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Early Restricted Unblinded PK Data Access (ERUPA): A Data-Centric, Firewalled Framework to Accelerate PopPK and ERES Deliverables

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ABSTRACT

Population PK (PopPK) and exposure–response (ERES) deliverables are frequently on the regulatory critical path, and programming bottlenecks around data access, specifications, and traceability can jeopardize accelerated submission timelines. ERUPA (Early Restricted Unblinded PK Data Access) and ESAP (Earlier SDTM/ADaM Access for PK and ERES) are AstraZeneca frameworks designed to front-load pharmacometric data preparation by providing restricted early access to unblinded PK and key baseline covariates and by prioritizing post-lock delivery of PK/ERES SDTM/ADaM datasets.

This paper describes ERUPA and ESAP specifically from a pharmacometric-programming viewpoint. We outline how CPQP programmers operate inside a GxP firewalled environment; how harmonized PK data standards, PMx DaRT (Data Request Tool), and a standardized R/NONMEM ecosystem (MeRGE) reduce ambiguity and rework; and how timeline templates translate into day-by-day programming tasks. highlighting practical controls for data integrity, accidental unblinding, and documentation in the Trial Master File (TMF).

The goal is to provide a concrete playbook for pharmacometric programmers who need to deliver high-quality NONMEM-ready datasets and CRT packages under aggressive CDL-to-submission timelines, while maintaining study integrity and regulatory compliance.

INTRODUCTION

Regulatory expectations and portfolio growth are putting unprecedented pressure on pharmacometric workflows. AstraZeneca's 2030 ambition anticipates more submissions, shorter timelines, and sustained quality, making PopPK and ERES reports increasingly critical to overall submission readiness. Historically, pharmacometric programmers faced several recurring pain points:

- Late access to PK and covariate data, often only after Clinical Data Lock (CDL)
- Ambiguous or bespoke dataset specifications that require multiple iterations
- Non-standardized NONMEM datasets and code, leading to extensive QC and rework
- Manual and inconsistent CRT packaging for regulatory submission

ERUPA and ESAP were introduced as part of a broader initiative to transform pharmacometric processes from document-centric to data-centric operations, leveraging standardization, automation, and connected end-to-end workflows. ERUPA provides early, restricted access to unblinded PK concentrations and prespecified baseline covariates, while ESAP accelerates SDTM/ADaM delivery post-CDL for PK and ERES domains.

From a programming perspective, this transformation is less about "access to data" and more about how data are specified, stored, transformed, traced, and packaged under GxP constraints. This paper focuses on that programming lens.

ERUPA AND ESAP FROM A PROGRAMMER'S PERSPECTIVE

ERUPA: Early Restricted Unblinded PK Data Access

ERUPA is a controlled process that enables early access to unblinded PK concentrations and a targeted set of covariates such as demographics, dosing, and selected laboratory values, explicitly excluding safety and efficacy endpoints. The early data cut is transferred into a restricted area of the Clinical Data Repository (CDR), accessible only to named individuals in the ERUPA Charter. CPQP programmers within this firewalled team generate pharmacometric analysis-ready datasets (e.g., NONMEM input) to support pre-CDL PopPK modeling and report drafting.

Key characteristics for programmers:

- Data arrive via restricted SDTM/ADaM transfers into dedicated restricted folders.
- Randomization information is only visible inside the firewalled environment.
- Any outputs (datasets, logs, scripts) must remain within restricted locations.

ESAP: Earlier SDTM/ADaM Access for PK and ERES

ESAP focuses on post CDL operations: SDTM/ADaM datasets for PK and ERES are prioritized and refreshed with final data, typically no later than day 5 post CDL. This allows programmers to:

- Re run dataset creation scripts with final data
- Update NONMEM analysis-ready datasets
- Finalize CRT packages within the shorter submission window

ERUPA and ESAP turn pharmacometric programming into a two-phase effort: heavy front loading during ERUPA, followed by execution mode refinement after CDL.

Combined Operational Value

Together, ERUPA and ESAP achieve:

- Removal of PopPK from critical path
- Seamless transition from pre-CDL modeling to rapid post-CDL ERES analyses
- Submissions as soon as six weeks post-CDL
- Improved planning reliability and better resource forecasting

These efficiencies strongly align with modern regulatory expectations for data traceability, reproducibility, and lifecycle transparency.

GOVERNANCE AND STUDY INTEGRITY SAFEGUARDS

Maintaining scientific integrity and preventing bias during early access to unblinded PK data are principal priorities of ERUPA. Governance includes:

GxP Compliance & SOP-Driven Controls

- Formal ERUPA charter documenting roles, responsibilities, constraints, and escalation requirements.
- Role-based access controls ensuring only designated individuals access unblinded data.
- Secure, audit-trailed restricted folders in clinical data repositories.

Blinding Integrity Safeguards

- No post-baseline safety or efficacy variables are included in ERUPA transfers.
- Clear communication restrictions between blinded and unblinded teams.
- Accidental unblinding triggers immediate notification and quality event handling.

Data Representativeness Requirements

- ERUPA requires a minimum ~75% representativeness of PK data at data cut-off (DCO).
- PopPK analyses are designed to be resilient to up to 33% missing pivotal study data.

PROGRAMMING ROLES, GOVERNANCE, AND FIREWALLING

Role of the CPQP Programmer

Within the ERUPA/ESAP framework, the CPQP programmer is responsible for:

- Collaborating with the pharmacometrician to finalize dataset specifications.
- Creating and maintaining restricted folders and transfer areas in the CDR.
- Receiving unblinded SDTM/ADaM PK datasets and producing NONMEM ready datasets.
- Ensuring no unblinded data leave restricted locations or flow back to blinded teams.
- Providing datasets and metadata required for CRT packaging.

These responsibilities are codified in the internal AstraZeneca guidance “Preparing ERUPA Pharmacometric Analysis ready Datasets for Programming Team” and linked SOPs for early unblinded analyses and study blinding/unblinding.

Training, Authorization, and TMF Documentation

Unblinded programmers must:

- Complete ERUPA training, including the ERUPA Handbook, ERUPA Charter, and relevant SOPs.
- Sign an authorization memo acknowledging obligations to maintain confidentiality, which is then filed in the TMF.
- Understand communication rules with blinded team members and the use of the shadow communication team for any study level questions.

The “Pharmacometric Analyses of Early Unblinded Clinical Trial Data” SOP provides further details on governance of early unblinded analysis and alignment with Study Integrity Plans.

Managing Accidental Unblinding

In the rare event that potentially, unblinding information is disclosed to unauthorized personnel:

- The Programming Manager must be informed immediately.
- The incident is documented without further unblinding the project team.
- A quality event is raised in the Quality Events Management System.
- The affected individual may be removed from blinded activities.

These processes protect both study integrity and the credibility of ERUPA/ESAP as compliant mechanisms for accelerated analysis.

DATA STANDARDS AND SPECIFICATIONS FOR ERUPA

Harmonized Raw PK Data Model

A cross functional workstream established a harmonized raw PK data model for new studies, with a migration strategy for legacy datasets. For programmers, this means:

- Consistent structures for PC/ADPC domains and related covariate datasets
- Reusable mapping logic across compounds and studies
- Simplified QC and easier cross study pooling

PMx DaRT: From Concept to Dataset Specifications

PMx DaRT (Data Request Tool) is a browser based application that:

- Generates data specifications from predefined therapy area and analysis type templates.
- Supports real-time tracking of dataset timelines and resource assignments.
- Integrates with clinical trial metadata to auto populate study identifiers and key attributes.
- Provides audit ready issue logs, validation logs, and template SAS programs.

For pharmacometric programmers, DaRT moves the conversation from “what do you want in the dataset?” to “which standard template variant do we apply and how do we tailor it?”, reducing ambiguity and speeding consensus.

Standardized NONMEM Dataset Design

Using the harmonized raw PK model and PMx DaRT specifications, ERUPA encourages a common NONMEM input structure, for example:

- Core variables: ID, TIME, DV, AMT, EVID, CMT, MDV, WT, SEX, AGE, renal/hepatic covariates
- Standardized event handling for dose vs observation records
- Consistent handling of below LLOQ data, imputation strategies, and flags

While exact structures are tailored per program, the key idea is **reusable code** in the MeRGE ecosystem rather than bespoke one-off data steps for each study.

ERUPA PROGRAMMING WORKFLOW: STEP-BY-STEP

The ERUPA programming guidance lays out a clear, repeatable workflow.

1. Set Up Restricted Infrastructure

- Create restricted CDR folders for ERUPA SDTM/ADaM and NONMEM datasets.
- Configure permissions such that only chartered unblinded roles (programmers, pharmacometricians, selected Clinical Pharmacology and Quantitative Pharmacology (CPQP) scientists) have access.

2. Receive ERUPA SDTM/ADaM Data Cut

- Data Management and Analysis and Reporting (A&R) vendor deliver QA’d PK and covariate data per the agreed early DCO (~4 months pre-CDL).
- For external A&R models, the vendor supplies unblinded SDTM/ADaM PK datasets directly to the restricted area.
- For internal models, Biometrics provide blinded SDTM/ADaM while randomization codes are sent separately to the unblinded programming team, who then unblind in the restricted area.

3. Build Pharmacometric Analysis Ready Datasets

- Apply PMx DaRT generated specifications to derive NONMEM ready datasets.
- Implement standard derivations:
    - Baseline covariates (e.g., baseline creatinine, baseline body weight)
    - Time varying covariates as needed
    - Treatment arm derivation using randomized assignments
- Store all intermediate and final datasets in restricted folders only.

4. Transfer to Pharmacometrician

- Use the designated Transfer Area to provide NONMEM datasets to the pharmacometrician.
- Ensure all filenames and versioning follow CRT/eData naming standards to avoid downstream re-labeling.

5. Iterate and Document

- Capture any dataset issues in the audit ready issue log, linking them to source data and resolution steps.
- Update specifications and scripts under version control (e.g., GitHub within MeRGE).
- File the authorization memo, key programming notes, and deviations in the TMF as per guidance.

TIMELINES: THE SHORTENED SUBMISSION WINDOW THROUGH A PROGRAMMER'S LENS

The ERUPA/ESAP Timeline Template provides a detailed sequence of activities by function. Below is a condensed view focusing on CPQP programming:

- **15–18 months before CDL**
    - Initial ERUPA discussions at study kick-off; confirm whether A&R support is internal or external.
- **14–12 months before CDL**
    - CPQP Kick-Off; finalize CPQP strategy for PopPK/ERES.
    - Programmer collaborates on dataset specifications and restricted folder setup; ERUPA Charter drafted.
- **~4 months before CDL (ERUPA DCO)**
    - DM and iBA ensure QA'd PK data and header reconciliations are complete.
    - ERUPA raw data transfer and generation of unblinded SDTM/ADaM PK datasets.
- **30–20 business days before CDL**
    - CPQP programmer prepares NONMEM ERUPA datasets and transfers to pharmacometrician.
    - First and second drafts of PopPK model/report are developed using ERUPA datasets.
- **0–6 business days after CDL**
    - Final SDTM/ADaM delivered; programmer refreshes analysis ready datasets for PopPK and ERES.
- **10–20 business days after CDL**
    - Final PopPK and ERES models and reports are completed.

- Programmer supplies datasets and metadata for CRT package; CRT is submitted by day 21 postCDL.

This timeline enforces front-loading: most of the heavy programming and model-building work happens pre-CDL, so post-CDL activities are primarily updates and verification.

PRACTICAL LESSONS FOR PHARMACOMETRIC PROGRAMMERS

From early implementations and the broader pharmacometric process transformation, several key lessons have emerged:

1. **Invest in Standardization Early**
   Harmonized PK data models and specification templates pay off by enabling reusable code, easier QC, and smoother cross study comparisons.
2. **Treat ERUPA as a GxP Process, Not Just "Early Access"**
   Restricted folders, documented training, authorization memos, and strict communication rules are non-negotiable to maintain study integrity.
3. **Use PMx DaRT and MeRGE as Core Tooling**
   Automating the link from specification → dataset → model → TLF → CRT is the only way to scale under 6-week timelines.
4. **Document Everything for Auditability**
   Issue logs, validation logs, TMF documents, and Git history together provide a robust audit trail from raw data to regulatory submission.
5. **Collaborate Continuously with Pharmacometricians and Biometrics**
   Frequent, structured touchpoints (within firewall rules) minimize last-minute surprises and rework when specifications evolve.

RESULTS AND IMPACT

Across multiple program implementations, ERUPA + ESAP have demonstrated:

- **Substantial reduction** in CDL to submission timelines (achieving 6week delivery)
- **Higher quality** via standardized models, datasets, and CRTs
- **Efficiency gains** through reusable codebases and automated workflows
- **Improved audit readiness** due to harmonized standards and governance
- **Better scientific preparedness**, enabling early interrogation of PK trends and exposure response hypotheses

CONCLUSION

ERUPA and ESAP represent more than process tweaks; they are core enablers of a datacentric, automation ready pharmacometric ecosystem. For programmers, they bring clear standards, defined roles, and predictable timelines, but also demand rigorous adherence to GxP and blinding governance.

By combining harmonized PK data standards, PMx DaRT driven specifications, a standardized R/NONMEM environment (MeRGE), and the detailed ERUPA programming guidance, CPQP programmers can deliver high quality NONMEM ready datasets and CRT packages within six weeks of

CDL. This paper offers a practical blueprint for pharmacometric programming teams seeking to implement similar frameworks in their own organizations.

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