



RE-02: Learnings from an External Comparator Study Based on Real-World Data (RWD)/Real-World Evidence (RWE) in T-Cell Therapy for Solid Tumors

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Introduction and Purpose

- Premise:
 - Increased use of Real-World Data (RWD)/Real-World Evidence (RWE) to assess clinical endpoints and risks and benefits of treatment therapies
 - Effective method to support T-cell therapy (TCR-T) studies due to challenges with patient enrolment and complex study design
 - FDA now allows RWD data to be used as a comparator arm for drug development^[1]
- Purpose
 - To share learnings and best practices for programmers based on GSK's first external comparator arm study based on RWD/RWE

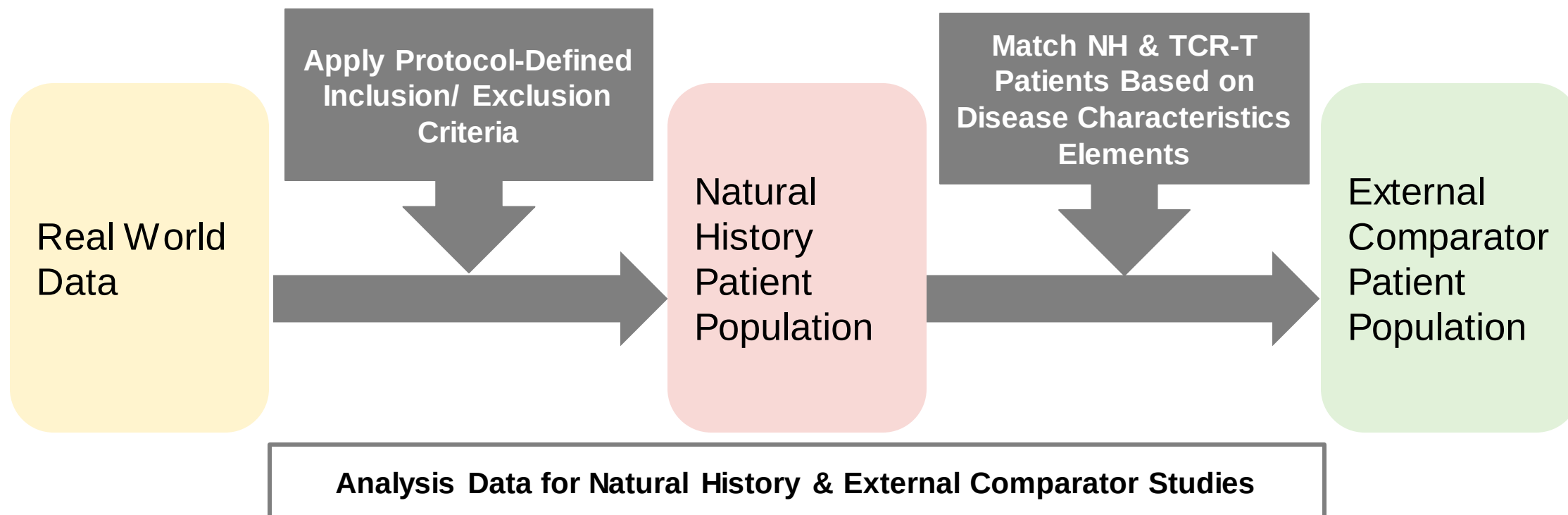
[1] Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry, Draft [November 2021]

Background

- **GSK RWD/RWE protocols:**
 - To study the natural history (NH) of advanced Synovial Sarcoma (SS) and Myxoid Round Cell Liposarcoma (MRCLS) patients
 - To provide an external comparator (EC) arm for a pivotal single arm, open label T-cell therapy study for patients with advanced SS and MRCLS
- FDA requires RWD data to be CDISC compliant for both SDTM and ADaM, and holds it to the same standards as those used for Randomized Controlled Trials (RCT) data^[2]

[2] Data Standards for Drug and Biological Product Submissions Containing Real-World Data, Draft [October 2012]

NH and EC Patient Population



- **Study documents, SDTMs, and ADaMs for NH and EC studies:**
 - Common CRF and SDTMs
 - Separate protocols, SAPs, and ADaM datasets
 - NH patients are matched using predefined disease characteristic elements from the interventional study to create the EC arm study analysis population (matching algorithm and elements outlined in the SAP)

A High-Level Overview of RWD/RWE Process

Step 3: Data Collection

(reliability, relevance, completeness, etc.)

Step 2: Data Source Selection

(EMRs¹, PROs², claims data, patient registries, PGHDs³, etc.)



Step 1: Study Planning

(feasibility, design & purpose, analysis specification, regulatory interactions*, etc.)

Step 4: Data Processing

(extraction, linking, cleaning, SDTM mapping, coding, etc.)

Step 5: Data Programming & Analysis

(ADaM development, imputations & derivations, reporting standards, analysis flags, comparability, etc.)

Step 6: Data Reporting

(publications, control arm, submission/post-submission, etc.)

RWD/RWE Process

1= Electronic Medical Records; 2= Patient Reported Outcomes; 3= Patient Generated Health Data

* Regulatory interactions occur throughout the study lifecycle.

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Learnings and Best Practices for Programmers



During SAP Development

- SAPs are required and help:
 - Define the analysis purpose, use, and population(s)
 - Define the programming rules and derivations
 - Provide the list of data items for the matching algorithm
 - Describe data limitations and the impact on the final analysis

- Programming should ensure that the SAP provides:
 - Clarity on the I/E criteria
 - Strategy to handle missing data or any gaps in the data due to database limitation
 - Comparable analysis population definitions
 - Clear definitions for the time-to-event (TTE) endpoints, censoring rules, and covariates

During CRF Development

- CRFs are not required but highly recommended to facilitate:
 - Reliable and relevant data collection
 - A harmonized data collection strategy
 - Traceability during and post analysis
 - Describe the relationship between data elements

- Programming should ensure that the CRF allows:
 - To capture all elements needed to accurately support the endpoints and analysis
 - Data collection and mapping to result in SDTM datasets which are comparable and traceable
 - For a CDISC compliant SDTM submission package

During ADaM Metadata Development

- ADaM metadata is required for regulatory submission and to meet FDA's CDISC compliance requirement

- Programming should ensure that ADaM specifications facilitate:
 - Correct interpretation, coding, and QC of all derivations
 - Proper documentation of all data transformations performed to conduct the analysis
 - Comparability of treatment study and real-world data
 - Adherence to ADaM IG principles and CDISC compliant ADaM submission package

Examples

General Considerations

Item	TCR-T Study	EC Study	Impact on EC Study
ATC coding	Source data contains all elements to facilitate ATC coding	Due to the non-standard nature of RWD, all elements may not be present to assign the ATC code accurately	Summaries based on ATC code were not reported
Efficacy secondary objectives	Data to derive efficacy endpoints is collected using RECIST 1.1 criteria using standard forms	RECIST 1.1 was not available	Various methods were specified in the SAP to derive response and data was analyzed as collected

Additional example available in the associated paper.

Examples

Data Items with Different Derivations

Data Items	TCR-T Study	EC Study
Index/reference date	T-cell infusion date	First treatment initiation date for the treatment of interest
Date of last contact	Derived based on a core oncology standard algorithm	Collected in the eCRF
Inclusion criteria	Participant has documented radiographic evidence of disease progression per RECIST v1.1 from prior line of therapy	Assume 2L+ patients have progressed

Additional example available in the associated paper.

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Wrap up

GSK

Overall Best Practices

- **Always** compare/review/check EC documents against the TCR-T study documents these are meant to support for comparability and accuracy
- **Always** document all data transformation rules and data limitations (expected and unexpected) to maintain traceability and reliability of the analysis
- **Always** review the P21 reports, SDRG and ADRG, define files (for data transformation and metadata), and ADaM specifications at each reporting milestone for compliance with CDISC and company specific standards
- **Always** maintain a record of key discussion and decision minutes regarding reporting and derivation of the covariates and matching algorithms for complete transparency and data integrity

Conclusion

- Use of RW data to support clinical endpoints or act as the comparator arm for T-cell therapy studies will significantly increase
- Lack of standardization and harmonization create unique challenges for clinical programmers
- Important to be aware of areas unique to RWD/RWE studies and requiring programming's input

Acknowledgements and Contact

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thank you!



For questions and feedback,
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