PharmaSUG 2023 - Paper SA-303

A Pain in My ISR
A Primer on Injection Site Reactions

Kjersten Offenbecker and Fox Mulder, GlaxoSmithKline, Inc.

ABSTRACT

We are all familiar with Adverse Events (AEs) and how to report them. But what about those special AEs that occur when your study product is an injectable? These special AEs are known as injection site reactions or ISRs and they are reported very differently than traditional AEs. In this paper we will explore what makes these AEs different and why they tend to be such a pain to programmers everywhere. We will not only explain what an ISR is and how it is different, we will also look at some examples of how they are reported and even how to help make them a little less of a pain.

INTRODUCTION

At one point or another we have all had some type of injection, whether for a vaccine or administration of an amazing pain medication or allergy shots. I do not know about you, but I am always sure it is going to hurt, at least a little. But many other not so pleasant reactions can occur because of putting a foreign substance in our bodies. In the world of pharmaceutical drug research and development we call these Injection Site Reactions (ISRs) and as we strive for better, more potent medications that we take less often, injectables are becoming increasingly common.

ISRs are Adverse Events (AE) but they are not quite the same as a headache or nausea. We need to look at other factors to help decide whether they cause a safety concern for our patients. Our goal is to make patients' lives last longer, cure diseases and improve overall quality of life.

Let us dig into what an ISR is, what are some of the common types, what typically causes them and most importantly how do we report and analyze them.

WHAT IS AN ISR?

Do you know what an ISR is? We thought we did but when we sat down to try and define it, we found it a bit more difficult than we thought. Isn't it just an Adverse Event (AE) which happens when a patient is poked with a needle of some sort or is it more complicated than that?

DEFINITION

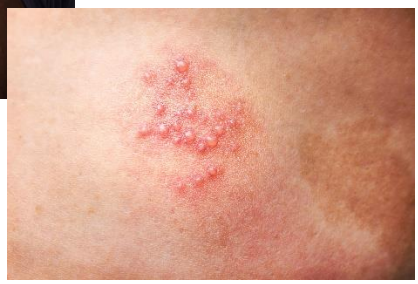
"An allergic, histaminic, or traumatic response of the skin and subcutaneous tissues to any substance introduced with a needle." (*Medical Dictionary*.2009).

Now it's clear, right? Maybe we need to dig just a little deeper.

- Allergic response: a response of your immune system to the injected substance.
- Traumatic response: damage to tissues from the needle or volume of the injection. There will be a traumatic response since an injection breaks the skin. The degree of that response depends on a variety of factors: the size of the needle, the skill of the practitioner, location of the injection, the mode of the injection (subcutaneous or intramuscular), etc.
- Histaminic response: the release of histamine by your body in response to the injection

COMMON TYPES

- Pain
- Swelling
- Erythema/Redness
- Induration (the thickening and hardening of soft tissues of the body, specifically the skin)
- Nodules (small, rounded lumps of matter distinct from their surroundings)
- Pruritus (severe itching of the skin)
- Tenderness
- Discoloration



COMMON CAUSES

- Device
- Operator error
- Drug/Medication/Investigational product
    - Is it the drug?
    - The volume?
    - The route of administration?
    - The speed of the injection?
- Drug interactions

ISR AS AN ADVERSE EVENT

ISRs can occur any time something is injected into the body with a needle; the needle breaks the skin and therefore is likely to cause some trauma to the body. Although we know this trauma will occur, we want to capture these events as AEs. I know what you're thinking; we know how to handle and report AEs, we do it all the time. Unfortunately, in some instances ISRs are more than your average AE. Let's explore this a little more.

WHEN TO TREAT JUST LIKE ANY OTHER AE

Let's imagine your study is investigating a breakthrough Oral product which will cure chronic stupidity. During the study, a patient receives a vaccine and develops swelling at the injection site. Is this an AE; is it an ISR? Since we are not studying the vaccine, we would treat this ISR just like any other AE we see in our study. That would be true even if our investigational production (IP) was an injection.

We want to treat ISRs that are a result of our IP differently than ISRs which are related to other injections. Why? Because every time our product is injected into a patient it is likely one of these ISRs will occur and as a result ISRs become study endpoints rather than just AEs.

ISR AS A STUDY ENDPOINT

When we start to think about an ISR as a study endpoint it can quickly become a bit overwhelming. What exactly do we want to report? Where will this data be stored? Can we use the ADAE dataset, or do we need something else?

Typically, when the Case Report Form (CRF) is developed, there is a separate form for ISRs, but the data is captured in the AE dataset and reported in the SDTM AE data. It is viewed as AE data.

CRF EXAMPLE

Event [Diagnosis Only (if known) Otherwise Sign/Symptom]

☐ Injection site abscess	☐ Injection site erythema	☐ Injection site pressure
☐ Injection site anesthesia	☐ Injection site hematoma	☐ Injection site soreness
☐ Injection site bruising	☐ Injection site hemorrhage	☐ Injection site swelling
☐ Injection site cellulitis	☐ Injection site itching	☐ Injection site tenderness
☐ Injection site discoloration	☐ Injection site induration	☐ Injection site warmth
☐ Injection site discomfort	☐ Injection site nodule	☐ Other
☐ Injection site erosion	☐ Injection site pain	

If Other Injection Site Reaction, please specify: _____

Start date (dd-mon-yyyy) _____
Start Time (00:00-23:59) _____
Start Time Unknown _____

Outcome

☐ NOT RECOVERED/NOT RESOLVED	☐ RECOVERED/RESOLVED WITH SEQUELAE
☐ RECOVERED/RESOLVED	☐ RECOVERING/RESOLVING

AE Frequency

☐ Single episode	☐ Intermittent

End date (dd-mon-yyyy) _____
End Time (00:00-23:59) _____
End Time Unknown _____

Action Taken with Study Treatment as a Result of the AE

☐ Dose increased	☐ Drug interrupted/delayed
☐ Dose not changed	☐ Drug withdrawn
☐ Dose reduced	☐ Not Applicable

Did the subject withdraw from study as a result of AE?

☐ No	☐ Yes

Maximum Grade or Intensity **(Record maximum grade or intensity throughout duration of event)**

☐ Mild or Grade 1	☐ Potentially
☐ Moderate or Grade 2	☐ Life-Threatening or Grade 4
☐ Severe or Grade 3	☐ Death or Grade 5

Grade or Intensity at onset of event **(Record grade or intensity at the onset of the event)**

☐ Mild or Grade 1	☐ Potentially
☐ Moderate or Grade 2	☐ Life-Threatening or Grade 4
☐ Severe or Grade 3	☐ Death or Grade 5

Relationship to Study treatment (Is there a reasonable possibility the AE may have been caused by the study treatment?)

☐ No	☐ Yes

Did the subject use or apply any treatment at home for the injection site related symptom? (If Yes, please record on Concomitant Medications page)

☐ Yes	☐ No

Was event serious? *If Yes, please complete the Serious Adverse Events eCRFs.

SDTM AE EXAMPLE

USUBJID	AEDECOD	AESEV	AESER	AEACN	AEREL	AEPATT	AEOUT	AETOXGR	AESTDTC	AEENDTC
000005	Injection site erythema	MODERATE	N	NOT APPLICABLE	Y	SINGLE EVENT	RECOVERED/RESOLVED	2	2022-07-12T08:50	2022-07-21T06:45
000005	Injection site pain	MILD	N	NOT APPLICABLE	Y	INTERMITTENT	RECOVERED/RESOLVED	1	2022-07-12T08:05	2022-07-18T07:00
000005	Injection site pruritus	MILD	N	NOT APPLICABLE	Y	INTERMITTENT	RECOVERED/RESOLVED	1	2022-07-18T21:00	2022-07-24T09:00
000005	Injection site swelling	MODERATE	N	NOT APPLICABLE	Y	SINGLE EVENT	RECOVERED/RESOLVED	2	2022-07-13T09:04	2022-11-07T10:58
000005	Injection site warmth	MILD	N	NOT APPLICABLE	Y	INTERMITTENT	RECOVERED/RESOLVED	1	2022-07-12T08:50	2022-07-19T07:50
000005	Neutrophil count increased	MILD	N	NOT APPLICABLE	Y	SINGLE EVENT	RECOVERED/RESOLVED	1	2022-07-14T08:00	2022-07-16T08:00
000005	White blood cell count increased	MILD	N	NOT APPLICABLE	Y	SINGLE EVENT	RECOVERED/RESOLVED	1	2022-07-14T08:00	2022-07-16T08:00
000016	Injection site erythema	MODERATE	N	NOT APPLICABLE	Y	SINGLE EVENT	RECOVERED/RESOLVED	2	2022-07-27T07:30	2022-08-08T10:19
000016	Injection site pain	MILD	N	NOT APPLICABLE	Y	INTERMITTENT	RECOVERED/RESOLVED	1	2022-07-26T12:45	2022-08-03T07:49
000016	Injection site swelling	MODERATE	N	NOT APPLICABLE	Y	SINGLE EVENT	RECOVERED/RESOLVED	2	2022-07-26T19:30	2022-10-17T09:00
000016	Injection site warmth	MILD	N	NOT APPLICABLE	Y	INTERMITTENT	RECOVERED/RESOLVED	1	2022-07-28T08:11	2022-08-03T07:49
001037	Injection site discomfort	MILD	N	DOSE NOT CHANGED	Y	SINGLE EVENT	RECOVERED/RESOLVED	1	2022-10-04T13:30	2022-10-04T13:40
001037	Injection site erythema	MODERATE	N	NOT APPLICABLE	Y	SINGLE EVENT	RECOVERED/RESOLVED	2	2022-10-04T14:28	2022-11-30T10:18
001037	Injection site pain	MILD	N	NOT APPLICABLE	Y	INTERMITTENT	RECOVERED/RESOLVED	1	2022-10-05T13:37	2022-10-10T13:43
001037	Injection site swelling		N	NOT APPLICABLE	Y	SINGLE EVENT	NOT RECOVERED/NOT RESOLVED		2022-10-04T14:28	
001037	Injection site warmth	MILD	N	NOT APPLICABLE	Y	SINGLE EVENT	RECOVERED/RESOLVED	1	2022-10-05T13:37	2022-11-02T14:00
001037	Post inflammatory pigmentation change	MILD	N	NOT APPLICABLE	Y	SINGLE EVENT	NOT RECOVERED/NOT RESOLVED	1	2022-11-30T09:45	

This CRF and resulting SDTM data example looks remarkably like what we capture for all AEs not just ISRs except for the very first question, that question really illustrates that this form is for ISRs. One other important bit of information we would like to collect is about the size of the ISR. We do not necessarily collect size for all ISRs but there are some that are important, particularly erythema and swelling but it could be any number of ISRs that we want to measure.

CRF EXAMPLE FOR ISR SIZE COLLECTION

Were any ISR evaluated?
- ☐ Yes
- ☐ No

Visit ISR evaluated _____

Event
- ☐ Injection site erythema
- ☐ Injection site swelling
- ☐ Injection site induration

Date ISR evaluated _____
Time ISR evaluated _____

Size of the ISR Dimension 1 (Length) (mm) _____
Size of the ISR Dimension 2 (Width) (mm) _____

Surface Area (ISR Dimension 1 x ISR Dimension 2) (mm2) _____

But where does this data go in SDTM? It ends up in FAAE.

SDTM FAAE EXAMPLE

SUBJID	FAREFID	FATEST	FASTRESN	VISIT	FADTC
000005	INJECTION SITE ERYTHEMA - 12 JUL 2022	Surface Area (Dim 1 x Dim 2)	2250	DAY 1	2022-07-12T20:19
000005	INJECTION SITE ERYTHEMA - 12 JUL 2022	Surface Area (Dim 1 x Dim 2)	4400	DAY 6	2022-07-17T08:23
000005	INJECTION SITE ERYTHEMA - 12 JUL 2022	Surface Area (Dim 1 x Dim 2)	1400	DAY 7	2022-07-18T07:53
000005	INJECTION SITE SWELLING - 13 JUL 2022	Surface Area (Dim 1 x Dim 2)	2100	DAY 3	2022-07-14T09:21
000005	INJECTION SITE SWELLING - 13 JUL 2022	Surface Area (Dim 1 x Dim 2)	2800	DAY 5	2022-07-16T13:52
000005	INJECTION SITE SWELLING - 13 JUL 2022	Surface Area (Dim 1 x Dim 2)	2400	DAY 8	2022-07-19T08:35
000005	INJECTION SITE SWELLING - 13 JUL 2022	Surface Area (Dim 1 x Dim 2)	1200	DAY 8	2022-07-19T11:03
000005	INJECTION SITE SWELLING - 13 JUL 2022	Surface Area (Dim 1 x Dim 2)	100	WEEK 12	2022-10-03T11:57
000016	INJECTION SITE ERYTHEMA - 27 JUL 2022	Surface Area (Dim 1 x Dim 2)	600	DAY 10	2022-08-04T10:33
000016	INJECTION SITE ERYTHEMA - 27 JUL 2022	Surface Area (Dim 1 x Dim 2)	3000	DAY 4	2022-07-29T22:00
000016	INJECTION SITE ERYTHEMA - 27 JUL 2022	Surface Area (Dim 1 x Dim 2)	1250	DAY 6	2022-07-31T11:09
000016	INJECTION SITE ERYTHEMA - 27 JUL 2022	Surface Area (Dim 1 x Dim 2)	1200	DAY 9	2022-08-03T09:16
000016	INJECTION SITE ERYTHEMA - 27 JUL 2022	Surface Area (Dim 1 x Dim 2)	800	DAY 9	2022-08-03T21:56
000016	INJECTION SITE SWELLING - 26 JUL 2022	Surface Area (Dim 1 x Dim 2)	2400	DAY 5	2022-07-30T10:51
000016	INJECTION SITE SWELLING - 26 JUL 2022	Surface Area (Dim 1 x Dim 2)	2000	DAY 5	2022-07-30T19:58
000016	INJECTION SITE SWELLING - 26 JUL 2022	Surface Area (Dim 1 x Dim 2)	1500	DAY 6	2022-07-31T11:08
000016	INJECTION SITE SWELLING - 26 JUL 2022	Surface Area (Dim 1 x Dim 2)	1000	DAY 8	2022-08-02T11:31
000016	INJECTION SITE SWELLING - 26 JUL 2022	Surface Area (Dim 1 x Dim 2)	800	DAY 8	2022-08-02T20:04
000016	INJECTION SITE SWELLING - 26 JUL 2022	Surface Area (Dim 1 x Dim 2)	1250	DAY 9	2022-08-03T09:15
001037	INJECTION SITE ERYTHEMA - 04 OCT 2022	Surface Area (Dim 1 x Dim 2)	1575	DAY 10	2022-10-13T13:03
001037	INJECTION SITE ERYTHEMA - 04 OCT 2022	Surface Area (Dim 1 x Dim 2)	1200	DAY 8	2022-10-11T14:10
001037	INJECTION SITE ERYTHEMA - 04 OCT 2022	Surface Area (Dim 1 x Dim 2)	750	DAY 9	2022-10-12T14:26
001037	INJECTION SITE ERYTHEMA - 04 OCT 2022	Surface Area (Dim 1 x Dim 2)	2025	WEEK 2	2022-10-17T10:03
001037	INJECTION SITE ERYTHEMA - 04 OCT 2022	Surface Area (Dim 1 x Dim 2)	900	WEEK 4	2022-11-02T10:48
001037	INJECTION SITE SWELLING - 04 OCT 2022	Surface Area (Dim 1 x Dim 2)	1200	DAY 10	2022-10-13T13:03
001037	INJECTION SITE SWELLING - 04 OCT 2022	Surface Area (Dim 1 x Dim 2)	2250	DAY 8	2022-10-11T14:10
001037	INJECTION SITE SWELLING - 04 OCT 2022	Surface Area (Dim 1 x Dim 2)	1600	DAY 9	2022-10-12T14:26
001037	INJECTION SITE SWELLING - 04 OCT 2022	Surface Area (Dim 1 x Dim 2)	150	WEEK 16	2023-01-24T13:44
001037	INJECTION SITE SWELLING - 04 OCT 2022	Surface Area (Dim 1 x Dim 2)	50	WEEK 20	2023-02-20T12:28
001037	INJECTION SITE SWELLING - 04 OCT 2022	Surface Area (Dim 1 x Dim 2)	750	WEEK 4	2022-11-02T10:48
001037	INJECTION SITE SWELLING - 04 OCT 2022	Surface Area (Dim 1 x Dim 2)	750	WEEK 6	2022-11-14T10:22
001037	INJECTION SITE SWELLING - 04 OCT 2022	Surface Area (Dim 1 x Dim 2)	19500	WEEK 8	2022-11-30T10:18

This data really does not fit nicely into the ADAE format and when summarizing AEs we typically display frequency counts and percentages. We summarize All AEs, Drug Related AEs, Serious AEs (SAEs), etc. But what other information do we want when we start thinking about ISRs?

Other information we may collect in relation to ISRs are things like Skinfold Thickness which is typically captured with the vital signs data as well as questionnaires like Patient Interpretation of Neuropathy (PIN) and Numeric Pain Rating Scale (NSR) geared toward pain and its overall effect on the patient's life.

ENDPOINTS

- Number of ISRs
- Event Characteristics (frequency counts)
    - Subject Level
    - Event Level
- Outcome (frequency counts)
    - Subject Level
    - Event Level
- Maximum Grade (frequency counts)
    - Subject Level
    - Event Level
- Action Taken (frequency counts)
    - Subject Level
    - Event Level
- Time to Onset (summary stats)
    - Event Level
- Duration (summary stats)
    - Event Level
- Duration at different grade levels (summary stats)
    - Event Level
- Rate of ISR Events Per Injection Visit (summary stats)
    - Calculated for each subject as the number of events experienced by the subject divided by the number of injection visits attended by the subject.
        - Event Level
- Needle Length Comparison
    - Event Level
- Size of ISR
    - Event Level
- Location of Injection

It may appear that we have most if not all this information in ADAE but when you consider the event level summarization and add in complexities like phase comparisons (Injection 1 vs Injection 2, Maintenance vs Follow-up, etc.) ADAE can quickly become really complicated. We have found it is much easier and much clearer to create a separate Basic Data Structure (BDS) dataset called ADAEISR.

ADAEISR

Now that we see why we need to capture this ISR data in its own dataset, ADAEISR let us look at what that might look like. The ADAE dataset is reported in the occurrence data structure (OCCDS), defined by CDISC (Clinical Data Interchange Standards Consortium) as the counting of subjects with a given record or term, and often includes a structured hierarchy of dictionary coding categories. Knowing that we will need to do more than just count subjects the best choice is the Basic Data Structure (BDS), which allows for greater flexibility to meet our analysis needs. A BDS dataset is long and narrow, using parameter variables (PARAM/PARMCD) along with value variables (AVAL/AVALC) to capture the data.

When thinking about the different endpoints we want to be able to display in our outputs using parameters will make the data easy to parse out into different sections. This structure will also allow us to capture both continuous and categorical data easily.

Let us first look at what our output might look like for a typical event-level ISR table:

We will likely have several sections of data that is best represented with counts:

Event-Level Summary of Injection Site Reaction Adverse Events by Preferred Term			
	Treatment A	Treatment B	Treatment C
Preferred Term: XXXXXXXXXXXX	(N=XXX)	(N=XXX)	(N=XXX)
Number of Events	XX	XX	XX
Event Characteristics (% based on all events)[1]			
Serious	XX(XX%)	XX(XX%)	XX(XX%)
Resulting in Hospitalization	XX(XX%)	XX(XX%)	XX(XX%)
Related to study treatment	XX(XX%)	XX(XX%)	XX(XX%)
Withdrawal from study	XX(XX%)	XX(XX%)	XX(XX%)
Outcome (% based on all events)			
RECOVERED/RESOLVED	XX(XX%)	XX(XX%)	XX(XX%)
RECOVERING/RESOLVING	XX(XX%)	XX(XX%)	XX(XX%)
RECOVERED/RESOLVED WITH SEQUELAE	XX(XX%)	XX(XX%)	XX(XX%)
NOT RECOVERED/NOT RESOLVED	XX(XX%)	XX(XX%)	XX(XX%)
FATAL	XX(XX%)	XX(XX%)	XX(XX%)
Maximum Grade (% based on all events)			
GRADE 1	XX(XX%)	XX(XX%)	XX(XX%)
GRADE 2	XX(XX%)	XX(XX%)	XX(XX%)
GRADE 3	XX(XX%)	XX(XX%)	XX(XX%)
GRADE 4	XX(XX%)	XX(XX%)	XX(XX%)
GRADE 5	XX(XX%)	XX(XX%)	XX(XX%)

But other sections are best represented with summary statistics.

Duration at Grade>=2, days [2]			
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
SD	XX.XX	XX.XX	XX.XX
Median	XX	XX	XX
Q1	XX	XX	XX
Q3	XX	XX	XX
Min.	XX	XX	XX
Max.	XX	XX	XX
Duration at Grade>=3, days [2]			
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
SD	XX.XX	XX.XX	XX.XX
Median	XX	XX	XX
Q1	XX	XX	XX
Q3	XX	XX	XX
Min.	XX	XX	XX
Max.	XX	XX	XX
AUC for Surface Area by Time Grade>=1, days*cm^2 [3]			
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
SD	XX.XX	XX.XX	XX.XX
Median	XX	XX	XX
Q1	XX	XX	XX
Q3	XX	XX	XX
Min.	XX	XX	XX
Max.	XX	XX	XX

And even some sections that need both represented.

Time of onset, days			
1-7	XX (XX%)	XX (XX%)	XX (XX%)
8-14	XX (XX%)	XX (XX%)	XX (XX%)
>14	XX (XX%)	XX (XX%)	XX (XX%)
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
SD	XX.XX	XX.XX	XX.XX
Median	XX	XX	XX
Q1	XX	XX	XX
Q3	XX	XX	XX
Min.	XX	XX	XX
Max.	XX	XX	XX
Duration, days			
1-7	XX (XX%)	XX (XX%)	XX (XX%)
8-14	XX (XX%)	XX (XX%)	XX (XX%)
>14	XX (XX%)	XX (XX%)	XX (XX%)
n	XX	XX	XX
Mean	XX.X	XX.X	XX.X
SD	XX.XX	XX.XX	XX.XX
Median	XX	XX	XX
Q1	XX	XX	XX
Q3	XX	XX	XX
Min.	XX	XX	XX
Max.	XX	XX	XX

Using the BDS data structure will allow us to capture all of this in one dataset. Looking at the specs for this dataset you will see that it is very clean and concise making it much easier to work with.

VARIABLE	LABEL	TYPE	LENGTH
TRTP	Planned Treatment	Text	21
TRTPN	Planned Treatment (N)	Integer	8
TRTA	Actual Treatment	Text	21
TRTAN	Actual Treatment (N)	Integer	8
COHORT	Cohort	Text	32
COHORTN	Cohort (N)	Integer	8
TRTSDT	Date of First Exposure to Treatment	Integer	8
TRTSTM	Time of First Exposure to Treatment	Integer	8
TRTSDTM	Date Time of First Exposure to Treatment	Integer	8
TRTEDT	Date of Last Exposure to Treatment	Integer	8
TRTETM	Time of Last Exposure to Treatment	Integer	8
TRTEDTM	Date Time of Last Exposure to Treatment	Integer	8
AEDECOD	Dictionary-Derived Term	Text	29
AEDECODN	Dictionary-Derived Term(N)	Integer	8
PARAM	Parameter	Text	40
PARAMCD	Parameter Code	Text	8
AVAL	Analysis Value	Integer	8
AVALC	Analysis Value (C)	Text	32

The key to BDS is the Value Level Metadata (VLM) and ensuring it is clear how the parameter level information is defined.

LIST_NAME	VALUE	VLM_LABEL	VLM_TYPE	COMP_METHOD_NAME	ORIGIN	COMMENT_TXT	SOURCE_VAR
ADAEISR.AVAL	PARAMCD EQ "ACTION	Action Taken	Integer		ASSIGNED	If ADAE.AEACN='DRUG WITHDRAWN' set to 1; If ADAE.AEACN='DOSE REDUCED' set to 2; If ADAE.AEACN='DOSE INCREASED' set to 3; If ADAE.AEACN='DOSE NOT CHANGED' set to 4; If ADAE.AEACN='DOSE INTERRUPTED' set to 5; If ADAE.AEACN='NOT APPLICABLE' set to 6	
ADAEISR.AVALC	PARAMCD EQ "ACTION	Action Taken	Text		PREDECESSOR		ADAE.AEACN
ADAEISR.AVAL	PARAMCD EQ "ADUR"	Duration	Integer		PREDECESSOR		ADAE.ADURN
ADAEISR.AVALC	PARAMCD EQ "ADURC"	Duration Group	Text		ASSIGNED	if 1<=AVAL<=7 set to '1-7'; if 8<=AVAL<=14 set to '8-14'; if AVAL>14 set to '>14'	
ADAEISR.AVAL	PARAMCD EQ "ADUR2"	Duration (Grade >=2)	Integer		ASSIGNED	ADAE.AENDY-ADAE.ASTDY+1 Where ADAE.AETOXGRN>=2	
ADAEISR.AVAL	PARAMCD EQ "ADUR3"	Duration (Grade >=3)	Integer		ASSIGNED	ADAE.AENDY-ADAE.ASTDY+1 Where ADAE.AETOXGRN>=3	
ADAEISR.AVAL	PARAMCD EQ "ADURC"	Duration Group	Integer		ASSIGNED	if 1<=ADAE.ADURN<=7 set to 1; if 8<=ADAE.ADURN<=14 set to 2; if ADAE.ADURN>14 set to 3	
ADAEISR.AVAL	PARAMCD EQ "EVECHAR"	Event Characteristics	Integer		ASSIGNED	If ADAE.AESER='Y' set to 1; If ADAE.AESHOSP='Y' set to 2; If ADAE.AREL='Y' set to 3; If ADAE.AEWD set to 4	
ADAEISR.AVAL	PARAMCD EQ "MAXTOX"	Maximum Toxicity	Integer		ASSIGNED	Maximum AETOXGRN by USUBJID and AEDCOD	
ADAEISR.AVALC	PARAMCD EQ "MAXTOX"	Maximum Toxicity	Text		ASSIGNED	If AVAL=1 set to "GRADE 1"; If AVAL=2 set to "GRADE 2"; If AVAL=3 set to "GRADE 3"; If AVAL=4 set to "GRADE 4"; If AVAL=5 set to "GRADE 5"	
ADAEISR.AVAL	PARAMCD EQ "MAX_SA"	Maximum Surface Area	Integer		ASSIGNED	Maximum of FAAE.FASTRESN where FAAE.FATESTCD="SAID1D2" by USUBJID, FAREFID	
ADAEISR.AVAL	PARAMCD EQ "NUMEVE"	Number of Events	Integer	ADAEISR_NUMEVE	DERIVED		
ADAEISR.AVALC	PARAMCD EQ "EVECHAR"	Event Characteristics	Text		ASSIGNED	If ADAE.AESER='Y' set to "Serious"; If ADAE.AESHOSP='Y' set to "Hospitalization"; If ADAE.AREL='Y' set to "Related to Study Treatment"; If ADAE.AEWD set to "Withdrawal from Study"	
ADAEISR.AVAL	PARAMCD EQ "NUMEVEGP"	Number of Occurrences	Integer		ASSIGNED	Set to numeric equivalent of AVALC per controlled terminology	
ADAEISR.AVALC	PARAMCD EQ "NUMEVEGP"	Number of Occurences	Text	ADAEISR_NUMEVEGP	DERIVED		
ADAEISR.AVAL	PARAMCD EQ "ONSET"	Time to Onset	Integer		ASSIGNED	ADAE.ASTDT-TRTSDT+1	
ADAEISR.AVAL	PARAMCD EQ "ONSETGP"	Time to Onset Group	Integer		ASSIGNED	if 1<=ADAE.ASTDT-TRTSDT+1<=7 set to 1; if 8<=ADAE.ASTDT-TRTSDT+1<=14 set to 2; if ADAE.ASTDT-TRTSDT+1>14 set to 3	
ADAEISR.AVALC	PARAMCD EQ "ONSETGP"	Time to Onset Group	Text		ASSIGNED	if 1<=AVAL<=7 set to '1-7'; if 8<=AVAL<=14 set to '8-14'; if AVAL>14 set to '>14'	
ADAEISR.AVAL	PARAMCD EQ "OUTCOME"	Outcome	Integer		PREDECESSOR		ADAE.AEOUTN
ADAEISR.AVALC	PARAMCD EQ "OUTCOME"	Outcome	Text		PREDECESSOR		ADAE.AEOUT

With all the groundwork laid we can create a dataset that is clear, concise and easy to use in order to create our desired outputs.

SUBJID	AEDECOD	PARAM	PARAMCD	AVAL	AVALC
000005	Injection site erythema	Action Taken	ACTION	6	NOT APPLICABLE
000005	Injection site erythema	Duration	ADUR	10	
000005	Injection site erythema	Duration at Grade (Grade>=2)	ADUR2	8	
000005	Injection site erythema	Duration Group	ADURC	2	8-14
000005	Injection site erythema	Event Characteristics	EVECHAR	3	Related to Study Treatment
000005	Injection site erythema	Maximum Grade	MAXTOX	2	Moderate or Grade 2
000005	Injection site erythema	Maximum Surface Area	MAX_SA	7800	
000005	Injection site erythema	Number of Events	NUMEVE	1	
000005	Injection site erythema	Number of Occurences	NUMEVEGP	1	One
000005	Injection site erythema	Time to Onset	ONSET	1	
000005	Injection site erythema	Time to Onset Group	ONSETGP	1	1-7
000005	Injection site erythema	Outcome	OUTCOME	1	RECOVERED/RESOLVED
000005	Injection site induration/swelling	Action Taken	ACTION	6	NOT APPLICABLE
000005	Injection site induration/swelling	Duration	ADUR	118	
000005	Injection site induration/swelling	Duration at Grade (Grade>=2)	ADUR2	113	
000005	Injection site induration/swelling	Duration Group	ADURC	3	>14
000005	Injection site induration/swelling	Event Characteristics	EVECHAR	3	Related to Study Treatment
000005	Injection site induration/swelling	Maximum Grade	MAXTOX	2	Moderate or Grade 2
000005	Injection site induration/swelling	Maximum Surface Area	MAX_SA	4000	
000005	Injection site induration/swelling	Number of Events	NUMEVE	1	
000005	Injection site induration/swelling	Number of Occurences	NUMEVEGP	1	One
000005	Injection site induration/swelling	Time to Onset	ONSET	2	

CONCLUSION

We have defined what an ISR is, how it is different from the other data we collect, especially AE data, and how to capture the data in a form that will make it easier to display and report. As our world evolves, we will likely see more and more medications administered as some type of injection. For us in the programming world this means we need to understand the uniqueness of the data we collect and how best to report it to those who need to see it and draw conclusions from it. The world of ISRs is complex but it is that complexity that makes it so much fun. Happy programming ☺

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Kjersten Offenbecker
Programming Leader
GlaxoSmithKline, Inc
Kjersten.x.Offenbecker@gsk.com

Fox Mulder
Principal Programmer/Analyst
GlaxoSmithKline, Inc.
Fox.A.Mulder@gsk.com