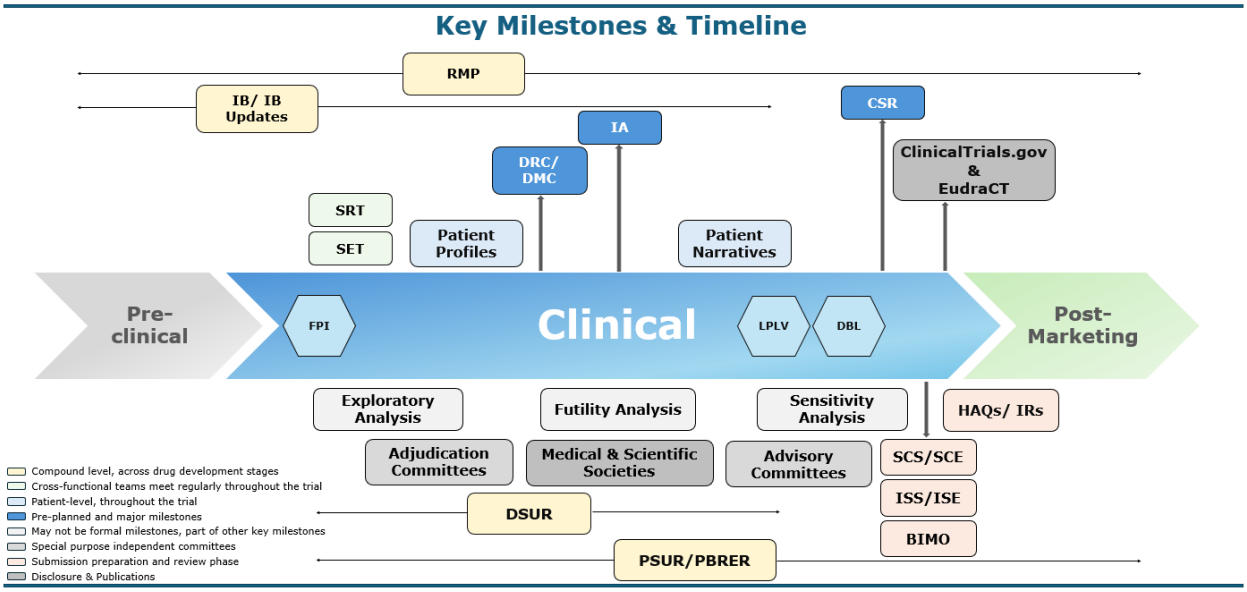
INTRODUCTION

The goal of this poster/paper is to help new statistical programmers in this highly research-oriented industry understand the various milestones we work on within clinical development, such as Data Monitoring Committee (DMC), Interim Analysis (IA), Clinical Study Report (CSR), Development Safety Update Report (DSUR), and Periodic Safety Update Report (PSUR) etc.

Disclaimer:
This poster/paper provides a general overview of the selected clinical trial milestones and is not comprehensive. Document names or milestone timing and frequencies can vary. The content presented is based solely on the authors' experience and publicly available resources.

FIGURE 1: KEY MILESTONES & TIMELINE

This figure shows the selected key milestones and their timing in the clinical trial journey — a quick visual reference before exploring each milestone in detail.



FPI – First Patient-In; LPLV – Last Patient Last Visit; DBL – Database Lock.
***Note:** Not all clinical trials necessarily undergo every milestone.*

CATEGORY-WISE SUMMARY OF KEY MILESTONES

The key milestones highlighted in the figure above are grouped into six categories based on their timing, purpose, and/or scope of analyses. Each table below summarizes the milestone's purpose, timing and frequency, scope, key decisions, and primary stakeholders, providing a structured overview of milestones throughout the study lifecycle, with easy-to-understand examples.

TABLE 1.1: PLANNING, SETUP & ONGOING OVERSIGHT MILESTONES

<table>
<tr><th colspan="3">IB/IB Update (Investigator's Brochure)</th></tr>
<tr><th colspan="2">Purpose</th><th>Timing/Frequency</th></tr>
<tr><td colspan="2">A central document summarizing safety, efficacy, PK and risks data from preclinical and clinical studies, helping investigators conduct trials safely and effectively.</td><td>▪ Initial version of IB may be created before the start of the first clinical trial.
▪ Then, annually or whenever new significant data arises, until last patient last visit (LPLV) in the final study.</td></tr>
<tr><th>Scope/
Key Deliverables</th><th>Key Decisions/
Outcomes</th><th>Key Stakeholders</th></tr>
<tr><td>- Lists expected serious adverse reactions (SARs)
- New AEs, SAEs, SUSARs
- Preliminary efficacy endpoint results
- PK/PD results (if available)</td><td>✓ Patient eligibility criteria
✓ Informed consent form development
✓ IB serves as a key resource for investigators</td><td>• Regulatory Medical Writing (RMW)
• Pharmacovigilance and Safety team
• Regulatory and Medical Affairs
• Investigators
• Ethics committees (IRBs/IECs)</td></tr>
<tr><th colspan="3">RMP (Risk Management Plan)</th></tr>
<tr><th colspan="2">Purpose</th><th>Timing/Frequency</th></tr>
<tr><td colspan="2">A comprehensive document that outlines strategies to identify, assess, monitor, and mitigate risks associated with an investigational product throughout its lifecycle, from preclinical to post-marketing, ensuring patient safety and assessing benefit-risk profile.</td><td>▪ Initial version of RMP, may be created before the start of the first clinical trial.
▪ Then, annually or whenever new significant data arises, throughout its lifecycle.</td></tr>
<tr><th>Scope/
Key Deliverables</th><th>Key Decisions/
Outcomes</th><th>Key Stakeholders</th></tr>
<tr><td>- New AEs, SAEs, SUSARs
- Exposure
- Identification of known and potential risks
- Missing safety information
- Risk minimization strategies
- Overall benefit-risk assessment</td><td>✓ Risk minimization decisions (dose adjustments)
✓ Updates to the product label (new warnings etc.)
✓ Long-term safety</td><td>• Regulatory Medical Writing (RMW)
• Pharmacovigilance and Safety team
• Regulatory and Medical Affairs
• Investigators
• Regulatory Authorities
• Health Economics & Outcomes Research (HEOR)</td></tr>
<tr><td colspan="3"><u>Additional details/ Example:</u>
○ Both IB/RMP are Compound-level activities and are living documents, providing up-to-date, unified and holistic view of investigational compound's safety and/or efficacy profile and risks data across all studies and indications, along with mechanism of action, dose formulation, administration etc.
○ Statistical Programming may not contribute to initial version of the IB/RMP, unless there is any data that needs to be summarized.</td></tr>
</table>

TABLE 1.2: DATA MONITORING & REVIEW MILESTONES

<table>
<tr><th colspan="3">SET (Study Evaluation Team)
&
SRT (Safety Review Team)</th></tr>
<tr><th>Purpose</th><th colspan="2">Timing/Frequency</th></tr>
<tr><td>A cross-functional team from within the study/project.

SET oversees the trial progress – focusing on strategy, operations, timelines, and scientific direction.

SRT reviews AEs, SAEs – focusing on day-to-day patient safety management during the trial and identify emerging safety signals.</td><td colspan="2">▪ SET meets regularly (weekly, bi-weekly, monthly, quarterly) – more frequently during early and critical phases, and less frequently during steady-state operations.

▪ SRT meets regularly (e.g. monthly, quarterly).

▪ Ad-hoc SET/SRT meetings can be requested, for additional data review, throughout the clinical study.</td></tr>
<tr><th>Scope/
Key Deliverables</th><th>Key Decisions/
Outcomes</th><th>Key Stakeholders</th></tr>
<tr><td>- Patient recruitment, Site performance etc.
- Evaluation of AEs and other safety
- Monitor SAEs, AESIs, SUSARs
- Dose limiting toxicity (DLTs)
- Review efficacy and PK/PD (if available)</td><td>✓ Operational decisions
✓ Dose escalation/Dose modification decisions
✓ MTD (Maximum Tolerated Dose) identification
✓ Recommend Phase 2 Dose (RP2D)</td><td>• Clinical Operations
• Central Monitoring
• Safety
• PK and Translational Research Scientist
• Investigators
• IRB/IECs (if needed)
• Regulatory Authorities (if needed)</td></tr>
<tr><td colspan="3"><u>Additional details/Examples:</u>
○ SET serves as the internal steering group -> Is the study on track overall?
- SET notices the patient enrollment is slower than planned and decide to add more sites in other countries.
- SET reviews preliminary efficacy and discuss preparing for Phase III planning.

○ SRT serves as the guardian of patient safety -> Are patients safe today?
- SRT observes several patients showing mild but consistent cardiac side effects, recommends adding extra ECG monitoring to the protocol.

○ SET/SRT meeting minutes/updates are filed and shared with investigators, ethics committees and authorities (as and if needed).</td></tr>
</table>

AEs – Adverse Events; SAEs - Serious Adverse Events; SUSARs - Suspected Unexpected Serious Adverse Reaction; AESIs– Adverse Events of Special Interest; IRB - Institutional Review Board; IEC - Independent Ethics Committee; PK/PD - Pharmacokinetics (PK) /Pharmacodynamics (PD); ECG - Electrocardiogram.

TABLE 1.2: DATA MONITORING & REVIEW MILESTONES (Continued…)

DRC (Data Review Committee) & DMC/ DSMB (Data Monitoring Committee / Data Safety Monitoring Board)	
Purpose	**Timing/Frequency**
A group of experts responsible for reviewing and evaluating clinical trial data throughout the study to ensure patient safety, maintain data integrity and quality, and monitor the overall conduct of the trial. ○ DMCs are external and independent. ○ DRCs are internal (sponsor), but independent of the study team.	▪ DRC meetings occur more frequently in early-stage studies to closely monitor enrollment, data quality and readiness. ▪ DMC meetings typically occur at pre-specified intervals (e.g., every 6–12 months) and/or are aligned with pre-planned milestones (e.g., interim analysis). ▪ Both DMC/DRC meetings may also be triggered when a defined number of participants are enrolled, treated, or completed specific study phases, as outlined in the protocol or respective charters.

Scope/ Key Deliverables	**Key Decisions/ Outcomes**	**Key Stakeholders**
- Support internal reviews and decisions - Data quality and integrity - DMC: may also include efficacy and futility analysis - DRC: Mainly used in Early Development (ED) and Clinical Pharmacology (CP) studies	✓ DRC/DMC Recommendations: ☐ No action. The study should continue as planned. ☐ Discontinue the ongoing study ☐ Modify the study design (e.g., sample size adjustment, dose changes).	Internal for DMC and DRC: • Medical monitoring • Global Medical Safety (GMS) or Therapeutic Area Safety Head (TASH) • Regulatory Affairs (if needed) • PK scientist (if needed) External for DMC: • Medical Expert • Biostatistics Expert • Safety Expert • PK scientist (if needed)

Additional details/ Examples:

○ DMC incorporates blinding and un-blinding procedures to minimize potential bias in trial conduct and data interpretation.
○ DMC and DSMB are interchangeable terms; "DMC" is more commonly used in Europe, while "DSMB" is preferred in the U.S.
○ DMC Members serve in an advisory capacity to the sponsor and vote on recommendations.

Example situations:

○ DRC reviewed interim data and identified that at site 101, three patients had identical serum M-protein values (1.2 g/dL) across four consecutive visits – recommended **close monitoring and an audit of the site** due to potential data integrity concerns.
○ DMC reviewed interim data and identified a higher-than-expected incidence of Grade 4 neutropenia and severe infections in the treatment arm and recommended **pausing enrollment** and implementing additional safety measures (dose reduction guidelines).

TABLE 1.2: DATA MONITORING & REVIEW MILESTONES (Continued…)

<table>
<tr><th colspan="3">Adjudication Committees</th></tr>
<tr><th colspan="2">Purpose</th><th>Timing/Frequency</th></tr>
<tr><td colspan="2">An independent group of experts that adjudicates (verifies or validates) critical clinical events or outcomes based on standardized criteria, to ensure uniform, unbiased, and consistent assessment of key trial endpoints that require clinical judgement.</td><td>▪ Ongoing throughout the trial - starts once events begin to accumulate. Frequency depends on event volume and data flow.</td></tr>
<tr><th>Scope/
Key Deliverables</th><th>Key Decisions/
Outcomes</th><th>Key Stakeholders</th></tr>
<tr><td>- Validate key endpoints (e.g., disease progression)
- Minimize site-level variability and bias
- Strengthen regulatory credibility and data integrity
- Document and maintain adjudication outcomes</td><td>✓ Final confirmation or rejection of suspected events
✓ Impact on primary/ secondary endpoints, safety profile, and regulatory submission</td><td>Independent and External:
• Medical experts (TA specific – Oncologist, Radiologist)
• Biostatistics expert</td></tr>
<tr><td colspan="3"><u>Additional details/ Examples:</u>
Example:
Investigator assessment: At week 8, the investigator reviewed CT and MRI scans of a patient and reported Progressive Disease (PD) due to a new lytic lesion in the pelvis.

Independent Review Committee (IRC) assessment: IRC reviews independently (blinded) all data including baseline, IMWG criteria, RECIST guidelines and determines:
- the "new" pelvic lesion was visible at baseline but was misclassified due to poor contrast resolution.
- The lesion had not increased in size
- No other lesions showed ≥25% increase in size.
Thus, patient did not meet the PD criteria.

<u>Decision:</u> The IRC reclassified the response as Stable Disease (SD).

○ Adjudication committees are generally therapeutic/disease area specific, below is a list of a few for quick reference –
Independent Review Committee (IRC)
Cardiovascular Events Committee (CEC)
Immune-Related Adjudication Committee (IRAC)
Gastrointestinal Adjudication Committee (GAC)
Adverse Event Adjudication Committee (AE AC)
Mortality Adjudication Committee (MAC)</td></tr>
</table>

IMWG – International Myeloma Working Group; RECIST - Response Evaluation Criteria in Solid Tumors; CT- Computed Tomography; MRI - Magnetic Resonance Imaging.

TABLE 1.2: DATA MONITORING & REVIEW MILESTONES (Continued…)

<table>
<tr><th colspan="3">Advisory Committees</th></tr>
<tr><th colspan="2">Purpose</th><th>Timing/Frequency</th></tr>
<tr><td colspan="2">An independent expert panels convened by health authorities (like the FDA or EMA), to provide objective, scientific, and public input on the safety, efficacy, and benefit-risk profile of investigational products.</td><td>▪ Typically, occurs once, during or post-submission phase. For high-risk/high-impact therapies – often, as needed.</td></tr>
<tr><th>Scope/
Key Deliverables</th><th>Key Decisions/
Outcomes</th><th>Key Stakeholders</th></tr>
<tr><td>- Review of NDA/BLA/MAA submission package</td><td>✓ Recommend approval, rejection, label updates or further studies to the health authorities.</td><td>• Voting members (8-15): Independent expert panel - clinicians, scientists, statisticians, pharmacologists etc.
• Regulatory counterparts
• Patients/ Public Representative (optional)</td></tr>
<tr><td colspan="3"><u>Additional details/ Examples:</u>
Example:
An early phase oncology trial showed high Overall Response Rate (ORR = 80%) and sponsor was seeking accelerated approval.
However, ODAC noted:
- Limited long-term data on durability of response.
- Safety concerns, particularly cytokine release syndrome (CRS) and infections.
- The need for confirmatory trials to validate clinical benefit.

<u>Decision:</u> ODAC voted 10–0 in favour of accelerated approval, with the condition that:
- The sponsor must complete confirmatory trials to verify clinical benefit.
- Post-marketing surveillance must monitor infection risks and CRS management.
The FDA later granted accelerated approval.

○ FDA has over 30 advisory committees across therapeutic/ disease areas; below is a list of some key committees for quick reference -
Oncologic Drugs Advisory Committee (ODAC)
Cardiovascular and Renal Drugs Advisory Committee (CRDAC)
Arthritis Advisory Committee (AAC)
Gastrointestinal Drugs Advisory Committee (GDAC)
Paediatric Advisory Committee (PAC)
Rare Diseases Advisory Committee (RAC)</td></tr>
</table>

NDA - New Drug Application; BLA - Biologics License Application; MAA - Marketing Authorization Application;
FDA - Food and Drug Administration; EMA - European Medicines Agency;

TABLE 1.3: ANALYSIS & REPORTING MILESTONES

<table>
<tr><th colspan="3">Exploratory Analysis</th></tr>
<tr><th colspan="2">Purpose</th><th>Timing/Frequency</th></tr>
<tr><td colspan="2">A systematic examination of data to identify patterns, relationships, and interesting insights without predefined hypotheses, to generate hypotheses, support decision-making, guide future research.</td><td>▪ More frequent in adaptive or early phase trials, often done before confirmatory analysis, before finalizing results.
▪ Also, post-trial to support future trial designs.</td></tr>
<tr><th>Scope/
Key Deliverables</th><th>Key Decisions/
Outcomes</th><th>Key Stakeholders</th></tr>
<tr><td>- Detect unexpected trends or anomalies in patient responses
- Identification of potential responder subgroups
- Generation of hypotheses
- Preliminary insights into dose–response relationships
- Data quality reports (outliers, inconsistencies)</td><td>✓ Adjusting study design or data collection strategies
✓ Refining hypotheses for confirmatory trials
✓ Post-trial, support future trial designs
✓ Selection of subgroups</td><td>• Regulatory affairs
• Safety</td></tr>
<tr><td colspan="3"><u>Additional details/ Examples:</u>
○ Exploratory analysis reveals a pattern that patients with higher baseline cholesterol levels tend to respond better to the medication, showing greater reductions in blood pressure and heart rate, leading to consider subgroup analyses or future targeted studies to confirm this finding.
○ Not a formal milestone, may be included within other key milestones.</td></tr>
</table>

TABLE 1.3: ANALYSIS & REPORTING MILESTONES (Continued…)

<table>
<tr><th colspan="3">Futility Analysis</th></tr>
<tr><th colspan="2">Purpose</th><th>Timing/Frequency</th></tr>
<tr><td colspan="2">Assesses interim data to see if the study treatment is unlikely to show benefit.
To stop trials early, saving time, resources, and avoid exposing patients to an ineffective or inferior treatment.</td><td>▪ Usually after 30-70% primary endpoint data accrued and are pre-planned in protocol or SAP.
▪ Typically, once but can have more if the trial duration is long.</td></tr>
<tr><th>Scope/
Key Deliverables</th><th>Key Decisions/
Outcomes</th><th>Key Stakeholders</th></tr>
<tr><td>- Primary endpoint evaluation (e.g., tumour response rate, progression-free survival)
- Secondary endpoints
- Safety data
- Pre-specified statistical thresholds for futility</td><td>✓ Stop the trial for futility - unlikely to meet primary endpoint; halt recruitment and treatment
✓ Continue the trial as planned
✓ modify sample size or design</td><td>• DMC members
• Regulatory Authorities (if needed)</td></tr>
<tr><td colspan="3"><u>Additional details/ Examples:</u>
○ Determines if the trial has a low chance of success -> Is it still worth continuing, or should we stop now?
○ Need not be a separate milestone - can be included within IAs/DMCs.

Example:
Analysis conducted after 30% of enrolled patients had completed at least 2 treatment cycles and Overall Response Rate (ORR) was assessable.
<u>Finding:</u> ORR in treatment vs control was minimal (22% vs 20%), low probability (<10%) of meeting the success criteria (ORR in treatment arm ≥ 40%).
<u>Decision:</u> DMC recommended stopping for futility (lack of efficacy) to avoid exposing additional patients to ineffective treatment and to save resources.</td></tr>
</table>

SAP – Statistical Analysis Plan; IA – Interim Analysis;

TABLE 1.3: ANALYSIS & REPORTING MILESTONES (Continued…)

<table>
<tr><th colspan="3">IA (Interim Analysis)</th></tr>
<tr><th colspan="2">Purpose</th><th>Timing/Frequency</th></tr>
<tr><td colspan="2">A planned evaluation of data collected during a clinical trial, before the final analysis, when ~50% of data accumulated. Conducted to assess safety, efficacy, futility and/or other important data at specific points during the study.</td><td>▪ Scheduled at predefined points, such as after a defined number of patients or events reach a milestone. Often mid-trial (e.g.50% of endpoint data accumulation) must be pre-specified in the protocol or SAP.
▪ Usually 1-2, but depends on the study's complexity, multiple cohorts, long-term studies may have more IAs before final analysis. Ex: IAs for each cohort.</td></tr>
<tr><th>Scope/
Key Deliverables</th><th>Key Decisions/
Outcomes</th><th>Key Stakeholders</th></tr>
<tr><td>- Includes all the collected data up to the data cut - safety, efficacy, PK/PD, Biomarker etc.
- DMC recommendations (if available)</td><td>☐ Continue as planned
☐ Stop early for safety concerns
☐ Stop early for futility (no benefit)
☐ Stop early for efficacy (if results are very positive)
☐ Modify the trial (e.g., change dosage or sample size)</td><td>• DMC members
• Regulatory authorities (if required)
• Principal Investigators (limited/ blinded)
• PK scientist (if needed)</td></tr>
<tr><td colspan="3"><u>Additional details/ Examples:</u>
At a planned interim analysis (after ~50% of patients had received at least 2 cycles and considerable efficacy assessments), it is observed that PFS and ORR in the treatment arm was significantly better than control, crossing the predefined efficacy boundary and recommended stopping the trial early for efficacy to allow earlier patient access to the drug and proceed with regulatory submission.</td></tr>
</table>

TABLE 1.3: ANALYSIS & REPORTING MILESTONES (Continued…)

<table>
<tr><th colspan="3">Patient Profiles
&
Patient Narratives</th></tr>
<tr><th colspan="2">Purpose</th><th>Timing/Frequency</th></tr>
<tr><td colspan="2">Review tools, used to present patient-level information, enabling reviewers to understand patient's journey through the trial.</td><td>▪ Generated throughout the study - during enrollment, DMCs, IAs, DBL (for data cleaning) and CSR (if needed for internal reference).
▪ Final narratives before CSR finalization.</td></tr>
<tr><th>Scope/
Key Deliverables</th><th>Key Decisions/
Outcomes</th><th>Key Stakeholders</th></tr>
<tr><td>- Visual or tabular, structured summaries in chronological order – dashboard style.
- Compiles individual subject's data across domains like AEs, Labs, Vitals, Exposure etc.</td><td>✓ Facilitate data reconciliation
✓ Support data cleaning, clinical monitoring
✓ Internal safety review and usually not submitted</td><td rowspan="2">• Regulatory Medical Writing (RMW)
• Pharmacovigilance/ Safety
• Medical monitors
• Narratives: Regulatory Authorities</td></tr>
<tr><td>- Descriptive, text-based summaries – story telling.
- Focus on specific clinical events like SAEs, Deaths, Discontinuations etc.
- Summary table with subjects meeting the criterions and individual narratives.</td><td>✓ Support external audit or inspection queries along with internal reviews, for Quality Assurance (QA).
✓ Final Narratives are included in the CSR as a part of regulatory submissions to support safety evaluation.</td></tr>
<tr><td colspan="3"><u>Additional details/ Examples:</u>
○ Profiles display a time-sequenced summary of patient data, to visualize the patient's clinical journey from initial screening to last contact.
○ Narratives are criteria based. Focuses on event description, context, and causality.

Patient Profiles example requests:
○ Medical monitor wants to review subjects with Grade ≥3 AEs.
○ DMC requests profiles for subjects with early discontinuation.

Patient Narratives example requests:
Please generate narratives for the patients meeting any of the following criteria:
1) Experienced a Serious Adverse Event (SAE).
2) Discontinued from study drug due to an AE.
3) Died during the study.</td></tr>
</table>

CSR – Clinical Study Report.

TABLE 1.3: ANALYSIS & REPORTING MILESTONES (Continued…)

<table>
<tr><th colspan="3">CSR (Clinical Study Report)</th></tr>
<tr><th colspan="2">Purpose</th><th>Timing/Frequency</th></tr>
<tr><td colspan="2">A formal, comprehensive document that presents the design, methods, statistical analyses, and provides complete results of a clinical trial.
It supports regulatory decisions on drug approval and labeling.</td><td>▪ Prepared after the database lock
▪ Should be finalized no later than one year of LPLV (last patient last visit)
▪ Typically, one CSR per study, however for example, if a study has multiple cohorts, each cohort may have its own CSR.</td></tr>
<tr><th>Scope/
Key Deliverables</th><th>Key Decisions/
Outcomes</th><th>Key Stakeholders</th></tr>
<tr><td>- Includes all the collected data safety, efficacy, PK/PD, Biomarker etc.
- EMA focusing on EU population, but accepts global data
- PMDA, focusing on Japan population, but accepts global data</td><td>✓ Approval/Rejection of the new drug
✓ Basis for labelling and prescribing information
✓ May be used for publications, scientific exchange or further research</td><td>• Regulatory Medical Writing (RMW)
• PK and Translational Research scientists
• Pharmacovigilance/ Safety
• Regulatory Affairs
• QA compliance
• Regulatory Authorities</td></tr>
<tr><td colspan="3"><u>Additional details/ Examples:</u>
○ CSR is a core document required by all major regulatory authorities as part of submission i.e. for EMA - Market Authorization Application (MAA), for FDA - New Drug Application (NDA)/ Biologics License Application (BLA), and Japanese NDA for PMDA in Japanese language.
○ FDA review timelines - Typically 6-12 months based on priority. Initial feedback, queries in first 2-3 months.</td></tr>
</table>

PMDA – Pharmaceuticals and Medical Devices Agency; EU - European Union.

TABLE 1.3: ANALYSIS & REPORTING MILESTONES (Continued…)

<table>
<tr><th colspan="3">Sensitivity Analysis</th></tr>
<tr><th colspan="2">Purpose</th><th>Timing/Frequency</th></tr>
<tr><td colspan="2">A method to check if clinical trial results remain consistent when the analysis is done using different approaches or assumptions. Ensures the reliability and robustness of the study conclusions.</td><td>▪ Conducted after primary analysis is completed.
▪ Typically, once per study, but may be repeated in response to regulatory queries or during submission preparation.</td></tr>
<tr><th>Scope/
Key Deliverables</th><th>Key Decisions/
Outcomes</th><th>Key Stakeholders</th></tr>
<tr><td>- Perform alternative analyses (e.g. different populations, censoring rules, missing data handling)
- Compare with primary analysis results to check robustness
- Summarize findings in CSR or appendices
- Support responses to Health Authority Questions (HAQs)</td><td>✓ Confirms whether conclusions remain consistent across scenarios
✓ Identify potential biases or limitations in the primary analysis
✓ Support regulatory submissions
✓ Build confidence for publications</td><td>• Regulatory Medical Writing (RMW)
• Regulatory Authorities</td></tr>
<tr><td colspan="3"><u>Additional details/ Examples:</u>
○ Not a formal milestone, but a statistical activity, may be incorporated within other key milestones.

Example:
Primary analysis using LOCF to impute missing data.
Perform Sensitivity Analysis using BOCF - assuming that if a patient dropped out, their HbA1c stayed the same as baseline (i.e., no improvement).
If the results still show effectiveness, confirming robustness of result.</td></tr>
</table>

LOCF – Last Observation Carried Forward; BOCF – Baseline Observation Carried Forward.

TABLE 1.4: SAFETY REPORTING MILESTONES

<table>
<tr><th colspan="3">DSUR
(Development Safety Update Report)</th></tr>
<tr><th colspan="2">Purpose</th><th>Timing/Frequency</th></tr>
<tr><td colspan="2">Annual report summarizing cumulative safety data from all ongoing clinical trials of an investigational drug, providing a comprehensive safety profile and support ongoing benefit–risk evaluation during clinical development.</td><td>▪ Submitted annually, based on Development International Birth Date (DIBD).
▪ Continues until the last patient’s last visit in the final study.</td></tr>
<tr><th>Scope/
Key Deliverables</th><th>Key Decisions/
Outcomes</th><th>Key Stakeholders</th></tr>
<tr><td>- Exposure, AEs, SAEs, SUSARs and other safety data
- Evaluation of identified and potential risks, safety signals
- Efficacy data</td><td>✓ Continue, modify, or halt development
✓ Communicate emerging risks to sites
✓ Amend RMP, update IB or protocols
✓ Benefit-risk assessment</td><td>• Regulatory Medical Writing (RMW)
• Pharmacovigilance/ Safety
• Regulatory Authorities</td></tr>
<tr><td colspan="3"><u>Additional details/ Examples:</u>
○ Compound level activity
○ Development International Birth Date (DIBD) is the date when the sponsor first gets regulatory authorization to conduct a clinical trial in any country worldwide.

DSUR example statements:
<u>Conclusion</u>: Cumulative safety data from ongoing trials show a consistent safety profile with no new significant signals. Three cases of pneumonitis were observed and will be monitored. Preliminary efficacy remains encouraging.
<u>Outcome</u>: Benefit–risk remains favourable; studies continue as planned with ongoing safety monitoring.</td></tr>
</table>

TABLE 1.4: SAFETY REPORTING MILESTONES (Continued…)

<table>
<tr><th colspan="3">PSUR (Periodic Safety Update Report)/
PBRER (Periodic Benefit-Risk Evaluation Report)</th></tr>
<tr><th colspan="2">Purpose</th><th>Timing/Frequency</th></tr>
<tr><td colspan="2">PSUR: Periodic summary of safety data from clinical trials (if ongoing) and real-world use (post-marketing). Focusing on new safety data from specific reporting period.

PBRER: Similar to PSUR, but it has a broader scope, providing a detailed comprehensive benefit–risk assessment.</td><td>▪ Every six months for first two years after post-marketing, then annually.</td></tr>
<tr><th>Scope/
Key Deliverables</th><th>Key Decisions/
Outcomes</th><th>Key Stakeholders</th></tr>
<tr><td>- Exposure, AEs, SAEs, SUSARs and other safety data
- Evaluation of identified and potential risks, safety signals
- PBRER: Efficacy data</td><td>✓ Continue safety monitoring
✓ Communicate emerging risks to sites/regulators
✓ Amend RMP, update IB or protocols
✓ PBRER: Benefit-risk assessment</td><td>• Regulatory Medical Writing (RMW)
• Pharmacovigilance/ Safety
• Regulatory and Medical Affairs
• Regulatory Authorities</td></tr>
<tr><td colspan="3"><u>Additional details/ Examples:</u>
○ Both are compound level activities. PSUR primarily summarizes new safety data from the latest reporting interval, with limited cumulative context, while the PBRER integrates both interval and cumulative data to deliver a comprehensive evaluation of the product's benefit–risk profile.
○ The PBRER evolved from the PSUR format after global harmonization (ICH E2C R2) in 2012.

PSUR example statements:
<u>Conclusion:</u> During the current reporting interval, 12 new cases of drug-induced pancreatitis were identified, including 3 fatalities. The cumulative evidence suggests a causal relationship.
<u>Outcome:</u> Regulatory authorities recommend temporary suspension of the product pending further investigation. The sponsor must submit a revised Risk Management Plan and initiate a targeted safety study.

PBRER example statements:
<u>Conclusion</u>: Cumulative Overall Survival benefit (24.1 vs 18.7 months); new pneumonitis risk (0.3%) identified; overall benefit–risk remains favourable.
<u>Outcome</u>: Benefit–risk balance remains positive; labelling updated to include new pneumonitis risk.</td></tr>
</table>

ICH – International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use;

E2C – Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs;

R2 - The second revision of the E2C guideline, finalized in 2012, which introduced the PBRER format.

TABLE 1.5: SUBMISSION PREPARATION & REVIEW MILESTONES

<table>
<tr><th colspan="3">SCS/SCE
(Summary of Clinical Safety/Efficacy)
&
ISS/ISE
(Integrated Summary of Safety/Efficacy)</th></tr>
<tr><th>Purpose</th><th colspan="2">Timing/Frequency</th></tr>
<tr><td>SCS/SCE: Detailed safety/efficacy summary from a specific clinical trial or a subset of trials.</td><td colspan="2">▪ Prepared at the end of trial, before CSR finalization.
▪ Usually once per study, though interim SCS/SCE may be prepared for regulatory reporting.</td></tr>
<tr><td>ISS/ISE: Comprehensive summaries of safety/efficacy data across all clinical trials for an investigational product.</td><td colspan="2">▪ Prepared at submission stage after all trials are completed. i.e. CSR finalized for all studies.
▪ Once per compound for submission
▪ Updated if new studies are completed before submission.</td></tr>
<tr><th>Scope/
Key Deliverables</th><th>Key Decisions/
Outcomes</th><th>Key Stakeholders</th></tr>
<tr><td>- AEs, SAEs, lab abnormalities and other safety
- Primary and secondary efficacy endpoints
- ISS/ISE: Pooled data, integrated analyses, aggregate incidence, exposure-adjusted event rates</td><td>✓ Support regulatory review and helps in preparing the full CSR.
✓ Approval or rejection of the drug by regulatory authorities like the FDA or EMA.</td><td>• Regulatory Affairs
• Safety
• Medical Monitor
• PK and Translational Research Scientist (If PK and Biomarker endpoints are included)</td></tr>
<tr><td colspan="3"><u>Additional details/ Examples:</u>
○ Both SCS/SCE and ISS/ISE provide summarized and interpretive narratives of safety and efficacy – clinical meaning, relevance and context, data interpretation and conclusions.
○ SCS/SCE: Descriptive, high-level for internal review, IB updates, protocol amendments, regulatory submissions.
○ ISS/ISE: Quantitative, factual statistics (all completed clinical trials, sometimes including ongoing studies), required for marketing applications (NDA/BLA/MAA).

<u>Example SCS text:</u>
Across the clinical program, 12 cases of severe neutropenia were reported. Most occurred within the first two cycles. No deaths were associated with these events. Overall, the SAE profile was clinically acceptable and manageable with supportive care.

<u>Example ISS text:</u>
In the pooled population (N=1,250), Grade ≥3 neutropenia occurred in 9.6% of patients in the treatment arm vs 3.1% in control (Risk Difference: 6.5%; 95% CI: 3.8–8.9). Median onset was 14 days, with higher incidence in patients ≥65 years (12.2%).</td></tr>
</table>

TABLE 1.5: SUBMISSION PREPARATION & REVIEW MILESTONES (Continued…)

<table>
<tr><th colspan="3">BIMO
(Bioresearch Monitoring)</th></tr>
<tr><th colspan="2">Purpose</th><th>Timing/Frequency</th></tr>
<tr><td colspan="2">An FDA program that performs monitoring activities (inspection, audit and reviews) to ensure data quality, accuracy, and compliance in clinical trials.</td><td>▪ BIMO inspections typically occur at submission review phase; often after submission but before final approval.</td></tr>
<tr><th>Scope/
Key Deliverables</th><th>Key Decisions/
Outcomes</th><th>Key Stakeholders</th></tr>
<tr><td>- Comply with standards
- Define.xml
- Reviewer's guides (ADRG, SDRG)
- Pinnacle21
- Analysis Results Metadata (ARM) [not mandatory]</td><td>✓ Confirmation that data standards and FDA submission requirements are met
✓ Confirming the transparency, traceability and reproducibility of results
✓ Impacts FDA's decision to approve or reject</td><td>• Regulatory Authorities (FDA BIMO team)
• QA/Compliance team
• Regulatory Affairs</td></tr>
<tr><td colspan="3"><u>Additional details/ Examples:</u>
○ Not every trial is inspected — FDA selects based on risk, importance of study, data anomalies, or sponsor's compliance history.
○ Inspections can also occur during trial conduct if issues are suspected.
○ ARM (Analysis Results Metadata), Define.xml, ADRG, SDRG, and Pinnacle21 checks are not milestones by themselves, but are essential components of the submission preparation process, alongside key milestones such as ISS/ISE and SCS/SCE.

Example:
<u>Finding</u>: The define.xml file specified units for the variable WEIGHT as "kg", while the metadata documentation indicated "lbs".
<u>Action</u>: Review and Update the Define.xml File - ensure that all variables are correctly defined, with accurate descriptions, formats, and units.</td></tr>
</table>

ADRG - Analysis Data Reviewer's Guide; SDRG - Study Data Reviewer's Guide.

TABLE 1.5: SUBMISSION PREPARATION & REVIEW MILESTONES (Continued…)

<table>
<tr><th colspan="3">HAQs/IRs
(Health Authority Questions/
Information Requests)</th></tr>
<tr><th colspan="2">Purpose</th><th>Timing/Frequency</th></tr>
<tr><td colspan="2">Regulatory Agencies raise questions when needing clarifications, and requests for additional data, analysis, to complete regulatory review/assessment.</td><td>▪ Post submission review phase
▪ Sometimes IRs can also occur pre-submission – specific queries, less formal.
▪ Ad-hoc questions/requests</td></tr>
<tr><th>Scope/
Key Deliverables</th><th>Key Decisions/
Outcomes</th><th>Key Stakeholders</th></tr>
<tr><td>- Submitted data, analyses
- HAQs: Respond to formal regulatory questions post-submission
- IR: Clarify specific data, analysis or document related queries requested by authority</td><td>✓ Support regulatory review
✓ May trigger additional tables, narratives and analysis</td><td>• Regulatory Affairs
• Pharmacovigilance/Safety
• Regulatory Authorities
• PK scientists/ Translational Research (if needed)</td></tr>
<tr><td colspan="3"><u>Additional details/ Examples:</u>
HAQ example:
Original Analysis (CSR) presented overall response rate (ORR) for overall and by gender.
i.e. ORR overall: 55% and ORR by gender: Male 53%, Female 57%
FDA request: Please provide ORR by age <65 vs ≥65, including 95% CI and p-values.

IR example:
Original Analysis (CSR) reported TEAEs by grade and SOC.
i.e. Most common ≥Grade 3 AE: neutropenia, 48%
FDA request: Provide a breakdown of Grade ≥3 neutropenia by age subgroup (<65 vs ≥65) and by baseline renal function (normal v/s impaired).</td></tr>
</table>

TEAEs – Treatment Emergent Adverse Events; SOC – System Organ Class;

TABLE 1.6: DISCLOSURE & PUBLICATIONS

<table>
<tr><th colspan="3">Medical and Scientific Societies</th></tr>
<tr><th colspan="2">Purpose</th><th>Timing/Frequency</th></tr>
<tr><td colspan="2">Professional organizations that bring together clinicians, researchers, regulators, and patients within a specific medical domain or disease area. Hubs for scientific exchange and collaboration.</td><td>▪ Ongoing trials should go for these annual or biennial exchanges.</td></tr>
<tr><th>Scope/
Key Deliverables</th><th>Key Decisions/
Outcomes</th><th>Key Stakeholders</th></tr>
<tr><td>- Publication ready outputs.
- Abstracts, posters, manuscripts and presentations by Clinical/Medical writing team.</td><td>✓ Disseminate clinical trial results
✓ Education and training for healthcare professionals
✓ Clinical guidelines & policy advocacy
✓ Journal publications
✓ Feedback may lead to additional analyses, protocol/IB/RMP updates, or influence future study designs.</td><td>• Healthcare professionals
• Regulators and Policymakers
• Clinical researchers
• Patients</td></tr>
<tr><td colspan="3"><u>Additional details/ Examples:</u>
○ Clinical/Medical Affairs to decide as to which society and at what stage of the trial. Example:
IMS - early in the phase I to share disease-specific exploratory data.
ASH - to share phase II safety.
ASCO - pivotal phase III data targeting broad oncology and regulatory audiences.

○ Sometimes feedback from such scientific societies, discussions may also trigger changes to the analysis methods. For example:
Original analysis - ORR reported for the overall efficacy population but no detailed subgroup analysis was performed.
Feedback suggested - High risk patients may respond differently, and the FDA may be interested in seeing ORR by cytogenetic risk.
Leading to addition of ORR analysis by subgroup cytogenetic risk (standard v/s high-risk).

○ Medical and Scientific societies are generally specific to therapeutic areas; below is a list of a few for quick reference-
American Society of Clinical Oncology (ASCO)
European Society for Medical Oncology (ESMO)
American Society of Haematology (ASH)
European Haematology Association (EHA)
International Myeloma Society (IMS)
American College of Cardiology (ACC)
European Society of Cardiology (ESC)</td></tr>
</table>

TABLE 1.6: DISCLOSURE & PUBLICATIONS (Continued…)

ClinicalTrials.gov & EudraCT (European Union Drug Regulating Authorities Clinical Trials)	
Purpose	**Timing/Frequency**
Public clinical trial **databases** for registering study protocols and **disclosing summary results in simple, layman-friendly language**. Promote transparency and ensure **public access** to clinical trial data.	▪ **Initial registration:** Before first patient is enrolled (or within 21 days of enrollment start in the U.S.). ▪ **Updates:** As needed (e.g., status changes, protocol amendments). ▪ **Results posting:** - For ClinicalTrials.gov, typically within 12 months of primary completion date (PCD). - For EudraCT, within 12 months of End of study (LPLV).

Scope/ Key Deliverables	Key Decisions/ Outcomes	Key Stakeholders
- Summary-level results in XML format: participant flow, baseline data, outcomes, adverse events - Ensure outputs align with CSR	✓ Compliance with regulatory requirements ✓ Ethical disclosure of study results ✓ Supports publications, journals and further research	• Regulatory Medical Writers (RMW) • Regulatory affairs • Clinical Operations • Principal Investigator

Additional details/ Examples:

- ClinicalTrials.gov: U.S. based registry managed by the National Library of Medicine (NLM), part of National Institutes of Health (NIH).
- EudraCT: EU registry managed by the European Medicines Agency (EMA).
- Similar Clinical trial registries exist in other countries as well like Japan, China, India and are recognized by WHO.
- Primary completion date (PCD): Date when data collection for the primary endpoint is finished for all participants.
- Statistical programmers are involved only at Disclosure/Results posting. No role at registry/updates.
- Links:
  https://clinicaltrials.gov/
  https://eudract.ema.europa.eu/

XML - Extensible Markup Language; WHO - World Health Organization.

DELIVERABLES, DECISIONS AND STAKEHOLDERS – AT A GLANCE

Below is a consolidated list of key deliverables, decisions, and stakeholders across all milestones discussed in this paper, presented here for quick reference.

Scope/ Key Deliverables

- Safety and Efficacy results
- Risks and Safety signals – new AEs, SAEs, SUSARs
- Monitor SAEs, AESIs, Lab abnormalities, Deaths and Discontinuations
- Exposure-response, Dose limiting Toxicities (DLTs)
- PK/PD results
- Data Quality & Integrity
- DMC/DRC Charters & Slides from Clinical
- Futility analysis
- Validate Key endpoints
- Review of NDA/BLA/MAA submissions
- Patient-level structured and text-based summaries
- Study and Safety Reports from Medical writing
- Integrated summaries
- Define.xml, Pinnacle21
- Reviewer's guides (ADRG), Analysis Results Metadata (ARM)
- Standards Compliance
- Robustness of results
- Summary level results in .xml format
- Publication ready outputs
- Periodic safety and benefit-risk assessments

Key Decisions/ Outcomes

- ✓ Recommendations from DRC/DMC/IA;
  - ☐ No action. The study should continue as planned
  - ☐ Modify the study design (e.g., dose adjustments)
  - ☐ Discontinue the ongoing study
    - Stop early for safety concerns
    - Stop early for futility (no benefit)
    - Stop early for efficacy (if results are very positive)
  - ☐ Recommended Phase 2 Dose (RP2D)
- ✓ IB serves as a Key resource for Investigators
- ✓ Risk minimization decisions
- ✓ Updates to the product label (new warnings etc.)
- ✓ Maximum Tolerated Dose (MTD)
- ✓ Facilitate data reconciliation, internal reviews, external audit or inspection queries
- ✓ Final confirmation or rejection of suspected events
- ✓ Recommend approval, rejection, label updates or further studies to the health authorities (FDA, EMA)
- ✓ Confirmation that data standards and FDA submission requirements are met
- ✓ Approval/Rejection of the new drug
- ✓ Confirms whether conclusions remain consistent
- ✓ Build confidence for publications
- ✓ Ethical disclosure of study results
- ✓ Publications, journals, Conferences and further research, education and training for healthcare professionals
- ✓ Long term safety

Key Stakeholders

Figure 2: Statistical Programmers collaborate with Biostatistics and Clinical teams, supporting cross-functional teams and delivering milestones to healthcare professionals, committees and regulatory bodies.

CONCLUSION

Statistical programmers, through the development of analysis datasets, tables, listings, and graphs, contribute to a wide range of decision-making milestones and play a key role in the clinical development process. Understanding each milestone — its purpose, scope, timing, and stakeholders — provides insight into how our work supports key decisions, regulatory submissions, and ultimately, patient care. Keeping the bigger picture in view helps us practice the “begin with the end in mind” principle, better align with stakeholders, and contribute meaningfully to the success of every clinical trial.

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