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DIABETES: Submission Data Standards and Therapeutic End Points

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia. It is caused by defective insulin secretion, resistance to insulin action, or a combination of both. Most patients with diabetes mellitus have either type I diabetes (insulin-dependent or early onset) or type II diabetes (with a complex pathophysiology). While there are drugs available with different mechanism of actions, the most recent under development include glycemic control based on changes in HbA1c where the primary data end point is reduction of HbA1c. The clinical trials now submit the data to the regulatory authorities using CDISC Standards. These standards provide rules for structuring information so data can be entered consistently reducing variability across trials submitted to the agency. The Submission Data standard (SDTM) developed by CDISC includes all the information collected during a study. A User Guide for Diabetes was recently developed under the CFAST initiative describing how to use the CDISC standards by identifying the common data elements. The purpose of the paper is twofold. Firstly, it attempts to briefly describe the development landscape of diabetic drugs with a focus of primary end points. Secondly, the data collected along with their standards published for Diabetes therapeutic area is discussed with a specific emphasis on SDTM.

INTRODUCTION

Diabetes results in high blood glucose levels when the body cannot use the insulin produced or when the pancreas does not produce enough insulin. Insulin is a hormone that regulates the blood glucose levels. The high blood glucose over time causes damage to nerves and blood vessels leading to serious complications including high blood pressure, cholesterol, heart disease, stroke, blindness and eye problems, kidney disease, amputations and array of microvascular complications. Diabetes was the seventh leading cause of death in the US in 2010 and the global prevalence of diabetes is estimated to be 9% among adults aged 18+ years. There are three main types of diabetes. First main type of diabetes is the Type 1 diabetes, where the pancreas produces little or no insulin at all and is prevalent in people under the age of 20. The causes of Type 1 are not known and the symptoms include excessive excretion of urine (polyuria), thirst (polydipsia), constant hunger, weight loss, vision changes and fatigue. Type 2 diabetes also called as non-insulin dependent occurs when the pancreas does not produce enough insulin or the body does not properly use it. About 90% of all diabetics are Type 2 and is largely the result of excess body weight and physical inactivity. The symptoms are often similar to Type 1 diabetes. The third type of diabetes is gestational where women can get it in the second trimester of pregnancy. Unlike Type 1 and Type 2, gestational diabetes often disappears after the baby is born. In addition to the three main types of diabetes, there is also a stage called pre-diabetes where the blood glucose level is higher than the normal range but not high enough to be clinically diagnosed as diabetes. People with pre-diabetes are considered at high risk of developing Type 2 diabetes later in life.

SURROGATE END POINT

HbA1c (Glycosylated hemoglobin) is formed when protein within the Red blood cells (RBCs) combines with glucose in the blood. As the amount of plasma glucose with the body increases, the fraction of glycosylated hemoglobin increases. Since RBCs lifespan in the body is 100-120 days, the HbA1c values can help measure the average blood glucose levels over that duration. Blood glucose level is the concentration of glucose in your blood at a single point of time, whereas HbA1c test serves as a marker of what your average levels are over a period of 3-4 months. HbA1c can be expressed in percentage (%) or mmol/mol. Any values between 4 - 5.9% for HbA1c are considered normal. The 2010 American Diabetes Association Standards of Medical Care in Diabetes added HbA1c ≥ 48 mmol/mol (≥6.5 %) as another criterion for the diagnosis of diabetes Table 1 list the target HbA1c values in Diabetes, Non-diabetics and pre-diabetic patients.

Although HbA1c level alone does not predict diabetes complications, good control is known to lower the risk of diabetes complications. It has been demonstrated in large scale clinical trials that improving HbA1c by 1% in patients with Type 1 or 2 diabetes reduces the microvascular complications by 25% where microvascular complications include Retinopathy, Neuropathy and Diabetic Nephropathy (kidney disease). Reductions in HbA1c directly reflect improvement in glycemic control. Glycosylated hemoglobin testing is recommended for both checking the blood sugar control in people who might be pre-diabetic and monitoring blood sugar control in patients with more elevated levels, termed diabetes mellitus. There is a significant proportion of people who are unaware of their elevated HbA_{1c} level before they have blood lab work. Therefore, HbA1c is considered a validated surrogate end point with a beneficial effect on the immediate consequences of diabetes.

Target Population	mmol / mol	%
Normal	20-41	4.0 - 5.9
Diabetes	48	6.5
Diabetes with higher risk of Hypoglycemia	59	7.5
Pre-Diabetes	41-48	5.9 - 6.5

Table 1. HbA1c values

ANTI-DIABETIC DRUGS

There are several drugs used for the prevention of hyperglycemia. Except Insulin, all are generally administered orally. Type 1 patients usually receive Insulin in the form of injection as the body is unable to produce insulin. A variety of oral hypoglycemic agents are used in Type 2 patients. Some categories along with their mechanism of action, molecules and common side effects are listed in Table 2.

ORAL HYPOGLYCEMIC AGENTS	MECHANISM OF ACTION	SIDE EFFECTS
SULFONYL UREAS Glyburide	Stimulate the release of insulin from pancreatic B-cells (can only be used in patients with some B-cell function)	Hypoglycemia Most common side effect; occurs more often in long-acting sulfs (i.e. glyburide and glimepiride)
MEGLITINIDES Repaglinide	Also, stimulate the release of insulin from pancreatic B-cells	Hypoglycemia, Weight Gain
BIGUANIDE Metformin	Decreases hepatic glucose output and increases insulin sensitivity (muscle, liver); Also, anti-lipolytic effect which decreases amount of free fatty acids.	Less likely to cause hypoglycemia; GI problems, diarrhea, Weight Loss
THIAZOLIDINEDIONES Pioglitazone (Actos)	Increase insulin sensitivity (muscle and liver) and decrease glucose production	Less likely to cause hypoglycemia, Weight Gain, Peripheral edema
ALPHA-GLUCOSIDASE INHIBITORS Acarbose (Precose)	Inhibit GI enzymes, alpha-glucosidases, which convert carbs into monosaccharides. This slows and limits the absorption of glucose.	Less likely to cause hypoglycemia, GI side effects, diarrhea.

Table 2. Classification of Anti-Diabetic Drugs

SUBMISSION DATA STANDARDS

FDA guidance on submitting the study data using CDISC standards is now available. The Therapeutic Area User Guide (TAUG) for Diabetes published under the CFAST project (joint initiative of CDISC and Critical Path Institute) describes how to use current CDISC standards for the collected data in a clinical trial.

SDTM

Study Data Tabulation Model (SDTM) is a CDISC standard that defines the structure and format for clinical trial data tabulations submitted as part of a product application to regulatory authorities. The SDTM domains commonly used in Diabetes include but not limited to: Adverse Events (AE), Clinical Events (CE), Concomitant Medication (CM), Demographics (DM), Device Exposure (DX), Device Identifier (DI), Disposition (DS), Exposure (EX), Findings About (FA), Laboratory Test Results (LB), Meals (ML), Medical History (MH), Procedure Agents (AG), Vital Signs (VS).

Ongoing Diabetes trials often collect data on diabetes history and its associated complications. Safety and Efficacy Assessments including Laboratory tests, lipid panel, kidney, liver function is assessed post diagnosis of diabetes to predict the treatment response. Routine data include Demographic information, Treatment information, Concomitant medication and vitals. Additional data specific to this therapeutic area include hypoglycemic events, Self-monitoring of blood glucose (SMBG), Continuous glucose monitoring (CGM), and Meal tolerance tests. SMBG and CGM help patients manage the disease closely and avoid its associated problems.

Hypoglycemic Events

Hypoglycemia is an event that indicates a drop in blood glucose concentration. Symptoms of Hypoglycemia range from sweating, dizziness and tremor, palpitations to seizures or loss of consciousness. Many Anti-hyperglycemic drugs available in the market already exhibit hypoglycemia as a common side effect due to which any molecule tested is a suspect for this unexpected event. The Investigator may decide if this event constitutes an adverse event of Special Interest. Usually an event such as hypoglycemia leads to additional data collection in the study. Depending on the protocol design, data captured could include:

- Signs and Symptoms of event
- Severity
- Occurrence, Outcome and Seriousness
- Current and Past treatment regimens
- Last Meal / Dose of Study Treatment
- Action taken in response to the event (i.e. Hospitalization, Food Intake)

Example 1: (For illustrative purposes only. The variables may not be in the actual order needed for submission. Due to space constraints, not all variables in the domain are shown)

Hypoglycemic Event Data									
CE Domain									
DOMAIN	USUBJID	CEPRESP	CETERM	CEOCCUR	CESTDTC	CEENDTC	RELMIDS	MIDS	MIDSDTC
CE	1001-01	Y	Hypoglycemia	N					
CE	1001-01	Y	Stress	Y	2010-01-12				
CE	1001-02	Y	Hypoglycemia	Y	2010-02-11T09:15				
FA Domain									
DOMAIN	USUBJID	FATESTCD	FATEST	FAOBJ	FAORRES	FADTC	RELMIDS	MIDS	MIDSDTC
FA	1001-02	HYPO1	When did the hypoglycemic event occur	Hypoglycemia	BETWEEN LUNCH	2010-02-12			
FA	1001-02	HYPO2	Awareness of hypoglycemic event	Hypoglycemia	SELF-AWARE	2010-02-12	DURING	HYPO1	2010-02-11T09:15
FA	1001-02	HYPO3	Signs and Symptoms Present	Hypoglycemia	Y	2010-02-12	DURING	HYPO1	2010-02-11T09:15

LB Domain									
DOMAIN	USUBJID	LBTESTCD	LBTEST	SPDEVID	LBORRES	LBDTC	RELMIDS	MIDS	MIDSDTC
LB	1001-02	GLUC	Glucose	X12-123	50	2010-02-12	AT TIME OF	HYPO1	2010-02-11T09:15
ML Domain									
DOMAIN	USUBJID	MLPRESP	MLTRT	MLOCCUR	MLDOSTXT	MLDTC	RELMIDS	MIDS	MIDSDTC
ML	1001-02	Y	TEST MEAL	Y	100%	2010-02-12	PRIOR TO	HYPO1	2010-02-11T09:15
CM Domain									
DOMAIN	USUBJID	CMCAT	CMTRT	CMSCAT	MLDOSTXT	CMSTDTC	RELMIDS	MIDS	MIDSDTC
CM	1001-02	ABC	DRUG X			2010			
CM	1001-02	ABC	DRUG X	HIGHLIGHTED DOSE	100 mg BID	2010-02-11T11:15	LAST DOSE PRIOR	HYPO1	2010-02-11T09:15
CM	1001-02	DEF	FOOD				AFTER	HYPO1	2010-02-11T09:15
CM	1001-02	DEF	DRINK				AFTER	HYPO1	2010-02-11T09:15
EX Domain									
DOMAIN	USUBJID	EXDOSE	EXTRT	EXSCAT	EXDOSU	EXSTDTC	RELMIDS	MIDS	MIDSDTC
EX	1001-02	50	XYZ		mcg	2009-12-11			
EX	1001-02	50	XYZ	HIGHLIGHTED DOSE	mcg	2010-02-09T08:15	LAST DOSE PRIOR	HYPO1	2010-02-11T09:15

Data collected for the hypoglycemic event is mapped to either CE or AE domain if the event is determined to be serious. Although SDTMIG and TAUG handle the hypoglycemia symptoms differently, it might be best to map additional information about the event and the triggering factors itself to FA instead of Supplemental or CE. Any laboratory measurements at the time of the event go into LB domain. Another new domain developed specifically for the handling to Meal data in Diabetes studies is ML. Data collected on Meals before a hypoglycemic event is recommended to map under ML domain. If meals were given for the treatment of hypoglycemia, it is considered an intervention and is mapped to routine concomitant medication (CM) domain. There might be additional data collected in a study after an event such as “Date of Last Study Drug Exposure” and its “Dose”. The example above shows how data can be represented using a subcategory (i.e. –SCAT) value of “HIGHLIGHTED DOSE”. A new SDTM concept was developed and introduced in the TAUG for diabetes known as “Disease Milestones” where two new domains have been introduced. Trial Milestones (TM) is being developed at the study level to capture the event and activities themselves while Subject Milestones (SM) summarizes the events at the subject level. These standards are still under development and have not been included as part of SDTMIG v3.2 foundational standards and included as part of the provisional diabetes TAUG. As part of the new concept, three new timing variables have been added: MIDS (Disease Milestone Name), RELMIDS (Temporal Relation to Disease Milestone) and MIDSDTC (Disease Milestone Date/Time).

Ambulatory Blood Pressure Measurements (ABPM)

There could be a dose-dependent increase in Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) associated with a compound. Primary Safety assessments of a study medication lowering blood glucose include monitoring of SBP and DBP. Ambulatory BP monitoring is performed by a portable device that measures and stores SBP, DBP and Pulse Rate (PR) at 20 to 30 minute intervals over a 24-hour period. The device would be attached to the arm and subjects are asked to wear the monitor usually for a 24-hour period. After the end of this period, the device is returned to the site for data processing. Upon return of the ABPM, the BP recordings must be uploaded to the ABPM vendor computer to ensure the data are valid. If >80% of readings are valid, the subject may proceed to the next visit. If <80% of the measurements are valid, the subject repeats ABPM within 24 hours. An advantage of

ABPM devices include monitoring of BP values constantly and is useful in identifying a drop or increase in values for a patient during different times of the day or night. Based on the study protocol, there could be specific events collected on the CRF that are monitored during the period the subject is wearing the ABPM device. This data is usually mapped to CE domain in SDTM. Actual values received from the ABPM vendor file would map to the VS domain. See an example below for sample ABPM data mapping to SDTM.

Example 2: (For illustrative purposes only. The variables may not be in the actual order needed for submission. Due to space constraints, not all variables in the domain are shown)

Ambulatory Blood Pressure Measurements

CE Domain

DOMAIN	USUBJID	CETERM	CEPRESP	CEOCCUR	CECAT	CESTDTC	CEENDTC	CESTTPT	CESTRTPT
CE	1001-01	Stress	Y	Y	EVENTS	2010-05-12	2010-01-12	AFTER	ABPM VISIT 2
CE	1001-01	Unusual Activity	Y	Y	EVENTS	2010-05-12	2010-01-12	AFTER	ABPM VISIT 2

VS Domain

DOMAIN	USUBJID	VSTESTCD	VSTEST	VSCAT	VSORRES	VSORRESU	VSDTC	VISITNUM	VISIT
VS	1001-02	SYSBP	Systolic Blood Pressure	AMBULATORY	148	mmHg	2010-02-12T10:00	2	VISIT 2
VS	1001-02	DIABP	Diastolic Blood Pressure	AMBULATORY	87	mmHg	2010-02-12T10:01	2	VISIT 2
VS	1001-02	MAP	Mean Arterial Pressure	AMBULATORY	190	BEATS/MIN	2010-02-12T10:02	2	VISIT 2

SUPPVS Domain

DOMAIN	USUBJID	QNAM	QLABEL	QVAL	IDVAR	IDVARVAL
SUPPVS	1001-02	TRUEFL	True Flag	Y	VSSEQ	1
SUPPVS	1001-02	RERROR	Read Error	N	VSSEQ	1
SUPPVS	1001-02	TYPE	Type Read	Repeat	VSSEQ	1

One may notice there could be some non-standard ABPM data collected such as whether the data recorded for the vitals is valid or not, error codes collected by the device when no results are available and type of reads. The non-standard structure as seen in the example above can conveniently be moved into SUPPVS but the catch would be that the data collected at one time point would end up multiple times on every interval record. There could be additional issues if data related to monitoring has its own time points which cannot be represented well using supplementary domains. A need may arise where the sponsor chooses to develop a custom domain depending on the data collected supporting primary analysis that doesn't fit well in SUPPVS.

Self-Monitoring of Blood Glucose (SMBG)

The practice of measuring glucose levels by patients themselves is common in diabetes trials. SMBG readings are performed for the purpose of monitoring subject safety and may be checked as frequently as necessary to ensure subject safety. The subjects are asked to assess their glucose values at regular intervals as specified by the study protocol in order to make informed decisions on any hyperglycemia or hypoglycemia. Study Diaries often collect blood glucose measurements with clear instructions on how to record the SMBG values. Measurements obtained after administration of treatment are also recorded in the diary with the timing clearly marked. The example below shows how readings from a 4-point SMBG are recorded in SDTM. For discussion purposes, let's consider 4-point profile consists of fasting (pre-breakfast), pre-meal lunch, pre-meal dinner, and bed time.

Example 3: (For illustrative purposes only. The variables may not be in the actual order needed for submission. Due to space constraints, not all variables in the domain are shown)

Self-Monitoring Blood Glucose (SMBG) Data

LB Domain

DOMAIN	USUBJID	LBTESTCD	LBTEST	SPDEVID	LBORRES	LBDTC	LBTPT	LBTPTNUM	LBTPTREF
LB	1001-02	GLUC	Glucose	X12-123	118	2010-04-30	FASTING	1	BREAKFAST
LB	1001-02	GLUC	Glucose	X12-123	228	2010-04-30	PREMEAL	2	LUNCH
LB	1001-02	GLUC	Glucose	X12-123	106	2010-04-30	PREMEAL	2	DINNER
LB	1001-02	GLUC	Glucose	X12-123	182	2010-04-30	PREBED	3	BED TIME

DI Domain

STUDYID	DOMAIN	SPDEVID	DISEQ	DIPARMCD	DIPARM	DIVAL
ABC	DI	X12-123	1	TYPE	Device Type	GLUCOSE METER

The device used for measuring the glucose readings is usually identified by a unique identifier. For submission of SDTM data using the device standards, we need to format and submit a special-purpose domain (DI) that identifies a specific device unit. The intent of this SDTM dataset is to provide a consistent sponsor-defined identifier SPDEVID which is a required variable. This identifier is used for linking data across device domains independent of the level of granularity by which a device might be identified in a study. SPDEVID shown in the example above identifies the device. For more information please refer to the SDTMIG-MD (SDTM implementation guide for devices).

Continuous Glucose Monitoring (CGM)

Research indicates that hypoglycemia is common among certain group of patients even if their glycosylated hemoglobin (HbA1c) values are high. Unrecognized hypoglycemic episodes and nocturnal hypoglycemia are particularly concerning in those patients who may not be able to prevent subsequent episodes or may not awaken during symptoms of hypoglycemia at night. The hypoglycemia may worsen without intervention and may result in a severe hypoglycemic episode that the patient is unable to self-treat. CGM is performed using a tiny sensor device inserted under the skin to check glucose levels in tissue fluid monitoring the glucose values for up to 72 hours. This sensor can stay in place for several days to weeks. Patients are generally blinded to any real-time CGM device readouts to avoid potential bias until database lock. Data is compiled and processed using a CGMS system useful in identification of episodes of hyperglycemia as well as asymptomatic and nocturnal episodes of hypoglycemia.

The number of SDTM datasets created for CGM are driven by the data collected which could vary based on the objectives of the study, Data received from the CGM systems are often complicated including information associated with the active CGM monitoring period and its duration. Most trials monitor episodes or events of interest and their duration during the time the patient is exposed to the CGM device. While CE domain should be used for mapping the event itself and its durations, there could be additional CGM data based on the event day. The author suggests the use of FA domain (as shown above) to map this information.

Example 4: (For illustrative purposes only. The variables may not be in the actual order needed for submission. Due to space constraints, not all variables in the domain are shown)

Continuous Glucose Monitoring (CGM) Data

CE Domain

DOMAIN	USUBJID	CESPID	CETERM	CECAT	CESCAT	CEDUR	CETPT	CETPTNUM	CESTDTC
CE	1001-02	1-001	HYPERGLYCEMIA	CGM MONITORING	EPISODES (>200)	PT70M			2010-04-12T11:30
CE	1001-02	1-002	HYPERGLYCEMIA	CGM MONITORING	EPISODES (>300)	PT40M			2010-04-12T11:31
CE	1001-02	1-003	HYPOGLYCEMIA	CGM MONITORING	EPISODES (<70)	PT2H			2010-04-12T11:32
CE	1001-02	1-004	HYPOGLYCEMIA	CGM MONITORING	EPISODES (<50)	PT30M			2010-04-12T11:33
CE	1001-02	1-005	HYPOGLYCEMIA	CGM MONITORING		PT2H10M	NOCTURNAL	1	2010-04-12T11:34
CE	1001-02	1-006	HYPOGLYCEMIA	CGM MONITORING	MAJOR	PT20M	NOCTURNAL	1	2010-04-12T11:35

FA Domain

DOMAIN	USUBJID	FATESTCD	FATEST	SPDEVID	FAOBJ	FACAT	FAORRES	FAORRESU	FADTC
FA	1001-02	DUR	Duration of active CGM monitoring	X12-123	CGM	CGM MONITORING	24	HOUR	2010-04-12
FA	1001-02	NOCDUR	Nocturnal Duration of active CGM monitoring	X12-123	CGM	CGM MONITORING	6	HOUR	2010-04-12
FA	1001-02	TMSPT200	Time Spent during one single day of active monitoring period sensor Glucose values >180	X12-123	HYPERGLYCEMIA	CGM MONITORING	800	MIN	2010-04-12
FA	1001-02	EPI_GT200	No. of episodes with sensor glucose >200	X12-123	HYPERGLYCEMIA	CGM MONITORING	2		2010-04-12
FA	1001-02	EPI_GT300	No. of episodes with sensor glucose >300	X12-123	HYPERGLYCEMIA	CGM MONITORING	4		2010-04-12
FA	1001-02	TMSPT70	Time Spent during one single day of active monitoring period sensor Glucose values <70	X12-123	HYPOGLYCEMIA	CGM MONITORING	120	MIN	2010-04-12
FA	1001-02	TMSPT50	Time Spent during one single day of active monitoring period sensor Glucose values <50	X12-123	HYPOGLYCEMIA	CGM MONITORING	30	MIN	2010-04-12
FA	1001-02	EPI_LT70	No. of episodes with sensor glucose >70	X12-123	HYPOGLYCEMIA	CGM MONITORING	3		2010-04-12
FA	1001-02	HYPOEPI	No. of major hypo episodes during 24 hour period	X12-123	CGM	CGM MONITORING	0		2010-04-12

ZX Domain

DOMAIN	USUBJID	ZXTESTCD	ZXTEST	SPDEVID	ZXCAT	ZXORRES	ZXORRESU	VISIT	ZXDTC
ZX	1001-02	MEANALL	Mean all sensor glucose values	X12-123	CGM MONITORING	215	mg/dL	VISIT 2	2010-04-12
ZX	1001-02	AUC200	AUC - Glucose > 200 mg/dL	X12-123	CGM MONITORING	3.5	min*mg/dL	VISIT 3	2010-04-12
ZX	1001-02	AUC300	AUC - Glucose > 300 mg/dL	X12-123	CGM MONITORING	5.5	min*mg/dL	VISIT 4	2010-04-12
ZX	1001-02	AUC70	AUC - Glucose < 70 mg/dL	X12-123	CGM MONITORING	5.1	min*mg/dL	VISIT 5	2010-04-12
ZX	1001-02	AUC50	AUC - Glucose < 50 mg/dL	X12-123	CGM MONITORING	4.5	min*mg/dL	VISIT 6	2010-04-12

DI Domain

STUDYID	DOMAIN	SPDEVID	DISEQ	DIPARMCD	DIPARM	DIVAL
ABC	DI	X12-123	1	TYPE	Device Type	CGM SENSOR

DX Domain

STUDYID	DOMAIN	SPDEVID	DXTRT	DXGRPID	DXPRESP	DXOCCUR	DXCAT	DXSTDTC	DXENDTC
ABC	DX	X12-123	CGM SENSOR	1	Y	Y	CGM MONITORING	2010-04-12	2010-04-13

There may be challenges to link every single finding back to the event available in CETERM. E.g. Overall Episodes during monitoring could include both hypoglycemic and hyperglycemic events. Such records were treated as stand-alone findings with an FAOBJ assignment of “CGM”. If there are any glucose readings they are collected separately on patient diaries as part of the SMBG and mapped to LB domain. While patients are exposed to this device, there could be additional device data collected utilizing the domains including DI, DT and DX. The durations and session timing during an active CGM period could be derived in the system based on episode, visit or day (E.g. Area under the Curve calculations for glucose readings). There is no guidance currently available in either the SDTMIG or Diabetes TAUG for handling such data. The author recommends the use of custom sponsor specific domain (i.e. ZX) for mapping this information. Finally, RELREC could be used for linking the data across these domains.

Glucose Tolerance Tests (GTT)

This is a procedure where glucose is administered to the patients on study treatment. Blood glucose measurements are taken after the test to check the levels of glucose.

Example 5: (For illustrative purposes only. The variables may not be in the actual order needed for submission. Due to space constraints, not all variables in the domain are shown)

Glucose Tolerance Tests (GTT)									
AG Domain									
STUDYID	DOMAIN	AGTRT	AGCAT	AGPRESP	AGOCCUR	AGDOSTXT	AGROUTE	AGSTDTC	AGENDTC
ABC	AG	GLUCOSE	GLUCOSE TOLERANCE TEST	Y	Y	100 MG	IV	2010-04-12T9:00	2010-04-12T9:01

As per Diabetes TAUG these are treated as challenge tests and mapped to a new SDTM domain, “AG” (Procedure Agents). Please note this domain is still available as draft and not a part of the foundational standards. The context in which the agent is used determines if it belongs in AG. For e.g. If meals were used in a tolerance test which has a similar approach as GTT, the data for meals would map to AG and not ML. Meals data domain (ML) was drafted for scenarios where data on regular meals related to a particular event (i.e. Hypoglycemia).

ADAM

Analysis Data Model (ADaM) is defined as a CDISC standard that provides structure and format for building analysis datasets supporting efficient generation, validation and review of analysis results. Diabetes TAUG draft supplement is now available for guidance on use of ADaM standards supporting the key statistical end points. ADaM BDS (Basic Data Structure) is the standard structure for analysis of several primary end points including continuous measures (i.e. HbA1c change from baseline or percent change from baseline results) and categorical measures (binary response). In order to analyze hypoglycemic event data, use of ADaM occurrence data structure is recommended. A further detail on the analysis type or the standard structure is beyond the scope of this paper.

CONCLUSION

FDA binding guidance on submitting the study data using CDISC standards is now available. SDTM foundational standards and Therapeutic Area User Guide (TAUG) for Diabetes published under the CFAST project (joint initiative of CDISC and Critical Path Institute) provides guidance on how to use current CDISC standards for diabetes data in a clinical trial.

REFERENCES

- http://www.cdc.gov/diabetes/pubs/statsreport14
- http://www.nlm.nih.gov/medlineplus/ency/article/003640.htm
- http://www.cdisc.org/therapeutic (TAUG “Diabetes”)
- http://cdisc.org/FDA-Final-Binding-Guidance-on-Standards
- http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064981.htm (Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention)

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RECOMMENDED READING

- CDISC SDTM Implementation Guide version 3.2 (available at www.cdisc.org/sdtm)
- CDISC ADaM Implementation Guide version 2.1 (available at www.cdisc.org/adam)

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