Paper DS06

Intervention ML: Mapping of Meal data.

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ABSTRACT

The focus of most bioavailability/bioequivalence trials is to determine the effect of food on the investigational medical product. Along with BA/BE studies, there are trials for conditions like diabetes where the information on meal consumed by the subject is of interest. The only option then is to create a custom domain to capture meal information. However, the Diabetes TAUG has ML data developed which can be used in BA/BE and several other trials that capture meal data. It then makes sense to map the food intake of the subject to ML instead of making use of custom domains. Meal is an Interventions domain where the focus is on details of meal consumed along with the timing and quantity of food intake by subject. This paper gives a brief overview of ML domain and its metadata (for SDTM and CDASH) and discusses some practical guidance with a few examples along with CRF annotations. It also explains how meal information is useful in BA/BE studies.

INTRODUCTION

In most of the BA/BE studies, meal data is important as study objective is to evaluate the effect of food on the Investigational product. The primary outcome measure of the same is the 90% confidence interval of the relative mean C_{max}, AUC_t and AUC_{inf} of the test to reference formulation is within 80% to 125%.

In diabetes trials, Meals given as part of

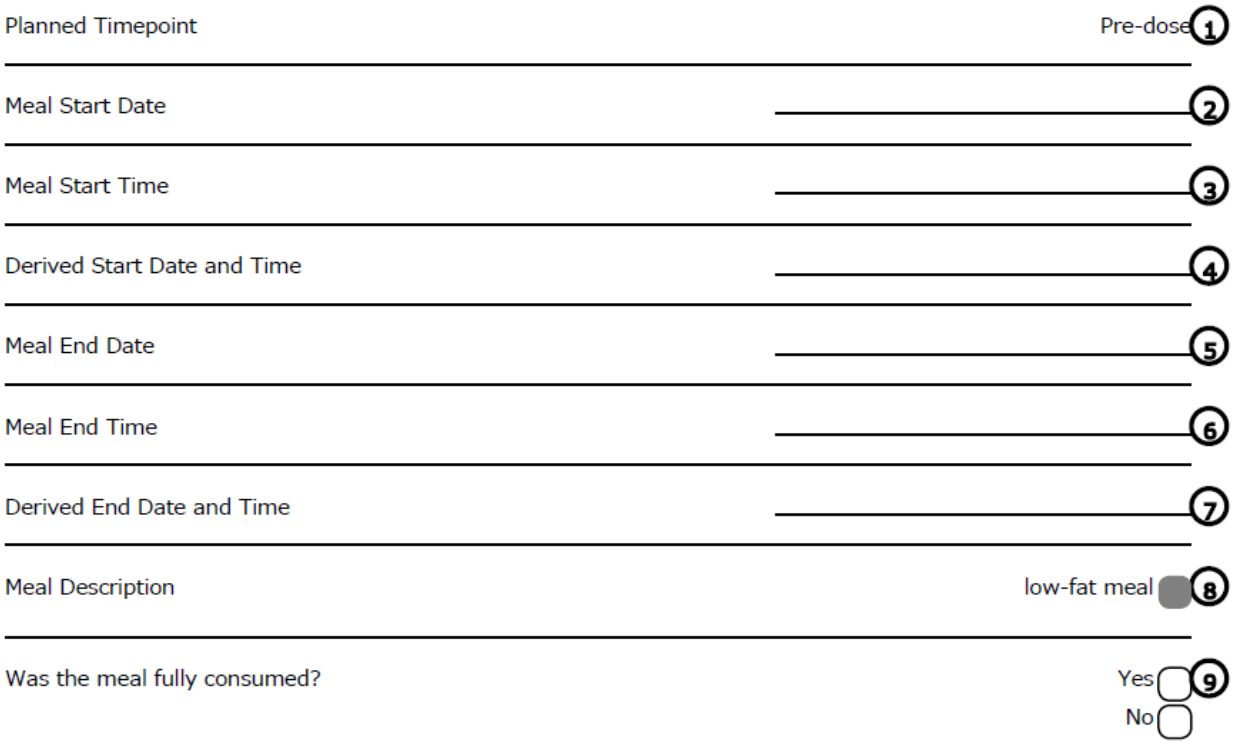
- Meal tolerance test
- Food and drink used to treat hypoglycemic events
- Meals taken in the normal course of events

Collection of meal data plays vital role in context with the objective of the trial. Before introduction of ML domain, traditional approach was to map subject meal information to custom domain. Various sponsor had their own standards to map this data to custom domain. It has been difficult for regulatory authority to review non-standard CDISC SDTM domain as the naming convention and variable names/labels not being consistent across sponsors. This paper will describe the CDASH and SDTM models for a typical Meal data collection.

Meal data is typically captured in below format on the CRF.

Form: Meal Summary

Was the Meal administered?	Yes ☐ 1 No ☐



CDASH MODEL:

The purpose of the CDASH Meal is to facilitate the collection of information that is comprehensive and relevant to the understanding of the MEAL administration that will allow for an assessment of food effect on the Investigational product.

Sr. No.	Question Text	Prompt	CDASH Variable Name	CDASH Core
1	What is the study identifier?	Protocol/Study	STUDYID	HR
2	What is the site identifier?	Site Identifier	SITEID	HR
3	What is the subject identifier?	Subject	SUBJID	HR
4	Were any Meal taken/Administered?	Any Meal	MLYN	O
5	What was the Meal Description/ administered/therapy?	Meal Description or Administration or Therapy	MLTRT	HR
6	Did the subject take the [pre-specific Meal]? Or Has the subject taken the [pre-specific Meal/treatment]?	Specific Meal/Treatment	MLOCCUR	O
7	What was the planned time point for study Meal taken?	Planned Time Point Name	MLTPT	R/C
8	Meal Start Date/Time	Start Date/Time	MLSTDAT/MLSTTIM	O
9	Meal End Date/Time	End Date/Time	MLENDAT/MLENTIM	O

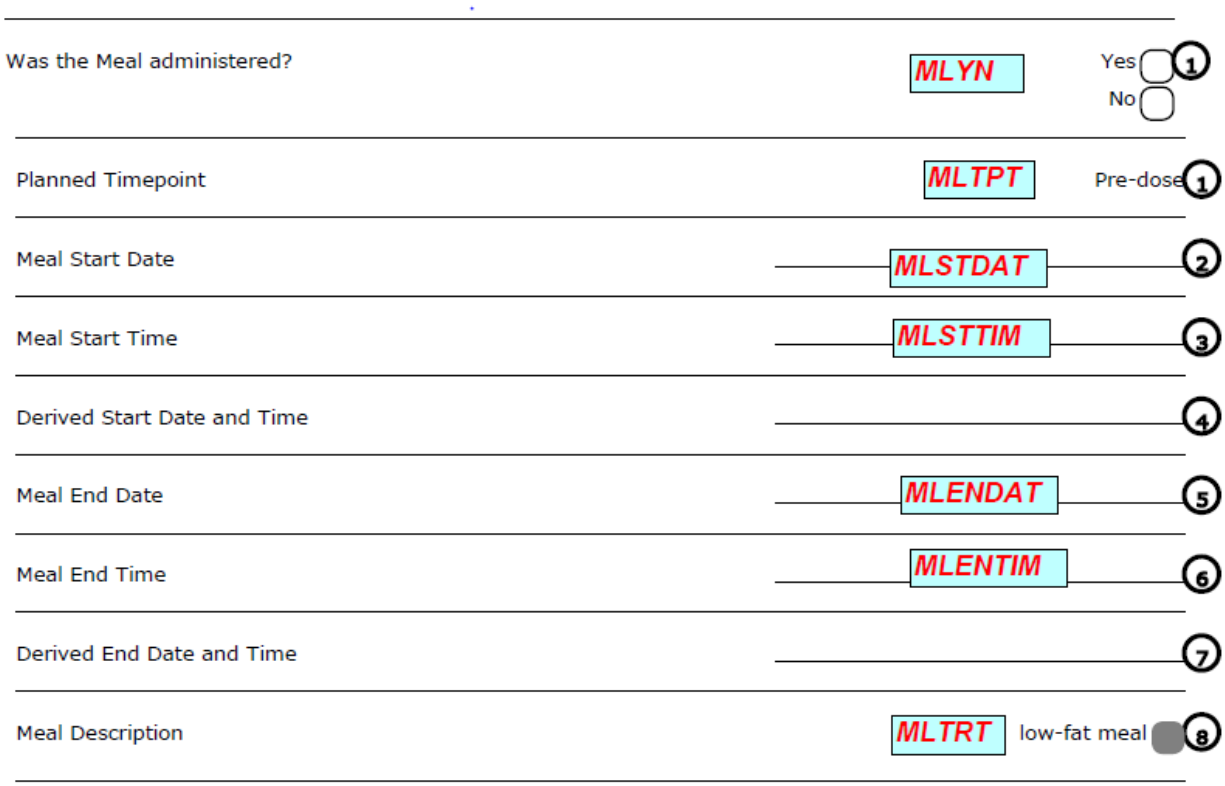
Note: HR: Highly Recommended
R/C: Recommended/Conditional
O : Optional

CDASH ANNOTATIONS

This is an example of ML CRF collecting the optional information around specific types of meal taken by the subject. The sponsor has included instructions on the CRF to capture date time per time-point per type of meal consumed.

Example Rave Annotation: There following examples were created using Medidata Rave's study build tool, Architect.

Form: Meal Summary



SDTM MODEL:

Information regarding the subject's meal consumption, such as fluid intake, amounts, form (solid or liquid state), frequency, etc., typically used for pharmacokinetic analysis.

One record per recorded meal per time point per subject.

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req
DOMAIN	Domain Abbreviation	Char	ML	Identifier	Two-character abbreviation for the domain.	Req
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core
MLSEQ	Sequence Number	Num		Identifier	Sequence Number given to ensure uniqueness of subject records within a domain. May be any valid number.	Req
MLGRPID	Group ID	Char		Identifier	Used to tie together a block of related records in a single domain for a subject.	Perm
MLSPID	Sponsor-Defined Identifier	Char		Identifier	Sponsor-defined reference number. Examples: a number pre-printed on the CRF as an explicit line identifier or record identifier defined in the sponsor's operational database. Example: line number on a meal page.	Perm
MLTRT	Reported Name of Meal	Char		Topic	Verbatim meal name that is either pre-printed or collected on a CRF.	Req
MLMODIFY	Modified Meal Name	Char		Synonym Qualifier	If MLTRT is modified, then MLMODIFY will contain the modified text.	Perm
MLDECOD	Standardized Meal Name	Char	*	Synonym Qualifier	Standardized or dictionary-derived text description of MLTRT or MLMODIFY if the sponsor chooses to code the meal. The sponsor is expected to provide the dictionary name and version used to map the terms utilizing the define.xml external codelist attributes.	Perm
MLCAT	Category for Meal	Char	*	Grouping Qualifier	Used to define a category of meal.	Perm
MLSCAT	Subcategory for Meal	Char	*	Grouping Qualifier	A further categorization of meal.	Perm
MLPRESP	ML Pre-Specified	Char	(NY)	Record Qualifier	Used to indicate whether (Y/null) information about the consumption of a specific meal was solicited on the CRF.	Perm
MLOCCUR	ML Occurrence	Char	(NY)	Record Qualifier	When the consumption of specific meal is solicited, MLOCCUR is used to indicate whether or not (Y/N) consumption of the meal occurred. Values are null for meals not specifically solicited.	Perm
MLSTAT	Completion Status	Char	(ND)	Record Qualifier	Used to indicate that a question about a pre-specified meal was not answered. Should be null or have a value of NOT DONE.	Perm
MLREASND	Reason Meal Not Collected	Char		Record Qualifier	Describes the reason meal was not collected. Used in conjunction with MLSTAT when value is NOT DONE.	Perm
MLINDC	Indication	Char		Record Qualifier	Denotes why a meal was taken or administered.	Perm
MLDOSE	Meal Consumption	Num		Record Qualifier	Amount of MLTRT taken.	Perm
MLDOSTXT	Meal Consumption Text	Char		Record Qualifier	Dosing amounts or a range of dosing information collected in text form. Units may be stored in MLDOSU. Example: 200-400, 15-20.	Perm

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core
MLDOSU	Consumption Units	Char	(UNIT)	Variable Qualifier	Units for MLDOSE, MLDOSTXT, and MLDOSTOT. Examples: ng, mg, or mg/kg.	Perm
MLDOSFRM	Meal Form	Char	(FRM)	Record Qualifier	Dose form for MLTRT. Examples: SOLID, LIQUID.	Perm
MLDOSFRQ	Meal Frequency per Interval	Char	(FREQ)	Variable Qualifier	Usually expressed as the number of repeated administrations of MLDOSE within a specific time period.	Perm
MLDOSTOT	Total Daily Consumption	Num		Record Qualifier	Total daily dose of MLTRT using the units in MLDOSU. Total dose over a period other than day could be recorded in a separate Supplemental Qualifier variable. MLDOSTOT should be used in addition to MLDOSE, and not in place of it.	Perm
MLDOSRGM	Intended Meal Regimen	Char		Variable Qualifier	Text description of the (intended) schedule or regimen for the Intervention. Examples: TWO WEEKS ON, TWO WEEKS OFF.	Perm
MLROUTE	Route of Administration	Char	(ROUTE)	Variable Qualifier	Route of administration for MLTRT.	Perm
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Perm
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter.	Perm
EPOCH	Epoch	Char	(EPOCH)	Timing	Trial Epoch of the Meal record. Examples: RUN-IN, TREATMENT.	Perm
MLSTDTC	Start Date/Time of Meal	Char	ISO 8601	Timing	Start date/time of the observation represented in IS0 8601 character format.	Perm
MLENDTC	End Date/Time of Meal	Char	ISO 8601	Timing	End date/time of the observation represented in IS0 8601 character format.	Perm
MLSTDY	Study Day of Start of Meal	Num		Timing	Study day of start of meal relative to the sponsor-defined RFSTDTC.	Perm
MLENDY	Study Day of End of Meal	Num		Timing	Study day of end of meal relative to the sponsor-defined RFSTDTC.	Perm
MLDUR	Duration of Meal	Char	ISO 8601	Timing	Collected duration for a meal. Used only if collected on the CRF and not derived from start and end date/times.	Perm
MLTPT	Planned Time Point Name	Char		Timing	Text Description of time when meal should be taken. This may be represented as an elapsed time relative to a fixed reference point, such as time of last meal. See MLTPTNUM and MLTPTREF.	Perm
MLTPTNUM	Planned Time Point Number	Num		Timing	Numerical version of planned time point used in sorting.	Perm
MLSTRTPT	Start Relative to Reference Time Point	Char	(STENRF)	Timing	Identifies the start of the meal as being before or after the reference time point defined by variable MLSTTPT.	Perm

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core
MLSTTPT	Start Reference Time Point	char		Timing	Description or date/time in ISO 8601 character format of the reference point referred to by MLSTRTPT. Examples: "2003-12-15" or "VISIT 1".	Perm
MLENRTPT	End Relative to Reference Time Point	Char	(STENRF)	Timing	Identifies the end of the meal as being before or after the reference time point defined by variable MLENTPT.	Perm
MLENTPT	End Reference Time Point	Char		Timing	Description or date/time in ISO 8601 character format of the reference point referred to by MLENRTPT. Examples: "2003-12-25" or "VISIT 2".	Perm

SDTM Annotations:

ML=Meals

Form: Meal Summary

Was the Meal administered? — *MLPRESP=Y* / *MLOCCUR* — Yes ☐ 1 / No ☐

Planned Timepoint — *MLTPT* — Pre-dose 1

Meal Start Date — *MLSTDTC* — 2

Meal Start Time — 3

Derived Start Date and Time — *[NOT SUBMITTED]* — 4

Meal End Date — *MLENDTC* — 5

Meal End Time — 6

Derived End Date and Time — *[NOT SUBMITTED]* — 7

Meal Description — *MLTRT* — low-fat meal ■ 8

ML DOMAIN

	STUDYID	DOMAIN	USUBJID	MLSEQ	MLTRT	MLPRESP	MLOCCUR	VISITNUM	VISIT	EPOCH
1	XXX-102	ML	XXX-102-001-0301	1	LOW-FAT MEAL	Y	N	3	Period 1 Day 1	PERIOD 1 BASELINE
2	XXX-102	ML	XXX-102-001-0301	2	LOW-FAT MEAL	Y	Y	10	Period 2 Day 1	PERIOD 2 BASELINE
3	XXX-102	ML	XXX-102-001-0302	1	LOW-FAT MEAL	Y	Y	3	Period 1 Day 1	PERIOD 1 BASELINE
4	XXX-102	ML	XXX-102-001-0302	2	LOW-FAT MEAL	Y	N	10	Period 2 Day 1	PERIOD 2 BASELINE
5	XXX-102	ML	XXX-102-001-0303	1	LOW-FAT MEAL	Y	Y	3	Period 1 Day 1	PERIOD 1 BASELINE
6	XXX-102	ML	XXX-102-001-0303	2	LOW-FAT MEAL	Y	N	10	Period 2 Day 1	PERIOD 2 BASELINE
7	XXX-102	ML	XXX-102-001-0304	1	LOW-FAT MEAL	Y	N	3	Period 1 Day 1	PERIOD 1 BASELINE
8	XXX-102	ML	XXX-102-001-0305	1	LOW-FAT MEAL	Y	Y	3	Period 1 Day 1	PERIOD 1 BASELINE
9	XXX-102	ML	XXX-102-001-0305	2	LOW-FAT MEAL	Y	N	10	Period 2 Day 1	PERIOD 2 BASELINE

ML DOMAIN (contd.)

	STUDYID	DOMAIN	USUBJID	MLSEQ	MLSTDTC	MLENDTC	MLSTDY	MLENDY	MLTPT	MLTPTNUM
1	XXX-102	ML	XXX-102-001-0301	1			.	.		.
2	XXX-102	ML	XXX-102-001-0301	2	2016-11-17T07:30	2016-11-17T07:36	15	15	PRE-DOSE	1
3	XXX-102	ML	XXX-102-001-0302	1	2016-11-03T07:40	2016-11-03T07:53	1	1	PRE-DOSE	1
4	XXX-102	ML	XXX-102-001-0302	2			.	.		.
5	XXX-102	ML	XXX-102-001-0303	1	2016-11-03T07:50	2016-11-03T07:53	1	1	PRE-DOSE	1
6	XXX-102	ML	XXX-102-001-0303	2			.	.		.
7	XXX-102	ML	XXX-102-001-0304	1			.	.		.
8	XXX-102	ML	XXX-102-001-0305	1	2016-11-03T08:10	2016-11-03T08:14	1	1	PRE-DOSE	1
9	XXX-102	ML	XXX-102-001-0305	2			.	.		.

Useful meal information in BA/BE studies:

In BA/BE cross over two period study we can easily identify Fast/Fed condition of subject by using Meal (ML) data.
Subject Meal Administration information is useful to identify Fasting and fed condition in demographics data.
We can easily correlate MLOCCUR variable with ACTARM variables and cross verify whether subject actually fasted during administration of investigational drug.
e.g. Subject 301
If MLOCCUR="N" i.e. meal was not administered to subject prior to medication i.e. it is Fasted in Period 1.

e.g. Subject 302
If MLOCCUR="Y" i.e. meal was administered to subject prior to medication i.e. it is Fed in Period 1.

DM (Demographics)

	STUDYID	DOMAIN	USUBJID	SUBJID	ARMCD	ARM	ACTARMCD	ACTARM
1	XXX-102	DM	XXX-102-001-0301	0301	C3BA	Cohort 3 : XXX (Fast) - XXX (Fed)	C3BA	Cohort 3 : XXX (Fast) - XXX (Fed)
2	XXX-102	DM	XXX-102-001-0302	0302	C3AB	Cohort 3 : XXX (Fed) - XXX (Fast)	C3AB	Cohort 3 : XXX (Fed) - XXX (Fast)
3	XXX-102	DM	XXX-102-001-0303	0303	C3AB	Cohort 3 : XXX (Fed) - XXX (Fast)	C3AB	Cohort 3 : XXX (Fed) - XXX (Fast)
4	XXX-102	DM	XXX-102-001-0304	0304	C3BA	Cohort 3 : XXX (Fast) - XXX (Fed)	C3BA	Cohort 3 : XXX (Fast) - XXX (Fed)
5	XXX-102	DM	XXX-102-001-0305	0305	C3AB	Cohort 3 : XXX (Fed) - XXX (Fast)	C3AB	Cohort 3 : XXX (Fed) - XXX (Fast)

CONCLUSION

With the introduction of ML data, meal data should be designed according to CDASH standards and further be modelled into SDTM ML domain. A variety of BA/BE and other therapeutic studies can make use of ML domain for the efficient analysis. This paper contains handy metadata for ML domain which will be helpful to the programmers/data managers.
Use of these data standards is also expected to benefit industry by streamlining the flow of data from collection through submission, and facilitating data interchange between partners and providers.

GROSSARY AND ABBREVIATIONS

AG	Procedure Agents
AUC	Area Under the Concentration-Time Curve
CDASH	Clinical Data Acquisition Standards Harmonization. This standard describes basic data collection fields.
CDISC	Clinical Data Interchange Standards Consortium, a Collaborative Group Member
Cmax	Maximum Observed Concentration
CRF	Case Report Form (sometimes Case Record Form). A printed, optical, or electronic document designed to record all required information to be reported to the sponsor for each trial subject.
ML	Meal
SDTM	Study Data Tabulation Model
TAUG	Therapeutic Area Data Standards User Guide

REFERENCES

Therapeutic Area Data Standards User Guide for Diabetes Version 1.0
Study Data Tabulation Model Implementation Guide: Human Clinical Trials Version 3.2

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CONTACT INFORMATION

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