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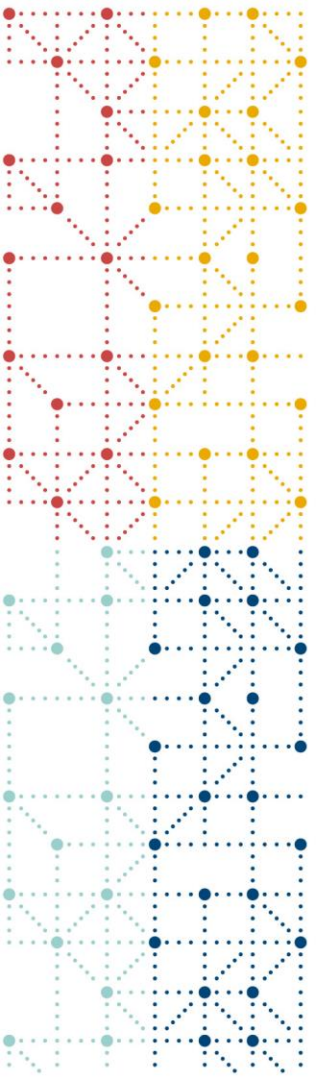
## ADAM Implementation of irAE Analysis

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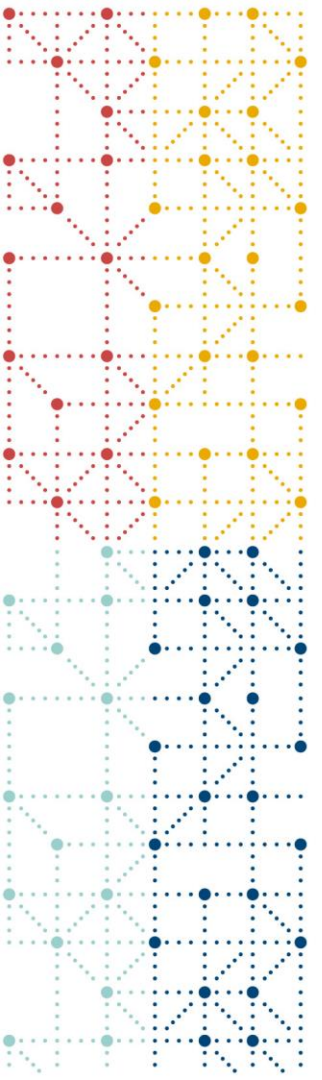
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# Agenda

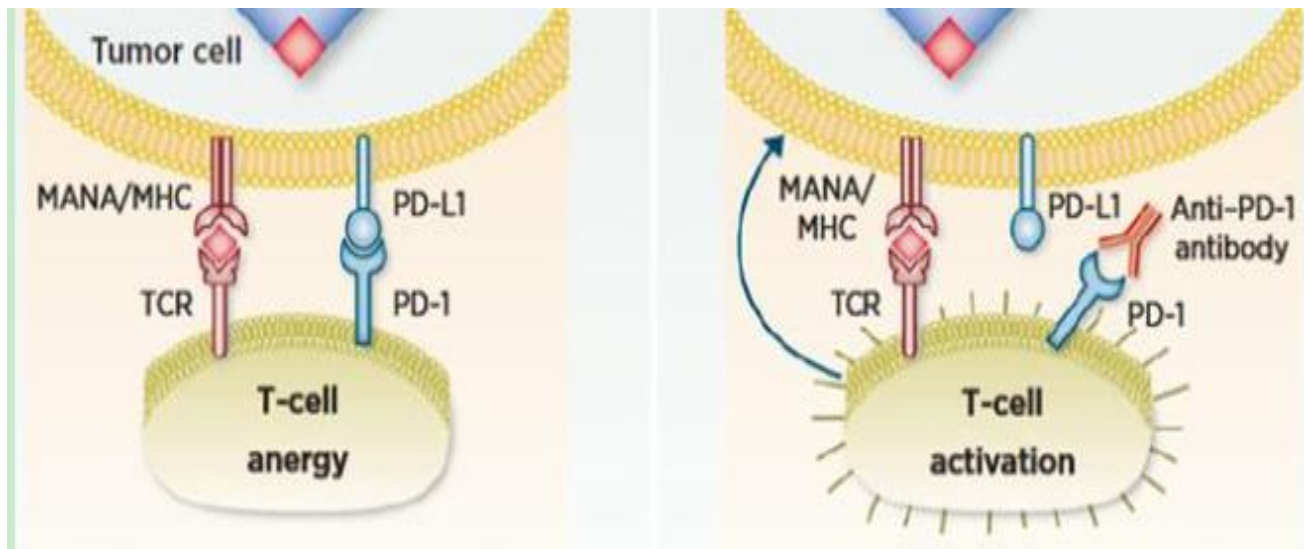
1. Introduction
2. The Classification of irAE
3. The Continuous irAE
4. Systemic Corticosteroids Usage



# 1. Introduction

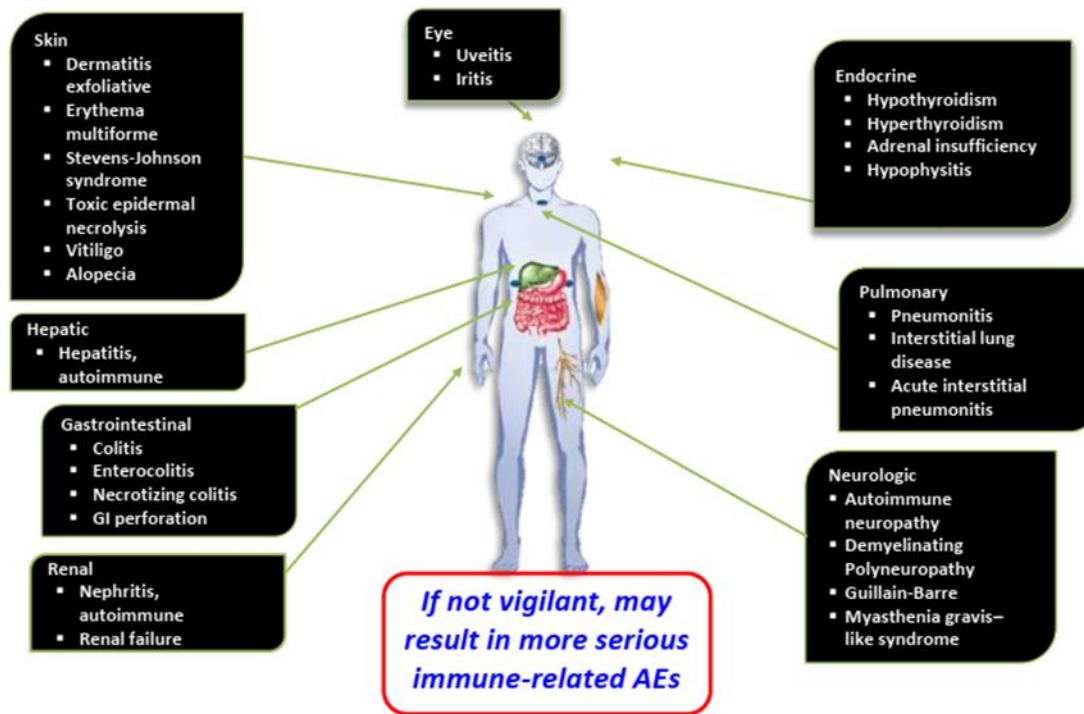
# Introduction

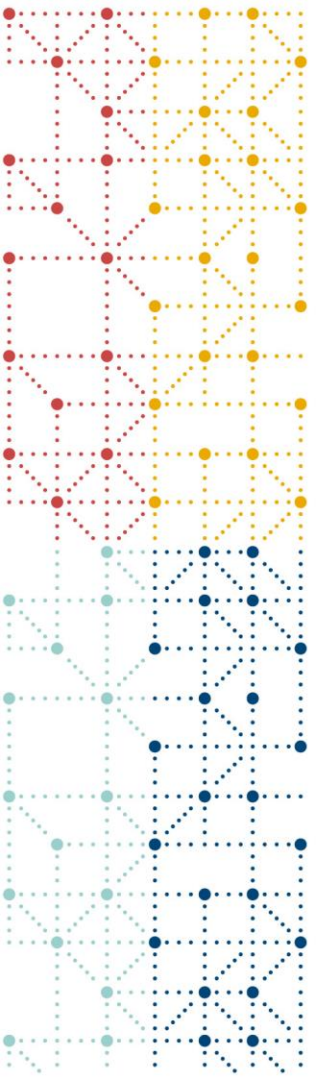
Immune checkpoint inhibitors have revolutionized the treatment of many different types of cancers.



# Introduction

Because the mechanism of action of this class of drugs is to block inhibitory signal that prevents activation of T cells there is a potential that these drugs may cause immune-related adverse events(irAE).





## 2. The Classification of irAE

# The Classification of irAE

We choose the standardized MedDRA query variables CQzzNAM to identify the classification of irAE in ADAE.

**Table 3.2.9.1 Standardized MedDRA Query Variables**

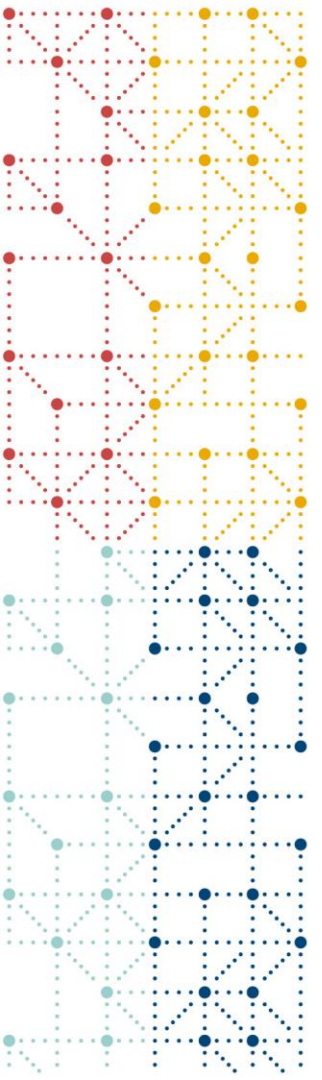
Variable	Label	CDISC Notes
CQzzNAM	Customized Query zz Name	The customized query(CQ) name or name of the AE of special interest category based on a grouping of terms. Would be blank for terms that are not in the CQ.



# The Classification of irAE

The group and subgroup of irAE is provided by sponsor physician. These variables can join ADAE by AEDECOD.

CQ01NAM	CQ01NAMN	CQ02NAM	CQ02NAMN
Lung toxicity (Pneumonitis)	1	Lung toxicity (Pneumonitis)	1
Hepatotoxicity (Hepatitis)	2	Hepatotoxicity (Hepatitis)	2
Gastrointestinal toxicity (Diarrhea/Colitis)	3	Gastrointestinal toxicity (Diarrhea/Colitis)	3
Renal toxicity (Nephritis/Renal insufficiency)	4	Nephritis	4
Renal toxicity (Nephritis/Renal insufficiency)	4	Renal insufficiency	5
Renal toxicity (Nephritis/Renal insufficiency)	4	Other nephrotoxicity	6
Endocrine toxicity	5	Hypothyroidism	7
Endocrine toxicity	5	Hyperthyroidism	8
Endocrine toxicity	5	Other thyroid diseases	9
Endocrine toxicity	5	Parathyroid disease	10
Endocrine toxicity	5	Hypophysitis	11
Endocrine toxicity	5	Adrenal insufficiency	12
Endocrine toxicity	5	Hyperglycaemia / Type 1 diabetes mellitus	13
Dermatologic toxicity	6	Dermatologic toxicity	14
Neurotoxicity	7	Neurotoxicity	15
Hematotoxicity	8	Thrombocytopenia	16
Hematotoxicity	8	Other hematotoxicity	17
Cardiovascular toxicity	9	Myocarditis	18
Cardiovascular toxicity	9	Other cardiovascular toxicity	19
Ocular toxicity	10	Ocular toxicity	20
Rheumatoid / Skeletal muscle toxicity	11	Rheumatoid / Skeletal muscle toxicity	21
Pancreatic toxicity	12	Pancreatic toxicity	22
Other toxicity	13	Other toxicity	23



### 3. The Continuous irAE



## The Continuous irAE

If the interval between different irAEs are  $\leq 3$  days within the same group for the same subject, the irAEs will be counted as one. Thus we need a new sequence number to identify the unique merged irAE.

# The Continuous irAE

Variable	Label	Derivation
CIAESEQ	Sequence Number of Continuous irAE	For irAE records: 1. Sort by variable USUBJID CQ01NAM CQ02NAM ASTDT AENDT AESEQ. 2. Loop the following steps for each value of CQ02NAM. 1) Retain CIAESDT CIAEEDT CIAEGRN 2) If first.CQ02NAM then do; Set CIAESEQ=1, CIAESDT=ASTDT, CIAEEDT=AENDT, CIAEGRN=ATOXGRN. 3) If not first.CQ02NAM then do: if ASTDT <= CIAEEDT+3 then set CIAEEDT= max(CIAEEDT, AENDT), CIAEGRN=max(CIAEGRN, ATOXGRN); else if ASTDT > CIAEEDT+3 then CIAESEQ+1, CIAESDT=ASTDT, CIAEEDT=AENDT, CIAEGRN=ATOXGRN.
CIAESDT	Continuous irAE Start Date	
CIAEEDT	Continuous irAE End Date	
CIAEGRN	Toxicity Grade for Continuous irAE (N)	
ANL01FL	Analysis Flag 01	

# The Continuous irAE

SUBJID	AEDECOD	CQ01NAM	CQ02NAM	ASTDT	AENDT	ATOXGRN	CIAESEQ	CIAESDT	CIAEEDT	CIAEGRN	ANL01FL
1001	Skin rash	Dermatologic toxicity	Dermatologic toxicity	2021-01-01	2021-01-05	2	1	2021-01-01	2021-01-05	2	
1001	Immune-mediated dermatitis	Dermatologic toxicity	Dermatologic toxicity	2021-01-07	2021-05-09	1	1	2021-01-01	2021-05-09	2	Y
1002	Iridocyclitis	Ocular toxicity	Ocular toxicity	2021-04-01	2021-04-23	2	1	2021-04-01	2021-04-23	2	Y
1002	Iridocyclitis	Ocular toxicity	Ocular toxicity	2021-08-07	2021-08-11	1	2	2021-08-07	2021-08-11	1	
1002	Iridocyclitis	Ocular toxicity	Ocular toxicity	2021-08-09	2021-11-16	2	2	2021-08-07	2021-11-16	2	Y

# A Case for Example

**Table 1 Summary of Time to Onset of Initial irAE and Time to irAE Remission – Subjects with irAE (Safety Analysis Set)**

irAE Group irAE Subgroup	Total (N=XX)
irAE Group #1 irAE Subgroup #1	
Time to Onset of the Initial irAE (months)	
n (%)	XX (XX.X)
Mean (SD)	XX.XX (XX.XXX)
Median	XX.XX
Min, Max	XX.X, XX.X
Time to irAE Remission (months)	
n (%)	XX (XX.X)
Mean (SD)	XX.XX (XX.XXX)
Median	XX.XX
Min, Max	XX.X, XX.X
irAE Subgroup #2	
...	
...	

# The Continuous irAE

**Time to onset of initial irAE (months)** = (Start date of first irAE within the irAE group – Date of first administration+ 1) / 30.4375.

Variable	Label	Derivation
AOCC01FL	1st Occur of irAE Flag	Flag the first record within CQ02NAM ordered by USUBJID, CQ01NAM, CQ02NAM, ASTDT, AESEQ
T2OCDUR	Time to Onset of First irAE	When AOCC01FL="Y", equals to (ASTDT-ADSL.TRTSDT+1)/30.4375

# The Continuous irAE

SUBJID	CQ01NAM	CQ02NAM	ASTDT	AENDT	ATOXGRN	CIASEQ	CIAESDT	CIAEEDT	CIAEGRN	ANL01FL	AOCC01FL
1001	Dermatologic toxicity	Dermatologic toxicity	2021-01-01	2021-01-05	2	1	2021-01-01	2021-01-05	2		Y
1001	Dermatologic toxicity	Dermatologic toxicity	2021-01-07	2021-05-09	1	1	2021-01-01	2021-05-09	2	Y	
1002	Ocular toxicity	Ocular toxicity	2021-04-01	2021-04-23	2	1	2021-04-01	2021-04-23	2	Y	Y
1002	Ocular toxicity	Ocular toxicity	2021-08-07	2021-08-11	1	2	2021-08-07	2021-08-11	1		
1002	Ocular toxicity	Ocular toxicity	2021-08-09	2021-11-16	2	2	2021-08-07	2021-11-16	2	Y	



# A Case for Example

**Table 1 Summary of Time to Onset of Initial irAE and Time to irAE Remission – Subjects with irAE (Safety Analysis Set)**

irAE Group irAE Subgroup	Total (N=XX)
irAE Group #1 irAE Subgroup #1	
Time to Onset of the Initial irAE (months)	
n (%)	XX (XX.X)
Mean (SD)	XX.XX (XX.XXX)
Median	XX.XX
Min, Max	XX.X, XX.X
Time to irAE Remission (months)	
n (%)	XX (XX.X)
Mean (SD)	XX.XX (XX.XXX)
Median	XX.XX
Min, Max	XX.X, XX.X
irAE Subgroup #2	
...	
...	

**T2OCDUR/AOCC01FL**



## The Continuous irAE

**Time to irAE remission (months):** The maximum duration from the first occurrence of irAE with maximum CTCAE grade to the final recovery/resolution.

- Note: 1. Only applied to the subjects with AE outcome as ‘Recovered/Resolved with Sequelae’ or ‘Recovered/Resolved’ .
2. A subject with multiple CTCAE grades for the same irAE group will be summarized under the maximum CTCAE grade recorded for the event.
3. If all irAEs with the same CTCAE grade are recovered/resolved, then use the one with maximum duration.

# The Continuous irAE

Variable	Label	Derivation
ANL01FL	Analysis Flag 01	Flag the last record within CIAESEQ ordered by USUBJID, CQ01NAM, CQ02NAM, CIAESEQ, ASTDT, AENDT, AESEQ
CIAEDUR	Duration of Continuous irAE (Months)	When ANL01FL="Y", equals to $(CIAEEDT - CIAESDT + 1) / 30.4375$
SUBREFL	Subject whose irAE Outcome is Recovered	Find the max(AOUTN) grouped by USUBJID, CQ01NAM, CQ02NAM, if max(AOUTN) in (1, 2), set to "Y". Merge back to all the records for that USUBJID, CQ01NAM, CQ02NAM  Note: AOUTN=1 means AE outcome is 'Recovered/Resolved' AOUTN=2 means AE outcome is 'Recovered/Resolved with Sequelae'
ANL02FL	Analysis Flag 02	When SUBREFL="Y" and ANL01FL="Y", flag the first record within CQ02NAM ordered by USUBJID, CQ01NAM, CQ02NAM, descending CIAEGRN, descending CIAEDUR, AESEQ

# The Continuous irAE

SUBJID	CQ01NAM	CQ02NAM	ASTDT	AENDT	ATOXGRN	CIAESEQ	CIAESDT	CIAEEDT	CIAEGRN	ANL01FL	ANL02FL
1001	Dermatologic toxicity	Dermatologic toxicity	2021-01-01	2021-01-05	2	1	2021-01-01	2021-01-05	2		
1001	Dermatologic toxicity	Dermatologic toxicity	2021-01-07	2021-05-09	1	1	2021-01-01	2021-05-09	2	Y	Y
1002	Ocular toxicity	Ocular toxicity	2021-04-01	2021-04-23	2	1	2021-04-01	2021-04-23	2	Y	
1002	Ocular toxicity	Ocular toxicity	2021-08-07	2021-08-11	1	2	2021-08-07	2021-08-11	1		
1002	Ocular toxicity	Ocular toxicity	2021-08-09	2021-11-16	2	2	2021-08-07	2021-11-16	2	Y	Y

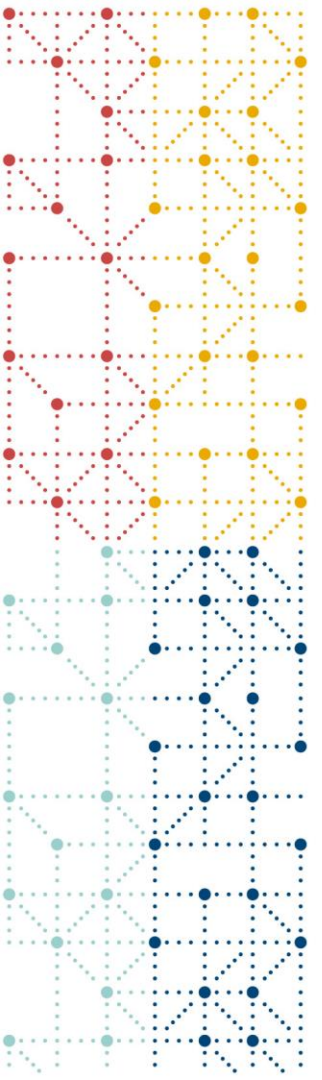
Note: we assume that the above subjects with AE outcome as  
 ‘Recovered/Resolved with Sequelae’ or ‘Recovered/Resolved’

# A Case for Example

**Table 1 Summary of Time to Onset of Initial irAE and Time to irAE Remission – Subjects with irAE (Safety Analysis Set)**

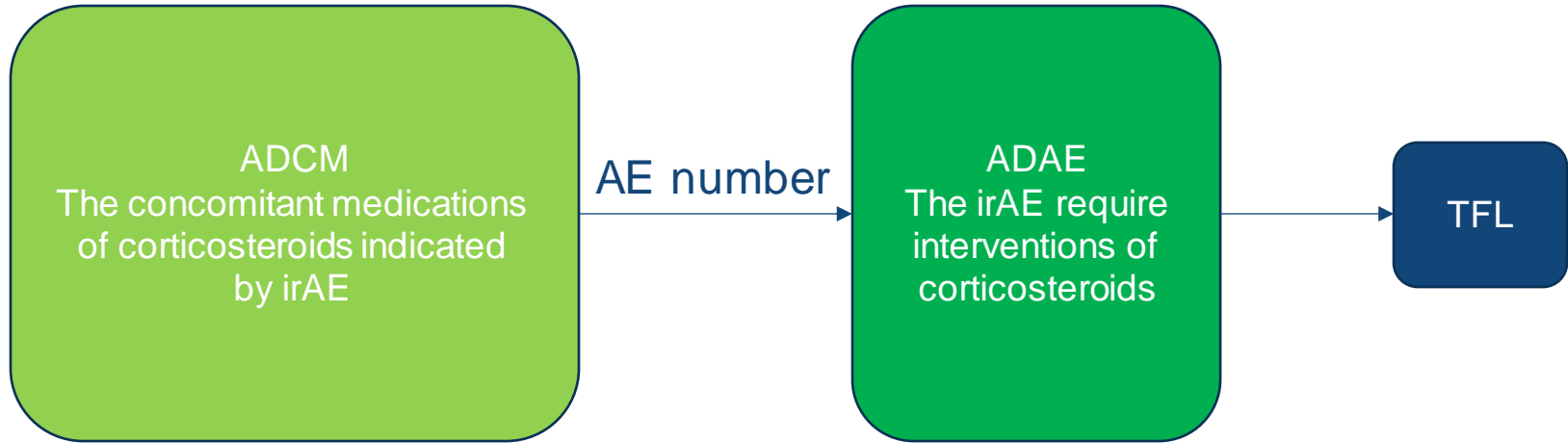
irAE Group irAE Subgroup	Total (N=XX)
irAE Group #1 irAE Subgroup #1	
Time to Onset of the Initial irAE (months)	
n (%)	XX (XX.X)
Mean (SD)	XX.XX (XX.XXX)
Median	XX.XX
Min, Max	XX.X, XX.X
Time to irAE Remission (months)	
n (%)	XX (XX.X)
Mean (SD)	XX.XX (XX.XXX)
Median	XX.XX
Min, Max	XX.X, XX.X
irAE Subgroup #2	
...	
...	

**ICAEDUR/ANL02FL**



## 4. Systemic Corticosteroids Usage

# Systemic Corticosteroids Usage



# Systemic Corticosteroids Usage

## □ ADCM

Variable	Label	Derivation
SCORTFL	Systemic Corticosteroids Flag	Flag the systemic corticosteroid medications using ATC variables per SAP.
PREDDOSE	Daily Equivalent Dose of Prednisone	Convert that daily dose for each steroid to the equivalent dose if they'd been on Prednisone using a conversion factor. =CMDOSE*Dosing times daily/FACTOR

The common conversion factors are shown as:

DRUG NAME	FACTOR
Betamethasone	0.16
Dexamethasone	0.16
Methylprednisolone	0.8
Prednisolone	1
Prednisone	1
Triamcinolone	0.8
Hydrocortisone	4
Cortisone	5



# Systemic Corticosteroids Usage

## □ ADAE

1. **The initial dose of systemic steroid therapy:** sum of the prednisone dose or total equivalent dose of all systemic steroids used on the first day for the subjects.
2. **High Starting Dose:** The dose of first occurrence of a dose of  $\geq 40$  mg/day prednisone or equivalent dose during the systemic corticosteroids therapy.
3. **Treatment duration:** The sum of the time of steroid use during the first irAE treated with high-dose steroids (excluding the time of withdrawal and the overlap of multiple steroids use).

# A Case for Example

Table 2 Summary of Dosage and Duration of Systemic Corticosteroids Usage – Subjects with irAE (Safety Analysis Set)

irAE Group irAE Subgroup	Total (N=XX)
irAE Group #1	
irAE Subgroup #1	
Subject without Systemic Corticosteroids Usage, n (%)	XX (XX.X)
Subject with Systemic Corticosteroids Usage, n (%)	XX (XX.X)
Starting Dose (mg/day)	
Mean (SD)	XX.XX (XX.XXX)
Median	XX.XX
Min, Max	XX.X, XX.X
High Dose, n (%)	XX (XX.X)
High Starting Dose (mg/ day)	
Mean (SD)	XX.XX (XX.XXX)
Median	XX.XX
Min, Max	XX.X, XX.X
Treatment duration (Months)	
Mean (SD)	XX.XX (XX.XXX)
Median	XX.XX
Min, Max	XX.X, XX.X
...	

# Systemic Corticosteroids Usage

## □ ADAE

Variable	Label	Derivation
ISDOSE	Initial Dose of Systemic Steroid	Merge ADAE and ADCM by USUBJID and AE number. Calculate the sum of all PREDDOSE in the earliest cm date within each AESPID and set the corresponding ADCM.ASTDT as CORSDT.
CORSDT	Corticosteroids Start Date	
HSDOSE	High Starting Dose	Merge ADAE and ADCM by USUBJID and AE number. Calculate the sum of all PREDDOSE for each ADCM.ASTDT within each AESPID, then select the earliest record where sum dose $\geq 40$ and set the corresponding ADCM.ASTDT as HCORSDT, if no record with DOSE $\geq 40$ , set to null.
HCORSDT	High Corticosteroids Start Date	
CORTDUR	Corticosteroids Treatment Duration (Months)	Merge ADAE and ADCM by USUBJID and AE number. Calculate the sum days of ADCM using ADCM.ASTDT and ADCM.AENDT within each CQ01NAM, CQ02NAM, CIAESEQ, and divided by 30.4375. Set to null if HCORSDT is missing. Note: If multiple treatments occur on the same day, only count once.

# Systemic Corticosteroids Usage

SUBJID	CQ01NAM	CQ02NAM	CIAESEQ	AESPID/ AENO in ADCM	ISDOSE	CORSDT	ANL03FL	HSDOSE	HCORSDT	ANL04FL
1001	Dermatologic toxicity	Dermatologic toxicity	1	1	100	2021-01-01	Y	100	2021-01-01	Y
1001	Dermatologic toxicity	Dermatologic toxicity	1	8	30	2021-02-10				
1002	Ocular toxicity	Ocular toxicity	1	2	10	2021-04-12	Y			
1002	Ocular toxicity	Ocular toxicity	2	9	25	2021-08-07				
1002	Ocular toxicity	Ocular toxicity	2	14	60	2021-09-09		60	2021-09-09	Y

Variable	Label	Derivation
ANL03FL	Analysis Flag 03	Flag the first record within CQ02NAM ordered by USUBJID, CQ01NAM, CQ02NAM, CORSDT, AESPID
ANL04FL	Analysis Flag 04	Flag the first record within CQ02NAM ordered by USUBJID, CQ01NAM, CQ02NAM, HCORSDT, AESPID

# A Case for Example

Table 2 Summary of Dosage and Duration of Systemic Corticosteroids Usage – Subjects with irAE (Safety Analysis Set)

irAE Group irAE Subgroup	Total (N=XX)
irAE Group #1	
irAE Subgroup #1	
Subject without Systemic Corticosteroids Usage, n (%)	XX (XX.X)
Subject with Systemic Corticosteroids Usage, n (%)	XX (XX.X)
Starting Dose (mg/day)	
Mean (SD)	XX.XX (XX.XXX)
Median	XX.XX
Min, Max	XX.X, XX.X
High Dose, n (%)	XX (XX.X)
High Starting Dose (mg/ day)	
Mean (SD)	XX.XX (XX.XXX)
Median	XX.XX
Min, Max	XX.X, XX.X
Treatment duration (Months)	
Mean (SD)	XX (XX.X)
Median	XX.XX (XX.XXX)
Min, Max	XX.X, XX.X
...	

**ISDOSE/ANL03FL**

**HSDOSE/ANL04FL**

**CORTDUR/ANL04 FL**



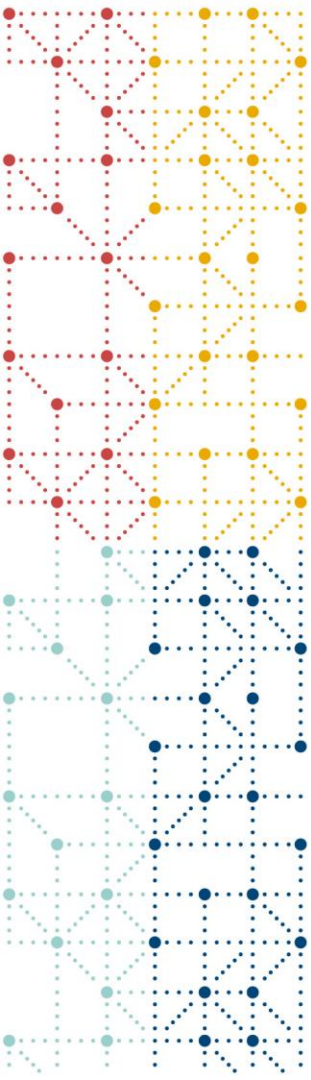
# Summary

The current literature on ADaM implementation of irAE is scanty. In this presentation, we built up ADAE variables related to irAE analysis step by step using existing ADaM variable and rules. It is hoped that it will provide a sufficient basis for people who need to implement irAE in ADaM for the first time.



# Reference

1. CDISC ADaM Occurrence Data Structure (OCCDS) (Version 1.0)
2. CDISC ADaM Implementation Guide (Version 1.0)
3. Management of IRAE, Prof Bernardo L. Rapoport, Medical Oncologist, Johannesburg



**Thank You!**

**cdisc**