Paper 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

Rabia Ahmad, GSK, Upper Providence, PA, USA

Abstract

With an increase in unique study designs, single arm studies, customized treatment, and development of therapies for rare diseases; traditional clinical trials can be time and resource intensive and, in some cases, can also have ethical implications. Due to this use of RWD/RWE is becoming a common and accepted method to support the clinical endpoints, and assess risks and benefits of treatment therapies, during submission and for post-marketing analysis. However, to conduct a successful RWD/RWE study, well-defined study documents; robust data integrity, and management plans; and thorough oversight at each step of the RWD/RWE study process are critical.

It is very clear that the enrollment challenges, and the ethical considerations of defining a randomized comparator arm for TCR-T for solid tumors; clinical programmers in the CGT space will witness a significant increase in the use of RWD. FDA's approval of using RWD as the comparator arm[1] will also accelerate this adoption. Keeping this in mind, it is important for programmers to be familiar with the regulatory guidelines and requirements for studies using RWD/RWE.

Purpose and Background

The purpose of this paper is to share learnings and best practices from two RWD/RWE studies supporting GSK's pivotal single arm, open label TCR-T for solid tumor protocol; and to highlight areas that came under programming's remit which generally would not for traditional clinical trials.

The learnings and best practices in this paper are based on the following protocols:

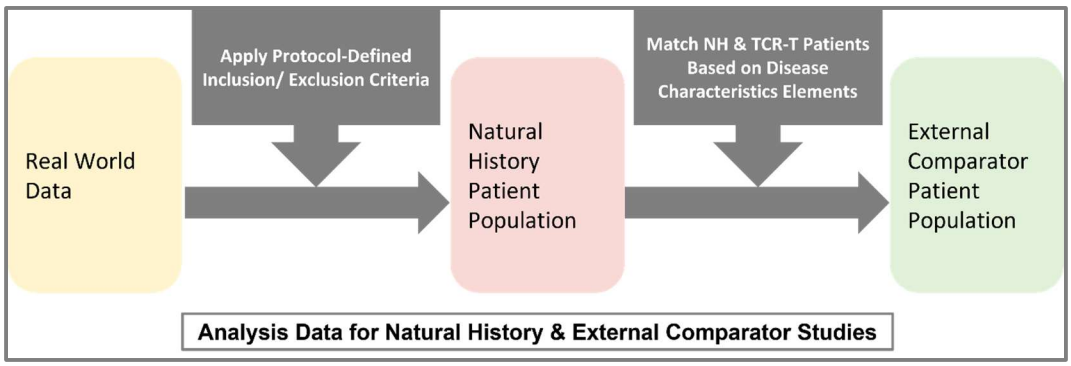
- To study the natural history (NH) of patients receiving systemic treatment for advanced Synovial Sarcoma (SS) and Myxoid Round Cell Liposarcoma (MRCLS)
- To provide an external comparator (EC) arm for a pivotal single arm, open labelled TCR-T study for patients with advanced SS and MRCLS

A Natural History (NH) study is a "preplanned observational study intended to track the course of the disease. Its purpose is to identify demographic, genetic, environmental, and other variables (e.g., treatment modalities, concomitant medications) that correlate with the disease's development and outcomes[2]".

An External Comparator (EC) arm is based on "outcomes in a group of people external to the trial, rather than to an internal control group consisting of participants from the same trial population assigned to a different treatment or no treatment[2]".

NH and EC Patient Population

The below figure shows the flow of NH and EC analysis data selection based on RWD.

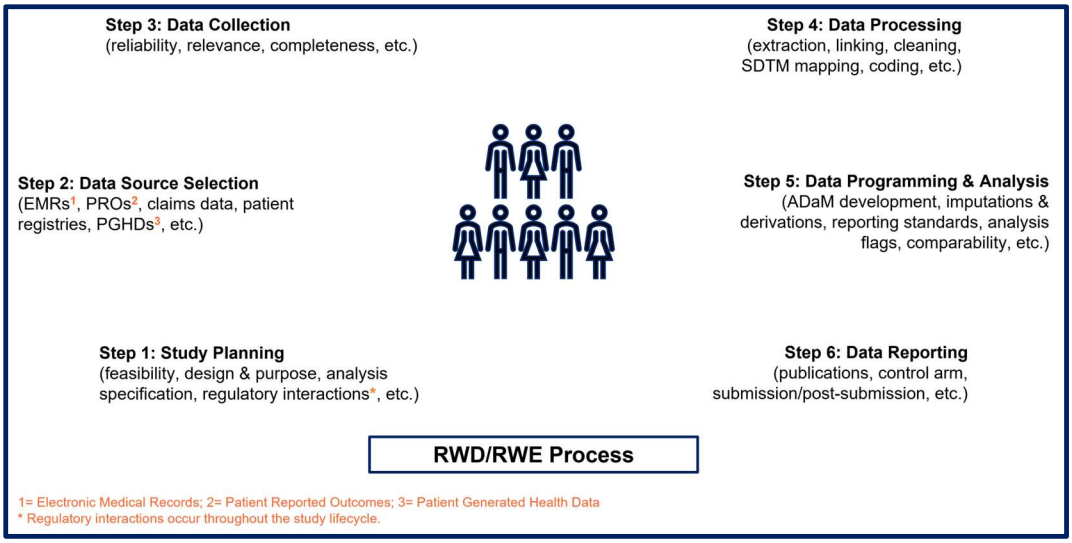


Each study had a separate protocol and SAP. Data was collected using a single CRF and was mapped to a common set of SDTM domains.

The NH patient pool was based on selecting patients from real-world data using a set of protocol-defined inclusion/exclusion criteria. Patients in the NH data were then matched to predefined disease characteristic elements from the interventional study to create the EC arm study analysis population. The matching algorithm and elements were outlined in the EC study SAP. Justification for using RWD to act as the comparator arm was provided in the EC study protocol.

The study was conducted by a third-party vendor, but GSK programming provided close oversight during each step, thoroughly reviewed all the documents, and ensured compliance with GSK and CDISC standards.

RWD/RWE Process and Challenges



The above figure gives a high-level overview of the steps making up the RWD/RWE process.

Few considerations for conducting RWD/RWE studies are detailed below. Please note that these do not make a comprehensive list; all are not specific to TCR-T for solid tumor studies; and all may not fall within programming's remit.

Frequent regulatory reviews and approvals[3]: FDA requires proof of the reliability, relevance, comparability, data integrity, and traceability (amongst other requirements) of RWD used to support the submitted analysis. In addition, clear rationale for using an external comparator arm and evidence that the protocol and SAP were finalized prior to conducting the analysis (to maintain objectiveness of the results) are also required.

Given that the use of RWD/RWE as a comparator arm and TCR-T for solid tumors are both new areas of research, ensuring regulatory acceptance of the study rationale; putting together strong data integrity and monitoring plans; documenting data transformation codes and algorithms; and maintaining comparability with the test study data are critical and require transparent communication with the regulatory authorities.

Non-standard/non-harmonized databases[3]: TCR-T studies enroll subjects based on very specific set of I/E criteria at various phases of the study. Data is collected in a uniform and controlled manner following specific guidelines to maintain traceability. Missing or seemingly incorrect data are queried and strict edit checks are performed to ensure accuracy. Due to the retrospective nature and lack of standardization, many of the data collection principles used for controlled clinical trials are difficult to apply in RWD/RWE studies. Often times real-world data is incomplete, spread across multiple differently structured databases, and not easily queried for missing or incorrect information.

Selecting the right database; defining a reasonable set of I/E criteria for data selection; and developing a robust data management plan are critical for generating reliable, complete, and fit-for-purpose real-world data.

Maintaining comparability between study treatment and RW data: In interventional studies, data for the comparator and treatment arms come from the same protocol, follow the same assumptions (i.e., I/E criteria, visit structure, controlled data collection, standard mapping, and coding, etc.) and collected under strictly controlled and harmonized settings. A good example is an RCT study, in which patients are randomly assigned to test and comparator treatment arms. Additionally, interventional studies follow standard data mapping and transformation methodologies (e.g., handling missing data, imputation rules, visit windowing, exposure calculations, etc.).

The above characteristics of interventional studies result in comparable treatment arms. However, real-world data does not meet these conditions and maintaining comparability of the test and EC data is not easy.

SDTM and ADaM development: FDA requires source and analysis RWD data to be CDISC compliant, and holds it to the same standards as those used for interventional study data[4].

Due to the non-standard characteristics of RWD, using standard CTs and derivations, assigning dictionary coding (e.g., MedDRA and CTCAE), and using SDTM and ADaM core variables, are not always possible. CDISC compliance also requires full traceability and reproducibility of the analysis and its source data.

Lack of uniformity and completeness of RWD databases, creates difficulty in creating CDISC compliant SDTMs and ADaMs. Some of these may be addressed by having an annotated CRF in place; documenting the RWD database characteristics and definitions of its data elements; and developing strong ADaM specifications which includes all derivations and conditions used to create the analysis datasets.

Learnings and Best Practices

Programming plays a wider role in RWD/RWE studies. They must acquire a deeper than expected understanding of the regulatory requirements, data management and analysis plans, and study design and rationale to successfully conduct an RWD/RWE study. Some areas where programing can add value and guidance during an EC study are detailed below. As with the challenges outlined in the previous section, this is not a comprehensive list.

Few general best practices during EC study conduct are:

- ***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

In case of the GSK studies, programming reviewed the NH and EC SAP, eCRF, mock shells, and ADaM specifications to ensure alignment across NH, EC, and TCR-T documents; that the NH study data contains all elements needed to create the subset population for the EC study; and that the data mapping, transformation, and reporting follows GSK's and CDISC standards to the maximum extent possible.

Programming also reviewed the data monitoring and cleaning plan to understand the inherent limitations of the source data, proactively develop new or modify standard ADaM data handling methods (based on the known/expected limitations), and to determine specific details or footnotes needed in the ADRG or TFLs, respectively. They also reviewed the data completion guidelines and edit checks, to ensure reliable and accurate data collection and to avoid unexpected data issues during ADaM development.

Programming *highlighted* non-programming related differences between the TCR-T and NH/EC studies; and *documented* differences impacting programming activities. Additionally, they noted all expected deviations from GSK or CDISC standards. This was done to provide evidence of accuracy and objectiveness of the analysis data.

During the review and development of the SAP/mock shells, eCRF, and ADaM specifications, programming ensured that each document contained clear details to facilitate accurate ADaM data development, and ensure a CDISC compliant submission package.

SAP development: SAP is required for any RWD/RWE study. When reviewing the SAP, programming ensured that it provided:

- a clear outline of the analysis purpose
- an accurate definition and use of the index/reference dates, analysis populations, covariates, efficacy endpoints, and censoring rules
- a reasonable list of I/E criteria
- a list of data items for the matching algorithm and a justification for selecting a particular algorithm one from the available literature
- details for any known data limitations and the impact on the analysis
- complete data handling rules for missing data, and data transformation rules and derivations for comparability with test data

eCRF development: CRF is not required but highly encouraged to monitor data collection; facilitate data cleaning and logic; ensure CDISC compliant SDTM domains; and collect fit-for-purpose and accurate data. When reviewing the eCRF, programming ensured that it provided:

- all elements needed to accurately support the endpoints, and derive the covariates
- accurate capturing of the index/reference dates
- correct logic, drop down menu items, and controlled terminologies to mirror CDISC CTs
- clear data completion guidelines

ADaM metadata development: ADaM metadata is required for regulatory submission and to meet FDA's CDISC compliance requirement. During ADaM metadata development, programming ensured that the specification contained or allowed:

- detailed derivations to facilitate accurate interpretation, coding, and QC of the endpoints and covariates
- correct derivation and imputation of the index/reference dates
- proper documentation of all ADaM data transformations performed to conduct the analysis
- comparability of the test treatment and real-world data
- adherence to ADaM IG principles and CDISC standards

Examples

Below are few general areas of considerations that programming was involved with during the SAP, CRF, and ADaM specifications development of the NH and EC studies.

Item	TCR-T Study	EC Study	Impact on EC Study
ATC coding	Source data contains all elements to facilitate ATC coding resulting in a one-to-one match between the medication and the assigned ATC code	Due to the non-standard nature of RWD, all elements may not be present to assign the ATC code accurately	It was decided to not report summaries based on ATC code and medication can be summarized using generic name or ingredient
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
Controlled terminologies	CRF is built and data is mapped to ensure use of CDISC defined CTs	Data was not collected in compliance with CDSIC standards, and it was possible that recoding may cause loss of traceability and/or introduce bias	Where possible and required proper documentation and justifications were provided for recoding of the data to allow comparability between EC and TCR-T studies and maintain source traceability

Below are a few examples of data items for which the derivations differed between the TCR-T and EC studies. Some of the data items, such as the last contact date, OS censoring, and line of treatment, are derived based on standard definitions or principles. These were not possible to use in the EC study due to unavailability or non-standard capturing of the RWD.

Programming ensured clear directions were provided in the SAP when reviewing the document.

Data item	TCR-T Study	EC Study
Index/reference date	T-cell infusion date	First treatment initiation date for the treatment of interest
Line of treatment	Determined by the investigator at each site	Based on a complex ADaM algorithm defined in the SAP
Lost to follow-up	Pre-defined in the protocol based on specific disposition milestones	Due to the absence of disposition milestones and/or death records, patients without any record of activity for more than 6 months were considered lost to follow-up (at the time of their last recorded activity)
Date of last contact	Derived based on a core oncology standard algorithm	Collected in the eCRF
Censoring for OS	For patients alive at time of analysis, OS data is censored at the date of last contact	For patients alive at the time of analysis, OS data is censored at the date of last recorded clinical activity
Inclusion criteria (a selected few)	Participant has documented radiographic evidence of disease progression per RECIST v1.1 from prior line of therapy	Assume 2L+ patients have progressed
	Measurable disease based on RECIST 1.1	Not applicable
	Age group specific performance status assessment data collected at protocol-defined visits	Availability of performance status data (later derived in ADaM)

Summary and Conclusion

Use of RWD to act as the comparator arm for TCR-T studies will significantly increase in the coming years. However, lack of standardization and harmonization of the real-world data creates unique challenges for clinical programmers. For a successful conduct, and accurate and reliable submission of EC studies using RWD programmers must be aware of the regulatory guidelines, areas of considerations (which do not fall within programming's remit when working on interventional studies), and best practices for working on an EC study as outlined in this paper.

When working on RWD/RWE study, programmers should:

- Adhere to regulatory guidelines
- Ensure robust data management strategy is defined, and standard mapping and coding are done at the SDTM and ADaM level
- Ensure that all key elements (listed in in the "Learnings and Best Practices" section) are captured in the study documents
- Provide thorough documentation of data transformation rules and methods to maintain traceability and reliability of the analysis data
- Clearly document data limitations and gaps and its impact on the analysis
- Develop CDISC compliant SDTM and ADaM submission packages

Abbreviations

2L	2nd Line of therapy
ADaM	Analysis Data Model
ADRG	Analysis Data Reviewers Guide
ATC	Anatomical Therapeutic Chemical

CDISC	Clinical Data Interchange Standards Consortium
CRF / eCRF	Case Report Form / electronic Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
EC	External Comparator
FDA	Food and Drug Administration
I/E	Inclusion/Exclusion
MedDRA	Medical Dictionary for Regulatory Activities
MRCLS	Myxoid Round Cell Liposarcoma
NH	Natural History
OS	Overall Survival
RCT	Randomized Clinical Trial
RECIST	Response Evaluation Criteria in Solid Tumors
RWD	Real-World Data
RWE	Real-World Evidence
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SS	Synovial Sarcoma
TCR-T	T-cell Receptor Therapy
TFL	Table, Listing, and Figures
TTE	Time-to-Event

References

- [1] Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry | FDA
- [2] Rare Diseases: Natural History Studies for Drug Development Guidance for Industry (fda.gov)
- [3] Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products (fda.gov)
- [4] Data Standards for Drug and Biological Product Submissions Containing Real-World Data | FDA

Acknowledgements

The author would like to acknowledge Menaka Bhor (GSK), Rebecca Greenwood (GSK), and Sally Chapman (Plus-Project) for their knowledge and guidance on the RWD/RWE process and challenges. The author would also like to acknowledge Adrienne Bonwick (GSK) for her senior review and input on the completeness and accuracy of the content of this paper and accompanying presentation.

Contact Information

The author values feedback, questions, and corrections. Please contact the author at:

Rabia Ahmad
GlaxoSmithKline
Email: rabia.x.ahmad@gsk.com