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### **How the release of the Asthma TA User Guide impacts an ongoing submission.**

Nick De Donder, Business & Decision Life Sciences, Brussels, Belgium

Céline Maréchal, Business & Decision Life Sciences, Brussels, Belgium

#### **ABSTRACT**

In December 2013, the Therapeutic Area Data Standards User Guide for Asthma was released in order to improve standardization of Asthma studies. This paper will present the way we at Business & Decision Life Sciences handled the conversion of several Asthma clinical trials for a FDA submission using SDTMIG V3.1.2 Amendment 1 before the release of the TA Asthma User Guide.

At the start of the project the Respiratory Physiology (RE) domain was under discussion in the draft version of Asthma User. For Questionnaires findings, the Asthma User Guide makes a difference between Symptom Assessment (in Findings about CE), and other questionnaires (in QS). Some differences are present in the way to collect Healthcare Resource findings. Regarding Asthma history, management of the date of diagnosis could be subject to multiple interpretation.

Whilst differences are present, we believe that, when working on a specific therapeutic area for which the CDISC user guide is not yet released, the use of SDTMIG is a good basis to follow.

#### **INTRODUCTION**

In December 2013, the Asthma User Guide was released to improve standardization of asthma studies and to ensure consistency between CDISC submissions for this specific therapeutic area which is a major public health problem.

The team at Business & Decision Life Sciences first got involved in the conversion of an Asthma project for a FDA submission using SDTMIG V3.1.2 Amendment 1 as the Asthma user guide was not yet available at that time.

In this paper we will present the way we handled the conversion of several Asthma clinical trials and compare it to the recently released user guide.

## **DIFFERENCES BETWEEN ASTHMA USER GUIDE v1.0 AND SDTMIG V3.1.2 AMENDMENT 1.**

At the beginning of this conversion project in 2013, Business & Decision Life Sciences used the different procedure based on the SDTM implementation guide (at that moment the version 3.1.2 A1) as no specific User Guide was present. After 6 month, the team has been informed of the development of a specific user guide focusing on Asthma and was able to obtain the draft version of this TA user guide.

However as our team was involved before the release of the Therapeutic Area Data Standards User Guide in conversion of Asthma project we needed to evaluate the impact of the release of this document, to judge what will be the major differences and to assess if we have to plan some updates for the projects.

We highlighted some differences that could have an impact. The main differences between the Asthma User Guide v1.0 and our asthma data converted to SDTMIG V3.1.2 Amendment 1 are detailed below.

### **POPULATION**

Our project on the asthma clinical studies uses the SDTMIG V3.1.2 A1 and looks at a mixed population of adults and children. However, the Asthma User Guide 1.0 is based on SDTMIG V3.1.3 and only focuses on an adult population.

### **RESPIRATORY PHYSIOLOGY DOMAIN**

The Respiratory Physiology (RE) domain including physiological findings related to the respiratory system, such as information relating to the lung or other organs involved in the breathing is a new domain created in the Asthma User Guide. This domain was under discussion in the draft version of Asthma User Guide and this version was used in our project.

When it was published as a final version in the Asthma User Guide 1.0 some new variables like SPDEVID (Sponsor Device Identifier) or REORREF (Predicted Value) were added to this domain.

SPDEVID is present to specify specific device used during respiratory measurement. It is an identifier which can be used to link data across dataset.

REORREF was created following the single reference result idea. Indeed RE test results are not considered as a normal range but more as a single predicted normal value. This variable refers to the reference result in original units and will be populated only for continuous results.

Example RE Domain dataset:

The table below provides an overview of a RE Dataset. In this example, we can observe that REORREF is only populated for continuous variable and not for predicted percent as there is no reference for this kind of test.

STUDYID	DOMAIN	USUBJID	SPDEVID	RESEQ	RETESTCD	RETEST	REORRES	REORRESU	REORREF
XXX	RE	XXX-000-001	AAA111	1	FVC	Force Vital Capacity	3.2	L	3.86
XXX	RE	XXX-000-001	AAA111	1	FVCPP	Percent Predicted Force Viral Capacity	83	%	

## ASTHMA SYMPTOM ASSESSMENT

All questionnaires and diaries were converted to the Questionnaire domain (QS) according to the SDTMIG V3.1.2 A1, whereas the Asthma User Guide makes a difference between questionnaires related to Asthma Symptom Assessment, which will be included in Findings About Clinical Events, and other standard questionnaires which are included in QS.

Indeed cough, wheezing, breathlessness, chest tightness and night-time awakenings are the most common symptoms presented by patients suffering from asthma.

Validated questionnaires exist to assess those symptoms. Often it is the impact of the symptoms on the daily activities or on the quality of the sleep during the night which will be used to assess those specific symptoms. Indeed sponsor can ask to the patient to evaluate the rating of the asthma symptoms by answering questions on the impact of one symptom on a specific activity and how he considers the severity of this impact.

According to the Asthma User Guide, episodes of asthma symptoms should be reported in Finding About Clinical Events with the kind of symptoms represented by FAOBJ (eg. FAOBJ = COUGH) and with questions which were asked to the patient characterised by FATEST (eg. Occurrence, Impact or Severity of the impact on an activity...).

## HEALTH CARE DATA

Frequency and duration of emergency rooms visits and hospitalizations are often collected in asthma studies. Those kind of data can provide more precise information on the severity of this disease.

To collect healthcare data we used the findings domain HU (Healthcare Resource Utilization) present in the reserved domain codes under discussion in the SDTMIG V3.1.2 A1. However, according to the Asthma User Guide v1.0 this information should be collected in the event domain HO (Healthcare Encounters).

We also put the related data in a SUPPHU domain while the Asthma User Guide use a Finding About Domain HO to collect related findings.

For example: If the occurrence of a hospitalization episode is reported in the HO domain, information on relationship between hospitalization and asthma or on the number of hospitalization episode occurring during a specified period,... can be found in the FAHO domain.

## **ASTHMA HISTORY**

Regarding Asthma history, we used the SC domain to manage the date of diagnosis rather than the MH domain used in the Asthma User Guide. In both cases, a dilemma is present between the date of diagnostic and the date of collection.

The Asthma User Guide recommend to use the MH domain. However the variable MHSTDTC is not referring specifically to the diagnosis date. In this situation, date of diagnosis could be handled as the result of a test –ORRES in a findings domain. But in this case the date will be considered as a result which is not the best way to proceed.

Moreover some misunderstandings could be present between the date of collection and the actual date of diagnostic. Indeed –DTC variables are often considered as time when data were collected in most of findings domain.

In our project, we used SC domain to manage the date of diagnosis and so in this case the date of diagnosis is reported in the variable SCORRES. However following SDTM rules, a date should not be handled as a finding. In order to resolve this issue, the date of diagnosis was not handled as a standard format DD MMM YYYY but as a duration with a format P22Y10M.

In conclusion, the date of diagnostic is a grey area with multiple interpretations which still needs discussion and dilemma between the date of diagnostic and the date of collection is present in both situations mentioned above.

## **AGENT PROCEDURE**

In the Asthma User Guide different new domains were created such as Agent Procedure (AG).

The AG domain is present to collect substances used during testing procedures and which are not given as medication or drug with therapeutic purpose (eg. Agent administrated during reversibility assessment).

In our project we used the CM domain to store substances used during testing procedures or rescue medications. However according to Asthma User Guide, the use of the CM domain for this kind of agents are not appropriate. Indeed some tests use agents which can also have a therapeutic goal (such as albuterol which is used as agent in reversibility procedure but which is also a bronchodilator given as medication) but other tests employ agents which are never considered as medication. For example during the bronchial allergen challenge test allergens are involved. That is why in this situation the Asthma User Guide considers that it is not appropriate to store this kind of data in the CM domain. In the same way, in our project we put rescue medication in the CM domain while it is clearly reported on the CRF that this should not be considered as concomitant therapy. Indeed the correct way to report it following the SDTMIG 3.1.2 A1 would be to put it in the CM domain with “rescue medication” as CMCAT variable. However according to the Asthma user guide this information should be captured in the AG domain.

However when you compare the structure of both datasets, there are not a lot of differences and the AG domain is very similar to the CM domain. The biggest difference is the use of the –INDC variable which is in general not populated in the AG domain. Indeed there is no indication for the agent which is used as part of a testing procedure.

## **OTHER NEW DOMAINS**

The SR domain is present in the Asthma User Guide to store results of allergen skin test used to determine allergen to which subject is reacting.

DI and DU also appear in the Asthma User Guide. The first one includes information to identify the device used for pulmonary function test (eg. Spirometer) for which results are reported in the RE domain and the second one reports other information on the device as for example the reference equation used

by the spirometer device. As explained above SPDEVID will be used as identifier to link those different datasets (RE vs DI vs DU).

The table below provides an overview of the differences that exist regarding where therapeutic area specific information can be stored when using the SDTMIG V3.1.2 A1 versus the final Asthma User Guide 1.0.

SDTMIG v3.1.2 A1		TA Asthma User Guide v1.0	
CM: Concomitant Medication		AG: Procedure Agents	
CM: Concomitant Medication		CM: Concomitant Medication	
AE: Adverse Event		AE: Adverse Event	
HU: Healthcare Resource Utilization		HO: Healthcare Encounters	
MH: Medical History		MH: Medical History	
Not present		RE: Respiratory Physiology: - SPDEVID - REORREF	
FA: Findings About	MH	FA: Findings About	MH
	AE		AE
			HO
Not present		SR: Skin Response	
Not present		DI: Device Identifier	
Not present		DU: Device-in-Use	

## CONCLUSION

Differences are present between data converted using only the SDTMIG V3.1.2 A1 and data converted using the Asthma User Guide v1.0 but these differences are quite limited.

Moreover, the Asthma User Guide is a guiding document and the SDTMIG is still the basis. Indeed, nothing in the Asthma User Guide supersedes the SDTMIG.

Hence, we believe that, when working on a specific therapeutic area for which the CDISC user guide is not yet released, the use of SDTMIG is a good basis to follow.

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## Contact Information

Nick De Donder  
Business & Decision Life Sciences  
Sint-Lambertusstraat 141 Rue Saint-Lambert  
1200 Brussels  
+32 (0)2 774 11 00  
[nick.dedonder@businessdecision.com](mailto:nick.dedonder@businessdecision.com)