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Know your PET: From the Scans to SDTM Datasets

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ABSTRACT

PET with the glucose analog FDG as a tracer is a mature and increasingly available clinical imaging technique used for diagnosing, staging, and detecting the recurrence of many cancers. US FDA and EMEA have approved FDG and authorized it as a diagnostic radiopharmaceutical in the diagnosis of infection. FDG-PET has rapidly gained importance in Lymphoma Clinical Trials with the 2014 Lugano Classification and more recent LYRIC. irRECIST and iRECIST, the latest response criteria for immunotherapies in solid tumors are also becoming more reliant on FDG-PET for assessing inflammation.

The role of FDG-PET has grown from a qualitative positive or negative response to a quantitative response with the use of Deauville five-point scale (2009) in assessment of treatment response in Hodgkin Lymphoma and certain types of non-Hodgkin lymphomas. Deauville score calculation involves consideration of various individual scores: $SUVmax_{target\ lesion}$, $SUVmean_{background}$.

The latest oncology trials are no longer driven by CT scans alone but are increasingly utilizing FDG-PET to deliver clearer efficacy data. With this paper, we would like to present the translation and mapping of the raw FDG-PET data into the appropriate SDTM Domains of PR, TU, TR and RS, derive the Deauville score, and how to use it in conjugation to CT Response, if existing, in derivation of the Overall Response.

INTRODUCTION

Invented in the mid-1970s, positron emission tomography (PET) rapidly gained importance in the fields of neurology and cardiology, as a valuable diagnostic tool. In a decade, it slowly garnered attention in the field of oncology and continues to be a reliable and consistent diagnostic imaging tool for various cancers. PET relies on biochemical or physiological phenomenon, unlike computed tomography (CT) or magnetic resonance imaging (MRI), which show anatomic detail. Figure 1 (Hg6996, PET/CT Scanner, n.d.) shows one of the latest PET/CT systems, which combines radiological (CT) and nuclear medicine (PET) imaging modalities, making it possible to add anatomical details to functional information.

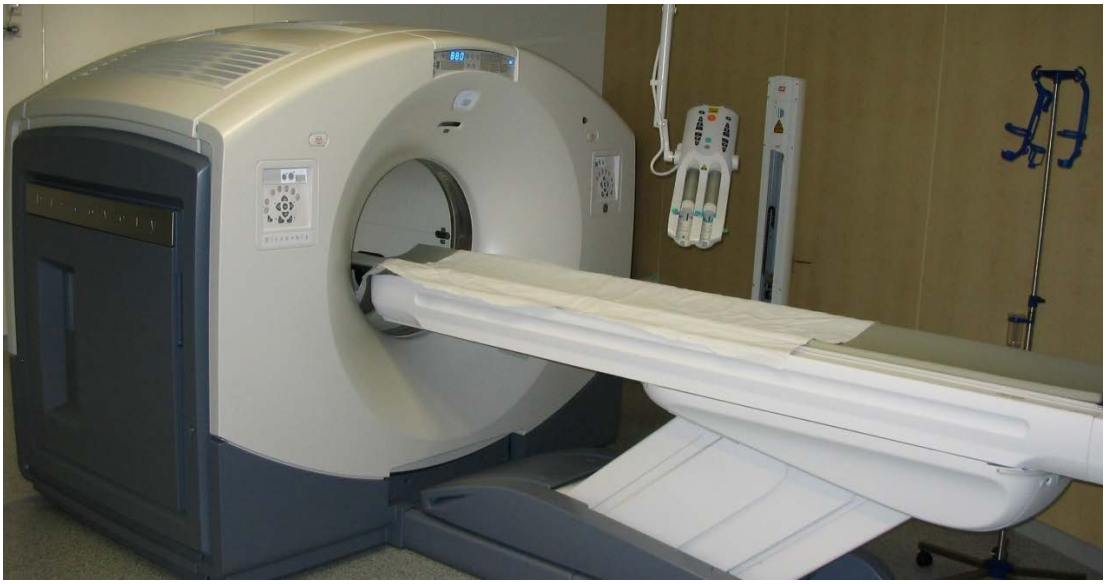

Figure 1. GE Discovery D600 PET/CT System.

Many different types of tracers are available for imaging with PET, but the majority of the oncology PET studies utilize an analogue of glucose, ^{18}F-2-fluoro-2-deoxy-d-glucose (FDG). Once FDG is injected into the patient's body, it actively reaches into the cells and distributes itself throughout the body, in a manner similar to glucose. However, inside the cells, FDG is trapped as the converted FDG-6-Phosphate in contrast to regular glucose, which is further broken down and utilized by the body. Due to the higher metabolic rate of tumor cells, they uptake and retain higher levels of FDG when compared to normal tissues, thus helping investigators distinguish between benign and malignant lesions when CT and MRI cannot (Griffeth, 2005). Figure 2 (Hg6996, Standardized uptake value, n.d.) illustrates the PET images taken across various anatomical planes, with a visualization of the contrast in FDG uptake.

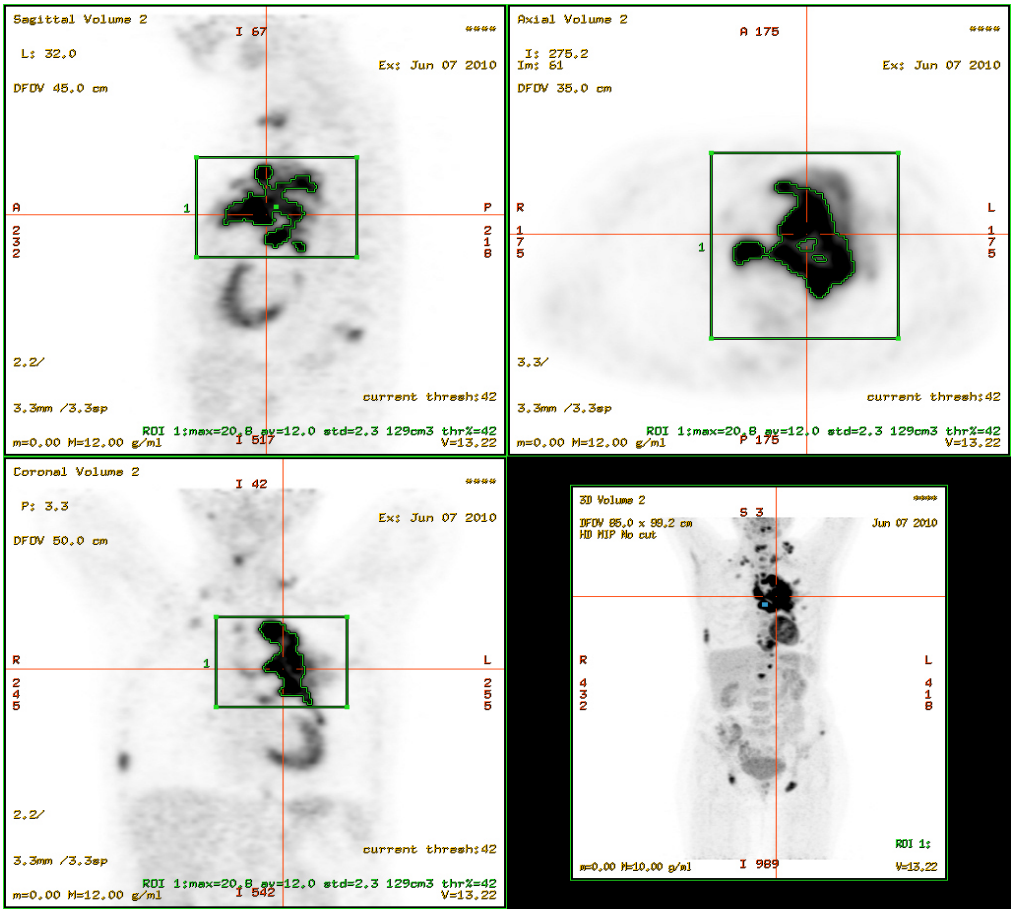

Figure 2. Example PET images across different anatomical planes

PET has become a reliable diagnostic imaging tool for staging, restaging, and response assessment of routinely FDG-avid positive lymphomas (e.g., diffuse large B-cell lymphoma [DLBCL], Hodgkin's lymphoma [HL]) (Cheson, et al., 2007). With the advent of the updated Lugano classification in 2014, FDG-PET-CT was formally included as a pre-treatment and staging diagnostic tool for FDG-avid lymphomas, utilizing the 5-point Deauville score for consistently assessing the scans across different time points. Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST 1.0), utilizes the peak standardized uptake value corrected for lean body mass (SUL_{peak}) instead of the widely used single-pixel maximum standardized uptake value (SUV_{Max}) shown in Figure 2. Thus, investigators are gaining new ways for reliable interpretation of the quantitative results of PET data. This translates to various new response variables in case report forms (CRFs), that clinical programmer then capture in the standard TU, TR and RS SDTM datasets.

Though the latest PET scan usually accompanies CT (PET/CT) for anatomic co-registration and attenuation correction, the CT portion of a PET/CT generally does not substitute for a diagnostic CT (e.g.,

CT Chest, CT Abdomen) for measuring lesions, and a CT scan becomes particularly important in assessing FDG-avid negative lesions. In a multi-site clinical trial, the limitation of unavailability of the same diagnostic imaging tool, owing to cost, across all the sites may result in mixed data involving CT, PET, and PET-CT scans. In this paper, we present one such example and demonstrate the mapping of the mixed data into relevant SDTM Tumor domains.

MAPPING TO SDTM

Our example lymphoma study "XYX567" follows the Revised Response Criteria for Malignant Lymphoma (Cheson, 2007). CT (CT of chest, neck, abdomen, and pelvis) and PET scans are required at baseline and at week 8 for restaging. A combined CT/PET may satisfy the requirements for CT and PET scanning for this study, as long as the CT portion of the scan is of diagnostic quality. We have summarized the tumor data of a subject at baseline and at week 8.

PROCEDURE (PR)

The PR domain contains the scan details of the subject. A pre-specified scan in the CRF will have a value of "Y" for PRPRESP, and PROCCUR's value conveys whether the pre-specified scan has taken place or not. In study "XYZ567", individual diagnostic CT scans and a whole body PET are pre-specified at baseline and week 8 visits, and the baseline assessments show details of all the pre-specified scans (Figure 3). However, a PET/CT scan is performed and as it is of sufficient diagnostic quality, provided the restaging assessments.

STUDYID	DOMAIN	PRSEQ	PRREFID	PRLNKGRP	PRTRT	PRPRESP	PROCCUR	PRLOC	VISIT	PRSTDTC
XYZ567	PR	1	IMG-00001	A1	CT SCAN	Y	Y	NECK	SCREEN	2010-01-01
XYZ567	PR	2	IMG-00002	A1	CT SCAN	Y	Y	ABDOMEN	SCREEN	2010-01-01
XYZ567	PR	3	IMG-00003	A1	CT SCAN	Y	Y	CHEST	SCREEN	2010-01-01
XYZ567	PR	4	IMG-00004	A1	CT SCAN	Y	Y	PELVIS	SCREEN	2010-01-01
XYZ567	PR	5	IMG-00005	A1	PET SCAN	Y	Y	BODY	SCREEN	2010-01-02
XYZ567	PR	6		A2	CT SCAN	Y	N	NECK	WEEK 8	
XYZ567	PR	7		A2	CT SCAN	Y	N	ABDOMEN	WEEK 8	
XYZ567	PR	8		A2	CT SCAN	Y	N	CHEST	WEEK 8	
XYZ567	PR	9		A2	CT SCAN	Y	N	PELVIS	WEEK 8	
XYZ567	PR	10		A2	PET SCAN	Y	N	BODY	WEEK 8	
XYZ567	PR	11	IMG-00006	A2	PET/CT SCAN			BODY	WEEK 8	2010-03-01

Figure 3. The PR domain with both CT, PET, and CT/PET scan details.

TUMOR IDENTIFICATION (TU)

TU domain contains the details of each target, non-target, and new lesion's location and methods used for its identification. In study "XYZ567" the inclusion criteria specify that baseline lesions should be FDG-avid positive per a whole body PET. Classification into target and non-target lesions is decided based on their measurements from CT scans. Hence, each lesion requires two methods of identification, unlike studies based on RECIST where a CT scan would suffice for identifying the lesions.

TUGRPID often groups the split or merged lesions in trial data. We leveraged TUGRPID to group the details of the CT scan with the corresponding PET scan used to identify a single lesion (Figure 4). TUGRPID=TN01 shows that a CT scan (TUREFID=IMG-00002) and a PET scan (TUREFID=IMG-00005) were used to identify a target nodal lesion at PARA AORTIC LYMPH NODE.

DOMAIN	TUSEQ	TUGRPID	TUREFID	TULNKID	TUTESTCD	TUSTRESC	TULOC	TUMETHOD	VISIT	TUDTC
TU	1	TN01	IMG-00002	TN01CT	TUMIDENT	TARGET NODAL	PARA AORTIC LYMPH NODE	CT SCAN	SCREEN	2010-01-01
TU	2	TN01	IMG-00005	TN01PET	TUMIDENT	TARGET NODAL	PARA AORTIC LYMPH NODE	PET SCAN	SCREEN	2010-01-02
TU	3	TN02	IMG-00004	TN02CT	TUMIDENT	TARGET NODAL	INGUINAL LYMPH NODE	CT SCAN	SCREEN	2010-01-01
TU	4	TN02	IMG-00005	TN02PET	TUMIDENT	TARGET NODAL	INGUINAL LYMPH NODE	PET SCAN	SCREEN	2010-01-02
TU	5		IMG-00006	NEW01	TUMIDENT	NEW	LUNG	PET/CT SCAN	WEEK 8	2010-03-01
TU	6		IMG-00006	NEW02	TUMIDENT	NEW	SPLENIC HILAR LYMPH NODE	PET/CT SCAN	WEEK 8	2010-03-01

Figure 4. The TU domain with tumor identification details.

TUMOR RESULTS (TR)

TR domain captures all the results associated with the scans. The TRTESTCD uses the standard test codes from the CDISC Controlled Terminology (National Cancer Institute, 2017), except for the PET specific sponsor codes of this example study: SUVBACK, SUVMAX, SUVMEAN, SDSUVMN, FDUPTK, and DUVSC.

Standardized uptake value, SUV is calculated as a ratio of tissue radioactivity concentration (e.g., in units [kBq/mL]) at time T, and administered dose (e.g., in units [MBq]) at the time of injection divided by body weight (usually in units [kg]). SUV on the highest image pixel in the tumor region is the SUV_{max}, and the averaged SUV) is the SUV_{mean}. Standard deviation of the SUV_{mean} and SUV of the background are also included in the data.

Deauville Score

In an effort to improve the comparisons among different machines and centers, and to standardize the interpretation of response to PET scans, a group of investigators met in Deauville, France, in 2009 and proposed a new approach. The Deauville score grades a scan from 1 to 5, with the score of 1 meaning no uptake consistent with lymphoma. All other scores are in relation to background uptake that is always present in the mediastinal blood pool and liver. The uptake in the mediastinal blood pool is consistently lower than in the liver. A score of 2 indicates uptake but at a lower value than in the mediastinal blood pool, 3 denotes uptake with an intensity between the mediastinal blood pool and liver, and 4 would be an uptake greater than in the liver. A score of 5 means a dramatic increase in uptake and/or new sites of involvement. Using this method, a Deauville score of 1 or 2 is accepted as a complete response to treatment and especially for interim scans, a score of 3 is also often taken as a complete response.

In Figure 5 below TRTESTCDs BKG1, BKG2, and BKG3 shown at the baseline visit represent the background determined based on the Region of Interest (ROI) drawn for the blood pool; the arch of the aorta at the aortopulmonary level, free from myocardial contamination; liver parenchyma; and also from muscle tissue of the anterior thigh, respectively. The corresponding background is chosen for each target lesion to derive the tumor to background ratio, used in the derivation of the Deauville score.

TRSEQ	TRGRPID	TRREFID	TRLNKGRP	TRLNKID	TRTESTCD	TRSTRESC	TRSTRESN	TRSTRESU	TRMETHOD	VISIT	TRDTC
1	TARGET NODAL	IMG-00002	A1	TN01 CT	LDIAM	50	50	mm	CT SCAN	SCREEN	2010-01-01
2	TARGET NODAL	IMG-00002	A1	TN01 CT	LPERP	20	20	mm	CT SCAN	SCREEN	2010-01-01
3	TARGET NODAL	IMG-00004	A1	TN02 CT	LDIAM	100	100	mm	CT SCAN	SCREEN	2010-01-01
4	TARGET NODAL	IMG-00004	A1	TN02 CT	LPERP	50	50	mm	CT SCAN	SCREEN	2010-01-01
5	TARGET NODAL	IMG-00002	A1	TN01 CT	TUMSTATE	PRESENT			CT SCAN	SCREEN	2010-01-01
6	TARGET NODAL	IMG-00005	A1	TN01 PET	FDGUPTK	POSITIVE			PET SCAN	SCREEN	2010-01-02
7	TARGET NODAL	IMG-00004	A1	TN02 CT	TUMSTATE	PRESENT			CT SCAN	SCREEN	2010-01-01
8	TARGET NODAL	IMG-00005	A1	TN02 PET	FDGUPTK	POSITIVE			PET SCAN	SCREEN	2010-01-02
9	TARGET NODAL	IMG-00002	A1	TN01 CT	AREA	1000	1000	mm2		SCREEN	2010-01-01
10	TARGET NODAL	IMG-00004	A1	TN02 CT	AREA	5000	5000	mm2		SCREEN	2010-01-01
11	TARGET NODAL		A1		SUMAREA	6000	6000	mm2		SCREEN	
12	TARGET NODAL	IMG-00004	A1		BKG1	0.3	0.3	ml/g	PET SCAN	SCREEN	2010-01-02
13	TARGET NODAL	IMG-00004	A1		BKG2	0.3	0.3	ml/g	PET SCAN	SCREEN	2010-01-02
14	TARGET NODAL	IMG-00004	A1		BKG3	0.2	0.2	ml/g	PET SCAN	SCREEN	2010-01-02
15	TARGET NODAL	IMG-00005	A1	TN01 PET	SUVMAX	1.9	1.9	RATIO	PET SCAN	SCREEN	2010-01-02
16	TARGET NODAL	IMG-00005	A1	TN02 PET	SUVMAX	2.5	2.5	RATIO	PET SCAN	SCREEN	2010-01-02
17	TARGET NODAL	IMG-00005	A1	TN01 PET	SUVMEAN	1.3	1.3	RATIO	PET SCAN	SCREEN	2010-01-02
18	TARGET NODAL	IMG-00005	A1	TN02 PET	SUVMEAN	1.5	1.5	RATIO	PET SCAN	SCREEN	2010-01-02
19	TARGET NODAL	IMG-00005	A1	TN01 PET	SDSUVMN	0.3	0.3	RATIO	PET SCAN	SCREEN	2010-01-02
20	TARGET NODAL	IMG-00005	A1	TN02 PET	SDSUVMN	0.4	0.4	RATIO	PET SCAN	SCREEN	2010-01-02
21	TARGET NODAL	IMG-00005	A1	TN01 PET	SUVBACK	1.3	1.3	RATIO	PET SCAN	SCREEN	2010-01-02
22	TARGET NODAL	IMG-00005	A1	TN02 PET	SUVBACK	1.7	1.7	RATIO	PET SCAN	SCREEN	2010-01-02
23	TARGET NODAL	IMG-00006	A2	TN01	LDIAM	10	10	mm	CT SCAN	WEEK 8	2010-03-01
24	TARGET NODAL	IMG-00006	A2	TN01	LPERP	10	10	mm	CT SCAN	WEEK 8	2010-03-01
25	TARGET NODAL	IMG-00006	A2	TN02	LDIAM	50	50	mm	CT SCAN	WEEK 8	2010-03-01
26	TARGET NODAL	IMG-00006	A2	TN02	LPERP	50	50	mm	CT SCAN	WEEK 8	2010-03-01
27	TARGET NODAL	IMG-00006	A2	TN01	TUMSTATE	ABSENT			CT SCAN	WEEK 8	2010-03-01

28	TARGET NODAL	IMG-00006	A2	TN01	FDGUPTK	POSITIVE			PET/CT SCAN	WEEK 8	2010-03-01
29	TARGET NODAL	IMG-00006	A2	TN02	TUMSTATE	PRESENT			PET/CT SCAN	WEEK 8	2010-03-01
30	TARGET NODAL	IMG-00006	A2	TN02	FDGUPTK	POSITIVE			PET/CT SCAN	WEEK 8	2010-03-01
31	TARGET NODAL	IMG-00006	A2	TN01	AREA	100	100	mm2		WEEK 8	2010-03-01
32	TARGET NODAL	IMG-00006	A2	TN02	AREA	2500	2500	mm2		WEEK 8	2010-03-01
33	TARGET NODAL		A2		SUMAREA	2600	2600	mm2		WEEK 8	
34	TARGET NODAL	IMG-00006	A2	TN01	SUVMAX	1.2	1.2	RATIO	PET/CT SCAN	WEEK 8	2010-03-01
35	TARGET NODAL	IMG-00006	A2	TN02	SUVMAX	1.0	1	RATIO	PET/CT SCAN	WEEK 8	2010-03-01
36	TARGET NODAL	IMG-00006	A2	TN01	SUVMEAN	0.7	0.7	RATIO	PET/CT SCAN	WEEK 8	2010-03-01
37	TARGET NODAL	IMG-00006	A2	TN02	SUVMEAN	0.7	0.7	RATIO	PET/CT SCAN	WEEK 8	2010-03-01
38	TARGET NODAL	IMG-00006	A2	TN01	SDSUVMN	0.2	0.2	RATIO	PET/CT SCAN	WEEK 8	2010-03-01
39	TARGET NODAL	IMG-00006	A2	TN02	SDSUVMN	0.2	0.2	RATIO	PET/CT SCAN	WEEK 8	2010-03-01
40	TARGET NODAL	IMG-00006	A2	TN01	SUVBACK	0.8	0.8	RATIO	PET/CT SCAN	WEEK 8	2010-03-01
41	TARGET NODAL	IMG-00006	A2	TN02	SUVBACK	0.6	0.6	RATIO	PET/CT SCAN	WEEK 8	2010-03-01
42	TARGET NODAL	IMG-00006	A2		DUVSC	2	2		PET/CT SCAN	WEEK 8	
43	NEW	IMG-00006	A2	NEW01	TUMSTATE	PRESENT			PET/CT SCAN	WEEK 8	2010-03-01
44	NEW	IMG-00006	A2	NEW01	LDIAM	50	50	mm	PET/CT SCAN	WEEK 8	2010-03-01
45	NEW	IMG-00006	A2	NEW01	LPERP	20	20	mm	PET/CT SCAN	WEEK 8	2010-03-01
46	NEW	IMG-00006	A2	NEW01	FDGUPTK	POSITIVE			PET/CT SCAN	WEEK 8	2010-03-01
47	NEW	IMG-00006	A2	NEW02	TUMSTATE	PRESENT			PET/CT SCAN	WEEK 8	2010-03-01
48	NEW	IMG-00006	A2	NEW02	LDIAM	50	50	mm	PET/CT SCAN	WEEK 8	2010-03-01
49	NEW	IMG-00006	A2	NEW02	LPERP	50	50	mm	PET/CT SCAN	WEEK 8	2010-03-01
50	NEW	IMG-00006	A2	NEW02	FDGUPTK	POSITIVE			PET/CT SCAN	WEEK 8	2010-03-01

Figure 5. The TR Domain with the results of both PET, CT, and PET/CT scans.

DISEASE RESPONSE (RS)

The RS domain contains the post-baseline assessments as shown in Figure 6. Based on the results shown in TR, the target lesions decreased in size as well as SUV at week 8, but the appearance of two new PET positive lesions resulted in an overall response of “Progressive Disease” (PD) as indicated in RSSTRESC.

DOMAIN	RSSEQ	RSLNKGRP	RSTESTCD	RSTEST	RSCAT	RSSTRESC	VISIT	RSDTC
RS	1	A2	OVRLRESP	Overall Response	CHESON MALIGNANT LYMPHOMA 2007	PD	WEEK 8	2010-03-01

Figure 6. The RS domain with the response information.

RELREC

The RELREC dataset is the key to link the related records across the different domains discussed above. The RELID identifies the related RDOMAINs (e.g., in Figure 7, RDOMAINs TU and TR have a common RELID “A”). IDVAR identifies the variables that serve as the key to merge the associated domains. RELTYPE on the other hand explains the relation between the associated domains (e.g., one record in TU can be associated with multiple records in TR).

STUDYID	RDOMAIN	IDVAR	RELTYPE	RELID
XYZ567	TU	TULNKID	One	A
XYZ567	TR	TRLNKID	Many	A
XYZ567	TR	TRLNKGRP	Many	B
XYZ567	RS	RSLNKGRP	One	B
XYZ567	PR	PRREFID	One	C
XYZ567	TU	TUREFID	Many	C
XYZ567	PR	PRLNKGRP	Many	D
XYZ567	RS	RSLNKGRP	One	D

Figure 7. The RELREC associating TU, TR, RS and PR with the respective keys.

CONCLUSION

We have attempted to summarize various details of the PET data and effectively capture it in appropriate SDTM domains for analysis. An efficient and organized SDTM dataset is vital to ascertain data traceability and makes it easier to update the downstream Analysis Data Model (ADaM) datasets, based on the statistician’s needs or FDA’s queries during the submission process.

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