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Programming and Reporting on a Master Protocol in Cell & Gene Therapy

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Abstract

Use of master protocol in oncology studies to evaluate multiple cancer therapies or cancer subpopulations in parallel has gained significant traction in recent years[1]. It is a well-accepted approach to expedite development and approval of oncology drugs and therapies in late phase trials. However, due to its recent application, there is a lack of industry guidance and established standards to manage the programming and reporting of data collected under these protocols. This paper aims to identify challenges, related to or impacting programming, encountered when working on a master protocol platform study evaluating T cell Receptor (TCR-T) therapy in solid tumors and provide approaches to addressing these challenges.

Purpose

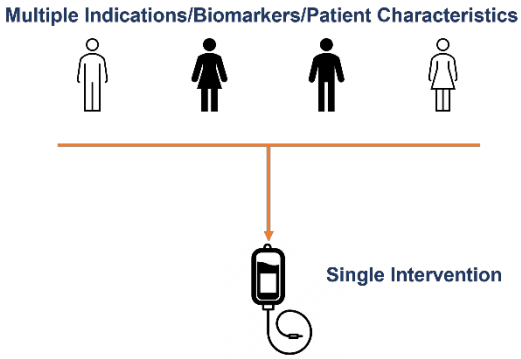
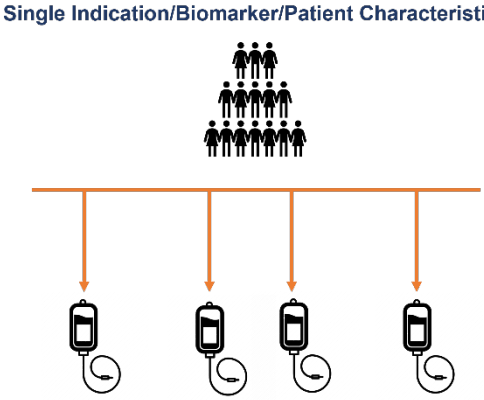
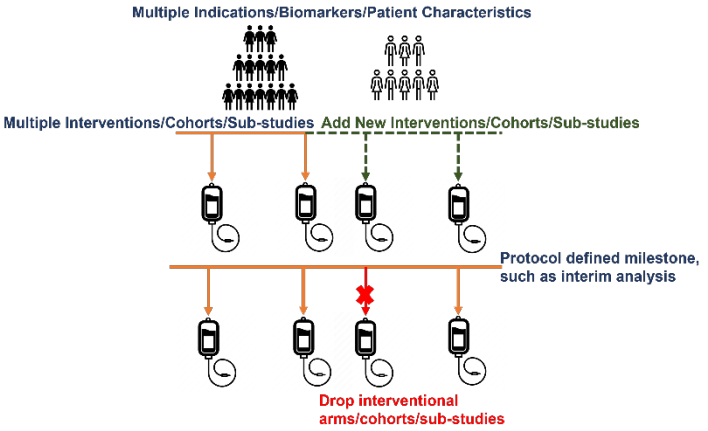
Although the benefits of a master protocol are well known, there is a noticeable absence of well-defined standards, and structured training to support programming and reporting. This leads to missed opportunities to improve, standardize, and document the process for future efficiencies, and avoid inconsistencies in reporting.

Cell and Gene Therapy (CGT) is a relatively new area within immuno-oncology (IO). Due to their unique study design, there is a lack of programming and reporting standards and guidance, and a concentrated effort to develop these.

The purpose of this paper is to bring few key challenges faced by GSK's CGT programmers working on master protocol based TCR-T studies to the wider programming community. The intention is to share best practices and kick-start cross-industry collaboration to develop programming standards for CGT studies based on master protocols.

Types of Master Protocol

There are three types of master protocol: umbrella, basket, and platform[2][3]. A brief description is given for each type below, however, this paper focuses on platform trials.

Basket: This design investigates single investigational treatment or combination of treatment for multiple disease types or indication.	 Figure 1: Basket Design
Umbrella: This design investigates multiple investigational treatment or combination of treatments for a single disease type or indication.	 Figure 2: Umbrella Design
Platform[4]**:** This design is based on elements from, one or both, basket, and umbrella trials. This can also be designed as a "perpetual" version of a basket or an umbrella design (i.e., allows research questions to be added overtime on the basis of ongoing findings).	 Figure 3: Platform Design

Advantages and Disadvantages of Master Protocols

Master protocols offer expedited drug development, operational efficiencies, reduced patient burden, and increased cost effectiveness, all leading to improved patient care in a timely manner. It also facilitates programming and reporting of integrated summaries of safety and efficacy (ISS & ISE) as the eCRF, databases are shared across substudies and/or cohorts.

However, to benefit from the advantages, a well thought out master protocol, and robust programming standards are needed. The absence of these can result in frequent protocol amendments, updates to eCRF design, deviation from standards, and custom programming. All of which increases the chances of data errors, changes to data collection & mapping, data cleaning issues, and loss of valuable time.

T-cell Study Design[5]

Adoptive T-cell therapies (such as, CAR-T, TCR-T, IL2, etc.) have unique study designs compared to traditional cancer therapies (such as, small molecule targeted therapies, hormone therapy, radiotherapy, chemotherapy, etc.).

Unique design characteristics include, multiple eligibility screenings, length of time between leukapheresis[6] and lymphodepletion[6], single treatment infusion, and reporting and analysis of adverse events.

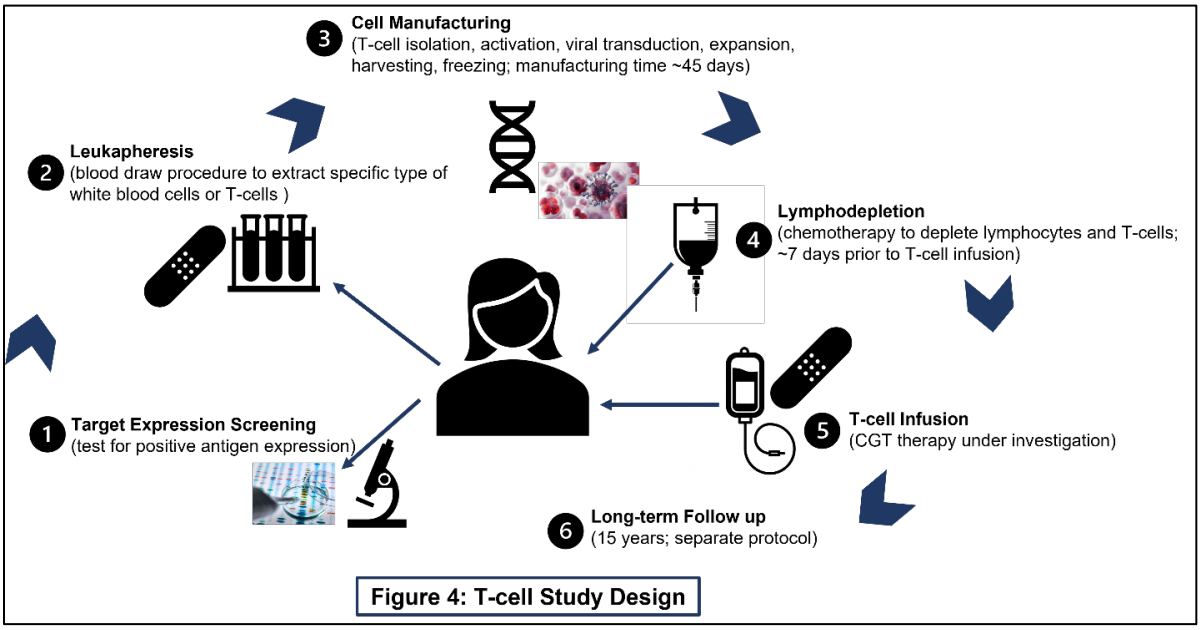


Figure 4: T-cell Study Design

The study design allows the patients to be re-screened for antigen testing, and to have repeat leukapheresis if needed. Long-term follow up of patients consists of 15 years per FDA guidelines on human gene therapy studies [7].

Challenges and Resolutions

The challenges are divided into two groups: related to master protocol and related to T-cell study design. Note: the team came across many challenges, of which few key ones are shared below.

Challenges Related to Use of Master Protocol

The flexibility of master protocols allows adding substudies, and cohorts with different disposition milestones, inclusion/exclusion criteria, line of therapy, etc. under one protocol. Due to the different criteria, using a master level eCRF and database makes it difficult to use standard data collection methods built for traditionally designed studies.

Example #1: Designing Master Level SDTM Trial Arm Domains

Situation: In a master protocol each substudy can have different study attributes, such as inclusion/exclusion (INC/EXC) criteria, due to different indication and/or different therapies and/or therapy combinations. However, currently there are no industry/CDISC guidance to capture substudy specific details in a consistent manner in the trial arm domains. An example is capturing substudy specific INC/EXC criteria in a single TI domain.

Domain	IETESTCD	IETEST	IECAT	TIVERS
TI	I02	IETESTx.	INCLUSION	YYYYID_00
TI	I03	IETESTx.	INCLUSION	YYYYID_00

Figure 5: SDTM.TI mapping for traditional studies

Domain	IETESTCD	IETEST	IECAT	IESCAT	TIVERS
TI	I0102	IETESTx. s1	INCLUSION	SUBSTUDY 1	YYYYID_00
TI	I0203	IETESTx. s2	INCLUSION	SUBSTUDY 2	YYYYID_00

Figure 5a: SDTM.TI mapping for Master Protocol studies with multiple sub-studies

Challenge	Resolution
Lack of industry guidance and company-specific standards	Referring to figure 5a, create unique TI.IETESTCD by adding (01,02, …, *n*) for each substudy and append TI.IETEST text with "S1", "S2", …, "S*n*" to indicate the substudy associated with each criteria.
Deviation from existing standards	

Another example is assigning ARM and ARMCD in the TA domain with multiple substudies, each with multiple treatments and doses. Currently the team is adding the substudy number, and treatment name when assigning ARM/ARMCD. They are also looking at other options, such as adding the different dose levels and phases. The below figure shows the current solution; however, this is a key area where some detailed industry guidance and standards will be extremely beneficial for the programming community.

Domain	ARMCD	ARM	TAETORD	ETCD
TA	S1A	Substudy 1, TxUI	1	SCREEN
TA	…	Substudy 1, TxUI	…	…
TA	S1A	Substudy 1, TxUI	n	FUPP
TA	S2B	Substudy 2, TxUI	1	SCREEN
TA	…	Substudy 2, TxUI	…	…
TA	S2B	Substudy 2, TxUI	n	FUPP

TxUI = Treatment under Investigation
Figure 6: ARM & ARMCD assignment in SDTM.TA domain

Example #2: Creating Separate SDTM Packages for Individual Substudies Based on Master Database

Situation: A platform master protocol trial can contain multiple compounds, plus pivotal and non-pivotal substudies; and it also allows for substudies to be added or terminated. However, all substudies share a common database. This results in complexities when creating pivotal or terminated substudy specific SDTM/ADaM packages during submission or reporting. This challenge can also arise for other key deliverables, such as, interim analysis, publication, etc.

Challenge	Resolution
Develop and document the strategy for selecting and separating substudy specific data	Create multiple reporting environment at source data level, enabling the substudy specific SDTMs to be stored and packaged separately. This also facilitates ADaM and TFL development as separate packages.
Ensure data traceability	
Modify existing standards	

Example #3: Managing Differences in Efficacy and Safety Analyses Mockups

Situation: Platform trials allow different compounds or combination therapies (with or without multiple dose levels) to be studied across different indications within the same protocol. This is particularly true for phase I studies, where many indications, therapies and dose levels can be added over time. In such cases, use of master protocol approach becomes highly efficient. On the other hand, this also makes use of standard mocks macros, and ADaM specifications challenging during programming. Developing separate displays is not preferred, as it results in large CSR packages, which are reported separately for each substudy/cohort.

Challenge	Resolution
Use of standard mock-ups and macros	Develop CGT specific standard mocks in collaboration with stats and clinical/safety as part of pre-programming activities. Finalize the display mock-ups early on in the process to ensure accurate and fit-for-purpose ADaM specifications/datasets.
Control number of displays produced per substudy	To avoid large CSR packages, all indications under investigation are summarized together

	in safety displays; but separate efficacy displays are developed for each indication.

Challenges Related to T-cell Study Design

Defining appropriate reference start date for different analysis, likelihood of patient receiving systemic therapies prior to lymphodepletion, and reporting of adverse event data are few unique characteristics of T-cell therapy study design. These result in some interesting questions and challenges, requiring out-of-the-box thinking.

Example #1: Defining Reference Start Dates for Different Analysis

Situation: Per protocol, CGT treatment starts at lymphodepletion. This is because, T-cell infusion (drug under investigation) cannot be administered without lymphodepleting (non-investigational/non-GSK drugs) the patient. In this case it is critical to correctly define and document the reference start date for different types of planned analysis for the study (e.g., disposition milestones, adverse events, etc.).

Challenge	Resolution
Protocol defined treatment starts at lymphodepletion, but time since treatment (to event start) is measured against T-cell infusion date.	Use lymphodepletion start date for all disposition milestones, and death on treatment. Use T-cell infusion date for Treatment Emergent Adverse Events, and time since treatment analysis. Document the decision and algorithms clearly in the SAP, ADaM programming specifications, and display footnotes.

Example #2: Reporting Adverse Events in Different Phases of a T-cell Therapy Study

Situation: The team addressed three key questions regarding AE reporting:

- Use of actual vs. planned treatment: In traditional Oncology studies, AE collection starts at randomization or dosing and is summarized for “actual treatment”. However, in TCR-T studies, AE collection starts at leukapheresis, which occurs few months before the T-cell infusion (actual treatment). A patient may die or withdraw during this time; hence, AE collected during the leukapheresis phase cannot be summarized under “actual treatment”.
- Defining Treatment Emergent Adverse Events (TEAEs): Lymphodepletion is the protocol-defined start of treatment, and generally happens seven days prior to the T-cell infusion. In this case, it is important to specify the correct reference start date to derive TEAEs.
- Reporting overlapping AEs: It is very common that AEs can start in one phase (e.g., pre-lymphodepletion) and end in a different phase (e.g., post T-cell infusion). It is also possible that an event changes grades/severity from one phase to another. Grade/severity changes between phases also impact accurate derivation of TEAE. In

such cases, clear specifications are needed at the study or project level on how to best report the overlapping AEs to avoid under or over reporting.

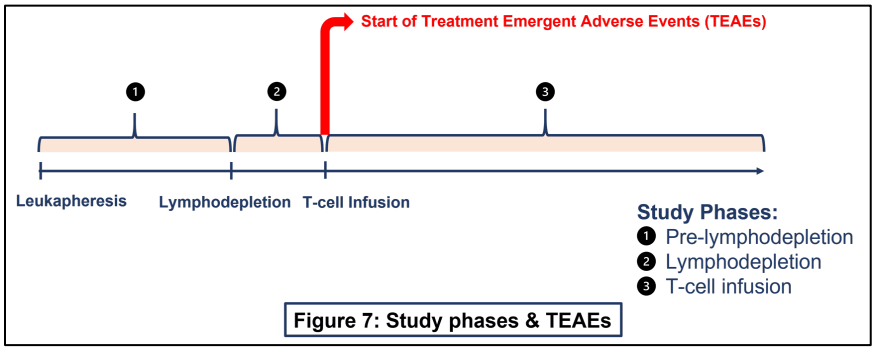


Figure 7: Study phases & TEAEs

Figure 7 shows the different study phases and T-cell infusion date as the reference date to determine TEAEs.

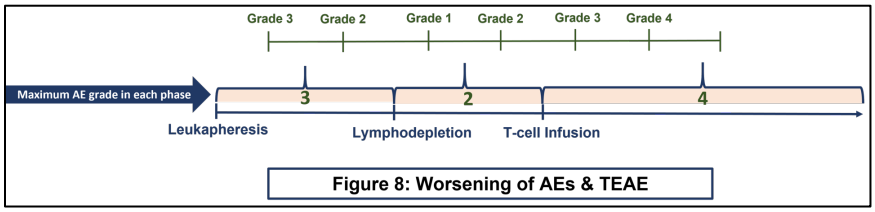


Figure 8: Worsening of AEs & TEAE

Figure 8 shows an AE event which starts as grade 3 following leukapheresis but then improves to grade 2. It improves to grade 1 following lymphodepletion but then worsens to grade 2. It worsens to grade 3 in the T-cell infusion phase, and then to grade 4 before resolving.

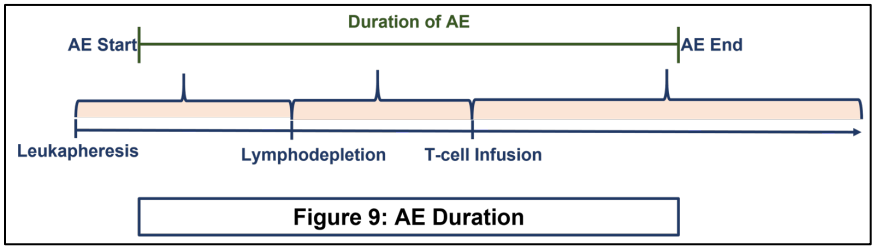


Figure 9: AE Duration

Figure 9 shows the overall event duration.

Challenge	**Resolution**
Define Treatment Emergent Adverse Events (TEAEs)	After examining multiple options with clinical/stats/safety, the study team decided to define TEAEs as "*AEs which start or worsen after the first T-cell infusion*". This definition aims to identify AE onset and exacerbation that may be attributed to T-cell infusion.

Define worsening of adverse events	For a single AE event with multiple grade changes within and between phases, the following is done: - Derive maximum grade within each phase - Compare change in maximum grade with the maximum grade of any time prior to phase - If maximum grade is greater than that of any time prior to the phase maximum grade then consider AE as worsened In figure 8 above, maximum AE grades are "2" and "4" in lymphodepletion and T-cell infusion phases, respectively. In this case the AE is considered to have worsened in the T-cell infusion phase. This AE event is also considered a treatment emergent AE per definition.
Define the onset and duration of adverse events spanning multiple phases	Due to lack of any guidance, different options were considered to best define AE duration. The team decided to calculate duration as AE end date – AE start date (figure 9), regardless of if AE started and ended in different study phases.
Summarize maximum grade for AEs spanning multiple phases	For AEs with start and stop dates in different study phases, the maximum grade in each phase is summarized & reported separately. In figure 8 above, the AE is summarized as grade 3, grade 2, & grade 4 in pre-lymphodepletion, lymphodepletion, and T-cell infusion phases, respectively.

Example #3: Receiving Full Line Systemic Therapy during Time between Leukapheresis and Lymphodepletion

Situation: Intent-to-Treat (ITT) analysis population is defined as all patients who started leukapheresis screening. The length of time between leukapheresis and lymphodepletion can be significant. Given the disease status of the patient population, there is a likelihood that full line systemic therapy may be required during this time. For protocols with substudies investigating previously untreated patients or specific number of prior therapies, this results in subject ineligibility from the study, analysis of prior anti-cancer therapies, and data handling and reporting challenges if the subject is moved from one substudy to a different one within the same protocol.

Challenge	**Resolution**
Handling and reporting of subject data in the primary substudy.	Subject is considered withdrawn from the substudy. All data up to the time of withdrawn is summarized and reported under ITT population.

Transferring subject data to a different substudy under the same protocol.	The subject is reconsented, and reenrolled in the new substudy with a new subject ID (SUBJID). Unique subject ID (USUBJID) clearly identifies the subject as being transferred from the parent substudy. All data is reentered into the new substudy and the subject data is reported using ITT population. For ongoing safety reporting, such as, iDMCs, the subject is included in both substudies under ITT population but counted only once in the total column and integrated displays. A footnote is added for clarity.

Recommendations

Based on the GSK's CGT programming experiences, the authors recommend the following:

1- Invest in resources to develop CGT specific end-to-end standards such as, eCRF design; SDTM mapping; ADaM specifications; derived data algorithms; terminologies; and display mocks. For example:
   a. At GSK, the CGT programmers are working on two initiatives to standardize CGT specific reporting standards based on current learnings.

2- Put together an industry level team of subject matter experts for CGT and master protocol studies to advise on existing standards and identify/explore new ideas to facilitate CGT specific programming and reporting activities. For example:
   a. FDA and PHUSE are jointly working to introduce a new AESI specific ADaM domain, ADCRSNT[8] for Cytokine Release Syndrome (CRS) and Neurotoxicity, which are common CGT adverse events.
   b. CDISC recently added two new SDTM finding domains CP (Cell Phenotype) and GF(Genomics findings) for storing CGT related data.

3- Involve the programming team early in the process, preferably during protocol development phase.
   a. Programmers can provide important insights from reporting perspective, and also bring past experiences and examples to benefit the ongoing work.

Conclusion

Due to the lack of programming standards, and guidance, working with master protocols is challenging and time and resource intensive. Similarly, the unique design of CGT studies requires new programming methodologies and standards.

With the growing number of CGT studies and the advantages of using master protocols, there is an immediate need of industry level collaboration to develop robust standards, best

practices, recommendations, and guidance. In addition to supporting programming activities, this will bring consistency for expedited regulatory reviews, and operational efficiencies.

References

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