STANDARDIZING EXPOSURE-RESPONSE DATA FOR MODELING AND SIMULATION USING CDISC PRINCIPLES AND {admiral}

Jeffrey Dickinson
Navitas Life Sciences
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Website LinkedIn

THE NEED FOR STANDARDIZED EXPOSURE-RESPONSE DATA

- **Challenges in ER Data Preparation**

  Inconsistent naming, limited variables, and heterogeneous data structures hinder reproducibility and regulatory review.

- **Benefits of Standardization**

  Harmonized ER data structures improve reproducibility, reduce errors, and enable the reuse of code and templates across studies.

- **Integration with Modern Tools**

  Standardized data facilitates use of pharmaverse tools for automated dataset construction, validation, and export.

- **Regulatory Alignment**

  Consistent naming and traceable data lineage ensure clarity and compliance with regulatory expectations.

BUILDING ON CDISC FOUNDATIONS FOR ER STANDARDIZATION

- **Leveraging CDISC Foundations**

  Existing CDISC models provide principles for consistent, analysis-ready ER dataset structures, even without official ER standards.

- **Time Alignment and Parameter Coding**

  The SDTM-PK guide supports handling time variables and parameter coding, aiding ER exposure window calculations.

- **Metadata Traceability and Automation**

  Emphasizing metadata traceability ensures clear documentation and supports automation tools to reduce errors and improve regulatory readiness.

- **ADaM Adaptation for ER Needs**

  ADaM conventions can be adapted to ER analyses, handling complex parameters and supporting subject and event-level records effectively.

OVERVIEW OF THE FOUR-DATASET ER FRAMEWORK

- **Foundational Dataset ADER**

  ADER provides 20 exposure metrics and 13 baseline covariates, enabling consistent exposure representation across analyses.

- **Efficacy Dataset ADEE**

  ADEE aligns exposure metrics with time-to-event efficacy parameters supporting survival models and event tracking.

- **Safety Dataset ADES**

  ADES integrates subject-level and event-level adverse event data capturing severity, relationship to drug, and timing.

- **Tumor-Response Dataset ADTRR**

  ADTRR supports longitudinal tumor-response modeling with lesion size, best response, and RECIST-aligned variables.

IMPLEMENTING ER STANDARDS USING THE PHARMAVERSE ECOSYSTEM

- **Standardized ER Framework**
  pharmaverse ecosystem offers validated modular functions for Exposure–Response dataset construction aligned to ADaM standards.
- **Advanced Oncology Data Tools**
  {admiralonco} provides tools for tumor size baselines, percent changes, and RECIST category derivations for oncology analysis.
- **Metadata Compliance Tools**
  Tools like {metacore} and {xportr} ensure regulatory compliance with automated specification checks and define.xml alignment.
- **Collaborative and Reproducible Workflow**
  Community-driven pharmaverse tools enable reproducible, version-controlled scripts promoting cross-team consistency and innovation.

BENEFITS OF STANDARDIZING ER DATA STRUCTURES

- **Operational Efficiency Gains**

  Standardizing ER data reduces redundant derivations and harmonizes variables for faster data analysis.

- **Improved Reproducibility**

  Consistent data templates allow reuse of analysis scripts, minimizing errors and inconsistencies.

- **Regulatory Clarity**

  Transparent data lineage and metadata adherence strengthen regulatory submissions and reviews.

- **Enhanced Cross-Study Integration**

  Harmonized exposure variables enable meta-analyses and integrated dose rationale across studies.

LIMITATIONS AND FUTURE DIRECTIONS FOR ER STANDARDIZATION

- **Current Framework Limitations**
  The ER framework mainly covers steady-state exposure and lacks support for time-varying dosing patterns and dynamic concentration metrics.
- **Challenges in Tumor Response Modeling**
  Real-world oncology requires complex adjudication beyond RECIST variables, including lesion confirmation and new lesion documentation.
- **Safety Analysis Limitations**
  Variability in adverse event coding and reliance on severity grading limit framework applicability in diverse safety analyses.
- **Future Directions and Collaboration**
  Broader community involvement and metadata standardization are vital, including cross-company working groups and industry collaboration.

TOWARD COMMUNITY-DRIVEN ER STANDARDS

- **Collaborative Framework Development**

  ER data standards require collaboration among diverse experts to create a flexible, evolving framework.

- **Multi-Organization Working Group**

  Creating a working group across organizations helps evaluate and refine the framework for various study designs.

- **Open-Source Development**

  GitHub-based contributions and shared libraries enable transparency, quality control, and organic evolution of ER standards.

- **Community Input and Alignment**

  Community feedback aligns the framework with CDISC initiatives, fostering standardization and reproducibility industry-wide

INTEGRATING STANDARDIZED ER DATA INTO MODELING WORKFLOWS

- **Standardized Dataset Structure**

  Consistent naming and formatting of ER data enables efficient reuse of modeling scripts across studies without modification.

- **Automation and Reproducibility**

  Integration with automation tools like targets and renv allows reproducible pipelines for derivation, modeling, and reporting.

- **Cross-Functional Collaboration**

  Standardized data supports collaboration between pharmacometrics and biostatistics teams using different modeling platforms.

- **Advanced Modeling Support**

  Pre-cleaned, standardized features enable advanced workflows including machine learning and Bayesian modeling approaches.

QUALITY CONTROL AND TRACEABILITY IN ER DATASET CONSTRUCTION

- **Standardized ER Framework**

  Provides predictable variable structures and naming, enabling robust quality control and traceability in datasets.

- **Automated QC Tools**

  pharmaverse tools like assertion functions and specification validation automate verification of dataset integrity.

- **Exposure Derivation Traceability**

  Explicit documentation of exposure calculations ensures accurate interpretation and reproducibility across studies.

- **Consistent Derivation Patterns**

  Applying repeatable code patterns reduces misclassification and aligns safety analyses with study requirements.

REGULATORY PERSPECTIVES ON ER DATA STANDARDIZATION

- **Challenges in ER Data Review**

  Inconsistent ER dataset structures complicate reviewers' understanding of exposure metrics and time-to-event calculations.

- **Standardized ER Framework Benefits**

  A CDISC-aligned framework offers systematic naming, traceability, and comprehensive exposure representations, aiding regulatory review.

- **Multiple Exposure Metrics Support**

  Including 20 exposure metrics supports regulatory expectations beyond just AUC and CMAX for thorough analysis.

- **Enhanced Regulatory Comparisons**

  Consistent ADEE, ADES, and ADTRR dataset structures enable clearer interpretation across studies and better dose-response communication.

CASE STUDY: APPLYING THE ER FRAMEWORK IN ONCOLOGY

- **Simulated Oncology Datasets**

  Simulated datasets reflect typical oncology trials with realistic tumor size and response distributions over multiple visits.

- **Exposure-Response Patterns**

  Exposure groups show expected divergence in tumor response and overall treatment effects across placebo, low, and high doses.

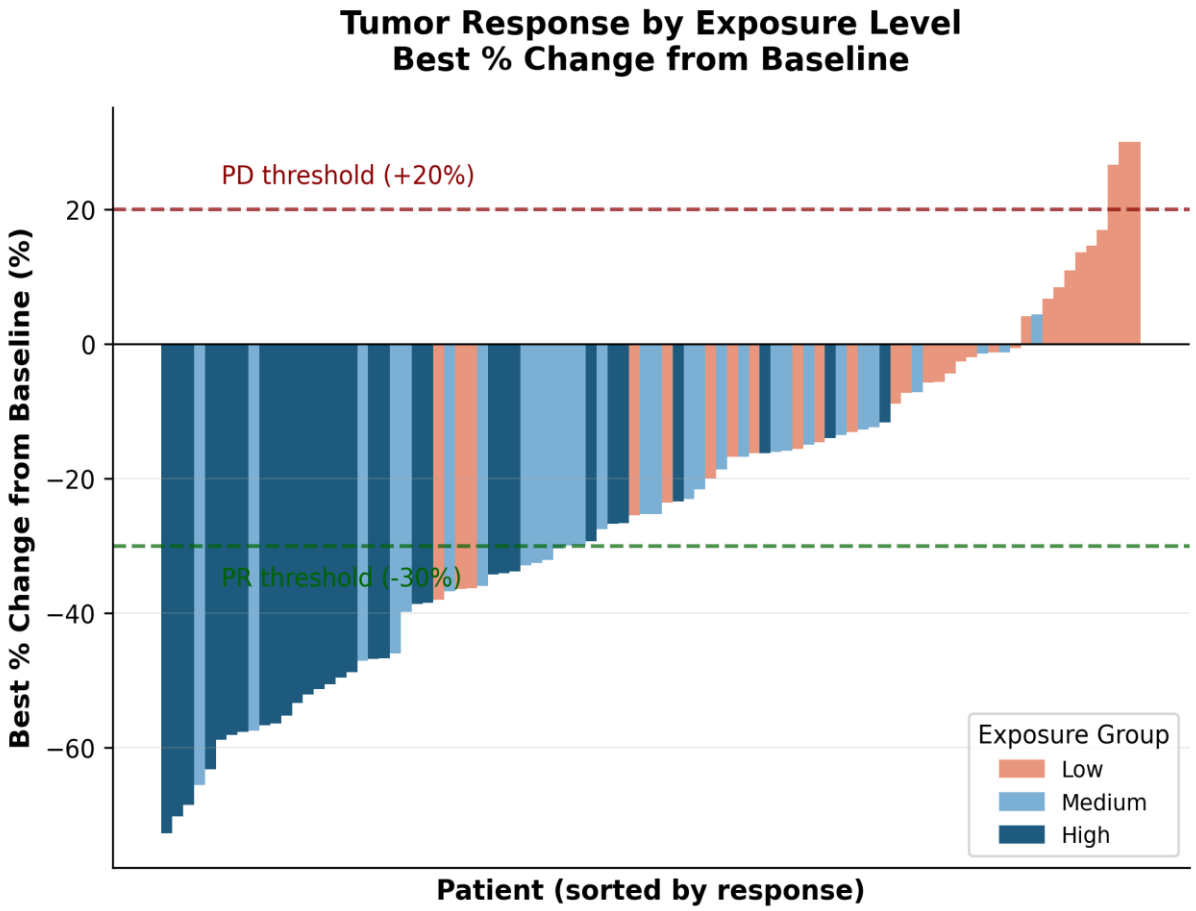
- **Safety and Adverse Events**

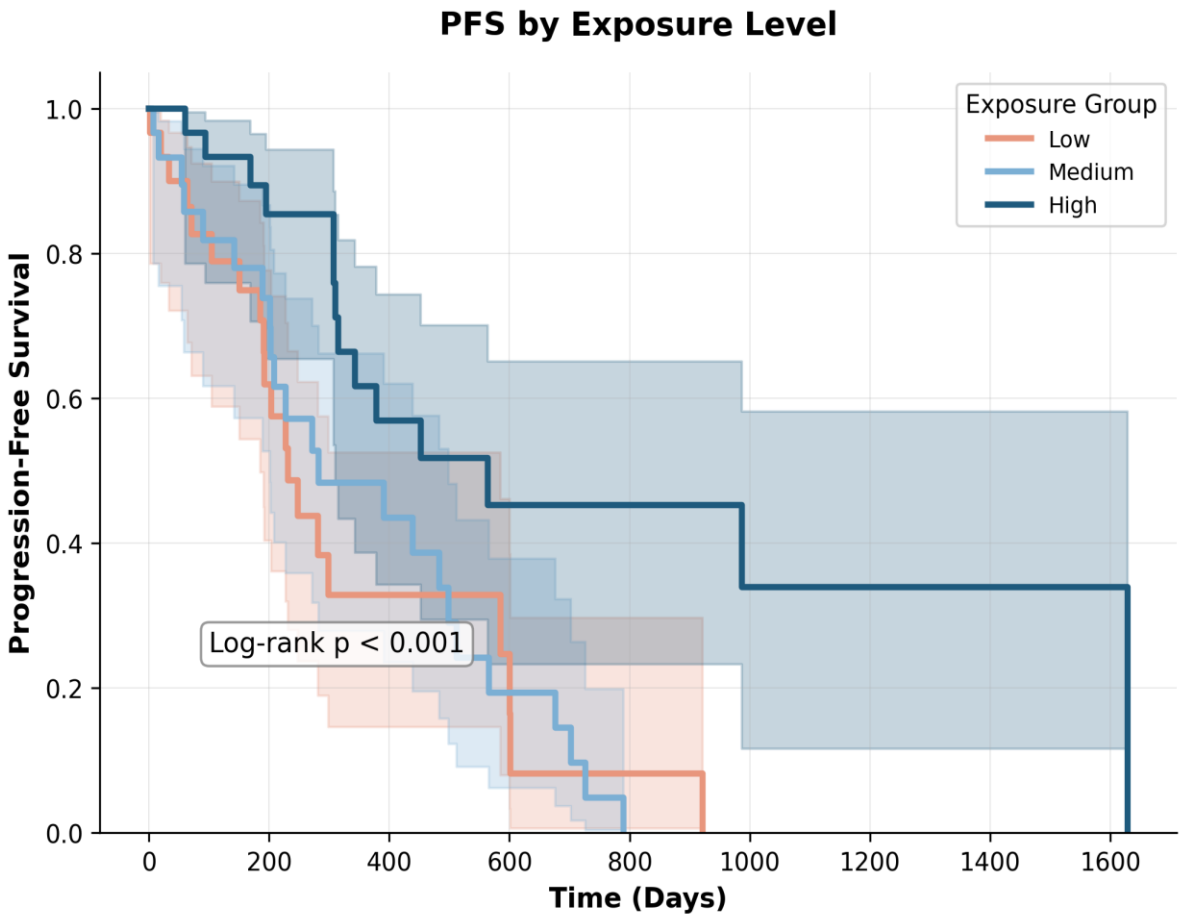
  Safety data illustrate adverse event burden distributions, enabling meaningful comparisons across exposure categories.

- **Modeling Exposure-Response**

  Integrated models such as Cox regression, logistic regression, and mixed-effects models provide interpretable exposure–response relationships.

EXPOSURE-RESPONSE RELATIONSHIPS: EXAMPLE ANALYSES





Key Findings:

PR Rate: Low (10%) → Medium (37%) → High (77%)

Median PFS: Low (232d) → Medium (282d) → High (564d)

Simulated data demonstrating ADTRR (waterfall) and ADEE (survival) applications

FROM FRAMEWORK TO STANDARD: PATHWAYS FOR INDUSTRY ADOPTION

- **Collaborative Pilot Testing**

  Multiple organizations conduct pilot tests to evaluate framework robustness across therapeutic areas and identify gaps.

- **Community Working Groups**

  Working groups formalize derivation logic, expand terminology, and develop implementation guides for the framework.

- **Open-source Collaboration**

  The pharmaverse ecosystem enables open-source contributions, validation, and consistent framework iteration.

- **Regulatory Alignment**

  Alignment with CDISC and PHUSE supports metadata integration and builds momentum for formal industry adoption.

EXAMPLE CODE

See Example Code

https://github.com/jeffreyad/er-standards/blob/main/programs/ad_ader.R

https://github.com/jeffreyad/er-standards/blob/main/programs/ad_adee.R

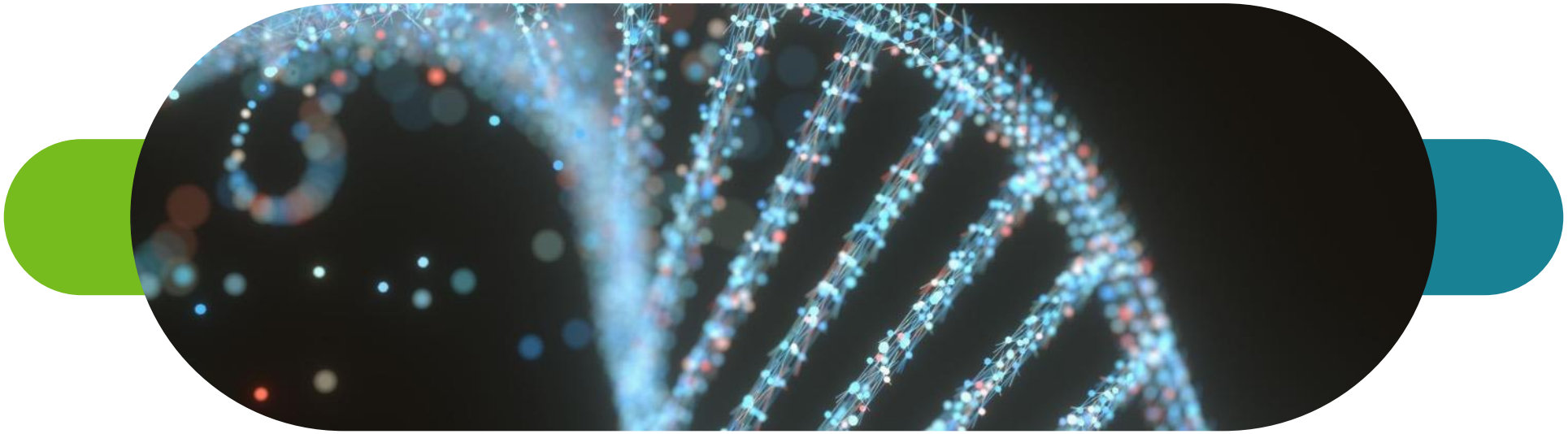
https://github.com/jeffreyad/er-standards/blob/main/programs/ad_ades.R

https://github.com/jeffreyad/er-standards/blob/main/programs/ad_adtrr.R

FOUR ER DATASETS: OVERVIEW

Dataset	Purpose	Structure	Key Features
ADER	Exposure foundation	Subject-level	Comprehensive exposure metrics
ADEE	Time-to-event efficacy	BDS (one/subj/param)	AVAL, CNSR, EVENT
ADES	Safety events	BDS + OCCDS hybrid	ASEV, AEREL, multi-level
ADTRR	Tumor response	BDS with visits	AVAL, CHG, PCHG, RECIST

WHY {admiral} AND pharmaverseADaM?



{admiral} Advantages

- ✓ Modular functions: derive_vars_*, dervive_param_*
- ✓ Validation built-in: assert_* functions catch errors early
- ✓ Metadata integration: Works with {metacore}, {xportr}
- ✓ Community-driven: pharmaverse ecosystem
- ✓ CDISC-aligned: Built with standards in mind

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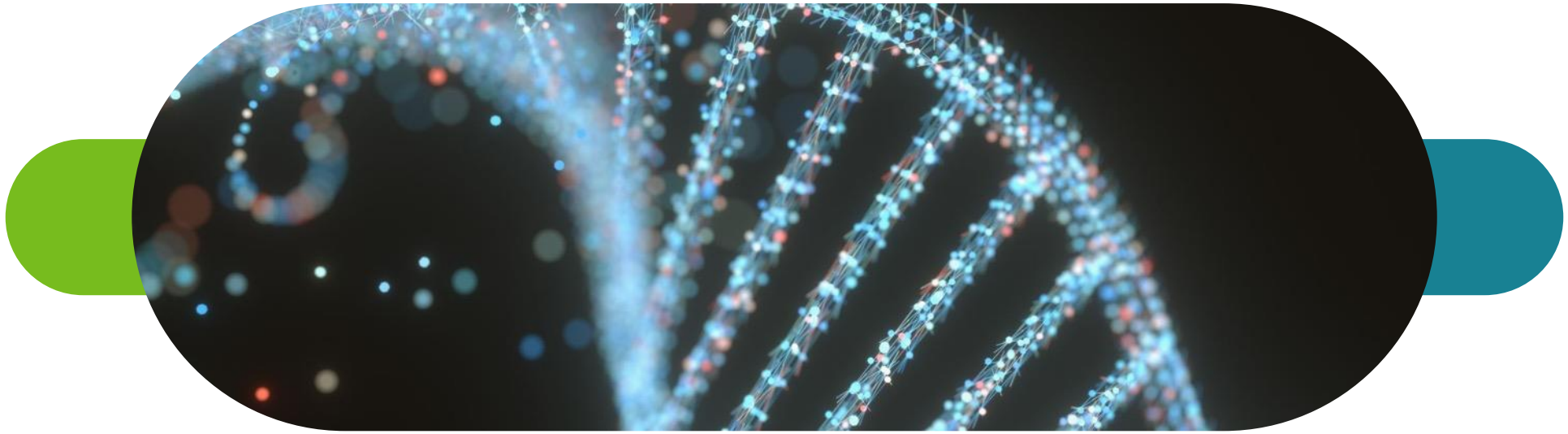


pharmaverseADaM Benefits

- ✓ Real example data: ADPP with actual PK parameters
- ✓ CDISC compliant: All datasets follow ADaM standards
- ✓ Ready to use: Extract AUCLST as AUCSS foundation
- ✓ Demonstrates real-world applicability

COMPARISON WITH TRADITIONAL APPROACH

Demonstrated improvements: 50-80% efficiency gains, enhanced reproducibility

Feature	Traditional	New Framework
Exposure variables	3-5	Comprehensive
Variable naming	Inconsistent	CDISC compliant
Transformations	Manual	Pre-computed
Documentation	External	Integrated specs
Structure	Single file	Domain-optimized
Reusability	Limited	High

Comparison of Exposure-Response ADaM Dataset Structures

Dataset	Structural Model	Data Grain	Core Content	Typical PARAMCD Examples	ER Analysis Focus
ADER	ADSL-based (subject-level)	1 rec/subject	Exposure metrics, baseline covariates, demographics	`AUC, CMAX, CTROUGH, DOSINT, RDOSINT`	*What patient/dose factors predict exposure?*
ADEE	ADTTE-based (time-to-event)	1 rec/subject/parameter	Event times, censoring indicators, exposure at event	`TTE, TTRESP, TTPROG, OS, PFS`	*How does exposure affect time to efficacy outcomes?*
ADES	ADAE-based (event + summary)	Event-level + subject totals	Individual AEs, exposure at AE, subject-level summaries	`AEINCID, AESEV, TTFAE, AEANY`	*What exposure levels increase safety risks?*
ADTRR	BDS-based (longitudinal)	1 rec/subject/visit/time	Serial measurements, change from baseline, response categories	`TUMSIZE, PCHG, BOR, RECIST`	*How does exposure drive response over time?*

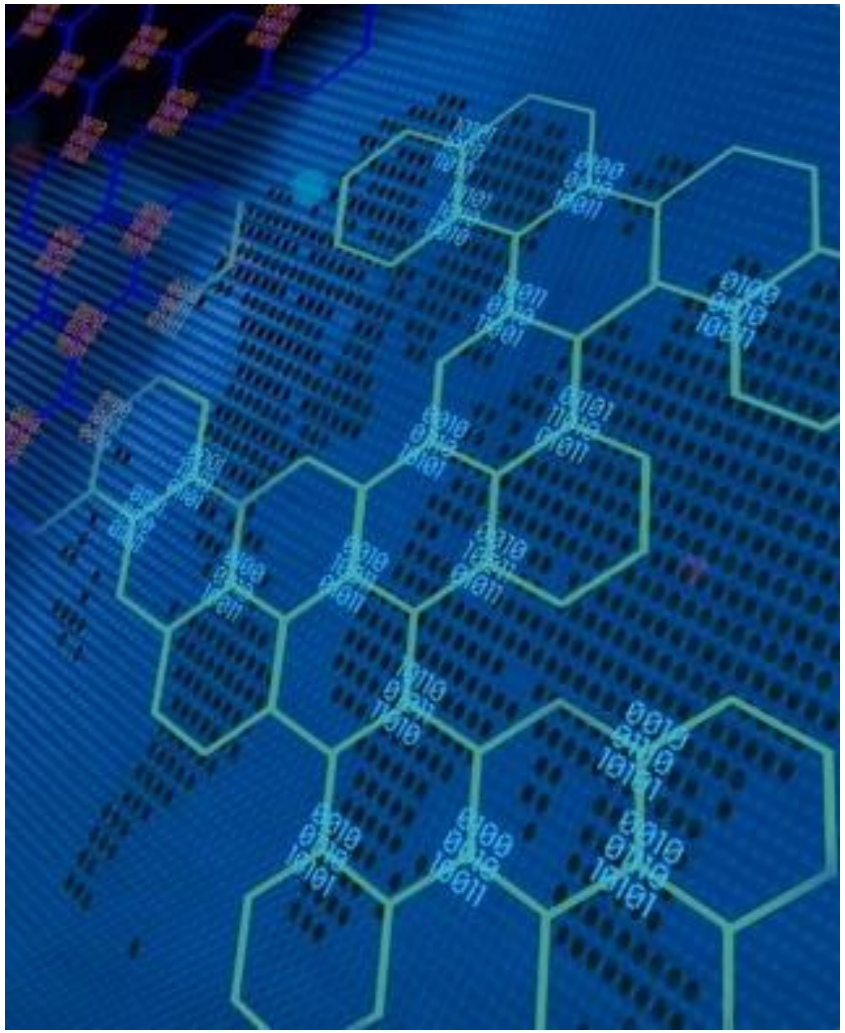
AE, Adverse Event; ADaM, Analysis Data Model; ADSL, Subject-Level Analysis Dataset; ADTTE, Time-to-Event Analysis Dataset; BDS, Basic Data Structure; ER, Exposure-Response; OS, Overall Survival; PFS, Progression-Free Survival

PATH FORWARD

Near-Term Steps

1. **Community Feedback**
   - Pilot testing in real studies
   - Refinement based on feedback
   - Edge cases and exceptions
2. **Extension Development**
   - Additional domains (ECG, vital signs, lab markers)
   - Advanced exposure metrics
   - Visualization templates
3. **Formalization**
   - Pharmaverse working group
   - {admiral} function extensions
   - Potential CDISC submission

GETTING STARTED TODAY



Resources Available

- GitHub repository: https://github.com/jeffreyad/er-standards
- Complete derivation scripts (ADER, ADEE, ADES, ADTRR)
- Example using pharmaverseadam::adpp
- ADaM specifications (P21 format + Excel)
- Metadata integration examples

Try It Yourself

- # Clone repository
- git clone https://github.com/jeffreyad/er-standards.git

- # Run derivations with pharmaverseadam
- source('programs/ad_ader.R') # Uses pharmaverseadam::adpp
- source('programs/ad_adee.R') # Time-to-event

Connect

- Email: jeff.dickinson@navitaslifesciences.com
- GitHub Issues: Feedback welcome
- Pharmaverse Slack: Join the discussion

7 KEY TAKEAWAYS

1 ER DATA NEEDS STANDARDIZATION

Current state: inconsistent, limited exposure coverage

2 FOUR SPECIALIZED DATASETS PROPOSED

ADER (foundation), ADEE (efficacy), ADES (safety), ADTRR (tumor)

3 FULL CDISC COMPLIANCE ACHIEVED

All variables ≤ 8 characters with systematic abbreviations

4 USES REAL pharmaverseADaM DATA

ADPP provides actual PK parameters for realistic demonstration

5 {admiral} WELL-SUITED FOR IMPLEMENTATION

Modular, validated, community supported

6 SIGNIFICANT BENEFITS DEMONSTRATED

50-80% efficiency gains, enhanced reproducibility, regulatory readiness

7

Community input needed for refinement and adoption

QUESTIONS?

Contact Information	
	jeff.dickinson@navitaslifesciences.com
GitHub	Jeffreyad
	https://www.linkedin.com/in/jeffreyad/
Resources	
Repository	https://github.com/jeffreyad/er-standards
pharmaverse	https://pharmaverse.org
Examples	https://pharmaverse.github.io/examples/

POWERING POSSIBILITIES
IN DRUG DEVELOPMENT

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Jeffrey Dickinson
jeff.dickinson@navitaslifesciences.com