ADRECIST: a fully derived disease evaluation dataset

Ping Zhang, C&SP, Johnson & Johnson

Meet the Speaker

Ping Zhang

Title: Statistical Programming Lead

Organization: Clinical & Statistical Programming, Johnson & Johnson

Ping Zhang graduated from China Pharmaceutical University in 2013. with 4 years of experience at PXL after graduation, I Joined Johnson & Johnson as senior statistical programmer in 2017. Currently working in a compound treating EGFR mutant NSCLC and has been supporting worldwide submission (including China NMPA).

Disclaimer and Disclosures

- The views and opinions expressed in the presentation and on the following slides are solely on my own, and do not necessarily reflect the views of Johnson & Johnson.

Agenda

1. Introduction of RECIST
2. Introduction of ADRECIST

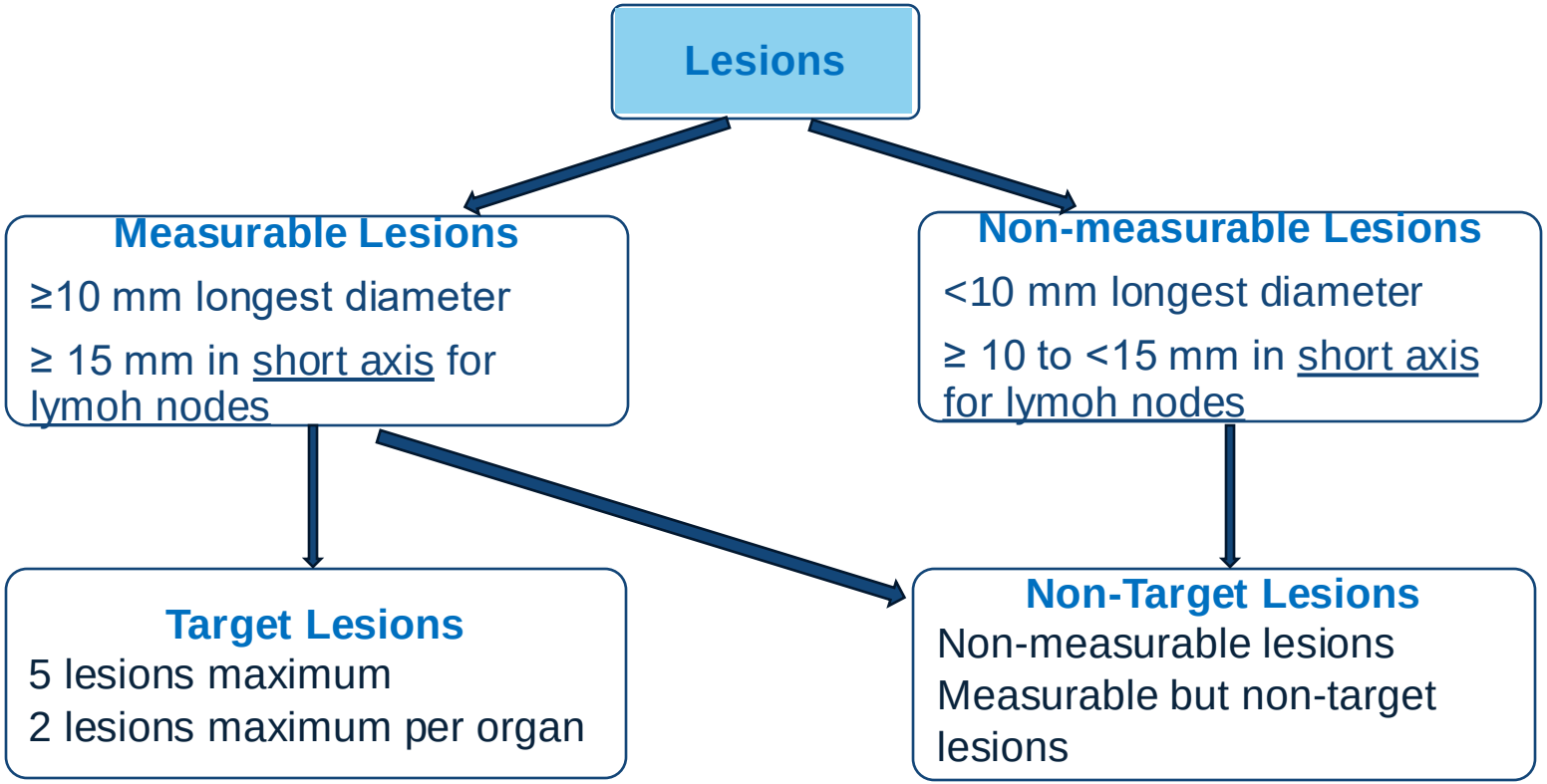
Introduction of RECIST

- What is RECIST?
- Basic Concepts of RECIST
- Response Evaluation

What is RECIST?

- **R**esponse **E**valuation **C**riteria **I**n **S**olid **T**umors
- V1.0 (2000) → V1.1 (2009)
- Objective criteria to evaluate tumor response in clinical trials.
- Measurement data translates into multiple endpoints: e.g.
  - Objective Response Rate (ORR)
  - Duration of Response (DoR)
  - Progression Free Survival (PFS)
  - Time to Progression (TTP)

Basic Concepts of RECIST



Response Evaluation– Target Lesions

Target Lesions Response	Criteria
Complete Response (CR)	**Disappearance of all target** lesions. Any pathological lymph nodes (whether target/non-target) must have reduction in short axis to <10 mm
Partial Response (PR)	At least a **30% decrease** in the sum of diameters to target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	At least a **20% increase** in the sum of diameters of target lesions, taking as reference the smallest sum on study(**Nadir**). In addition to the relative increase of 20%, the sum must also demonstrate an absolute **increase of at least 5 mm**.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Taking as reference the smallest sum diameters while on study.

Response Evaluation– Non-Target Lesions

Non-Target Lesions Response	Criteria
Complete Response (CR)	**Disappearance of all non-target** lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD (NN)	**Persistence** of one or more non-target lesions.
Progressive Disease (PD)	**Unequivocal progression** of existing non-target lesions.

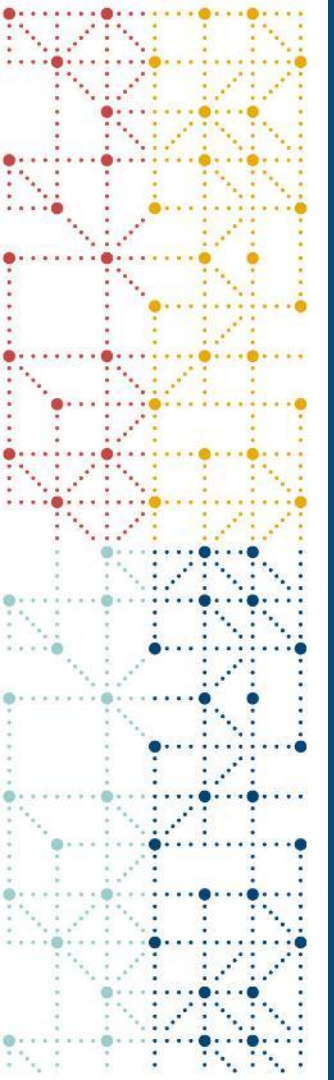
Response Evaluation– Overall timepoint response

Overall response takes into account:

- **Target** and **non-target** response
- Any appearance of **new lesions**

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.



Introduction of ADRECIST

- Why
- Programming Design
- Usages

Why?

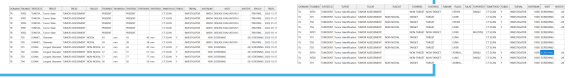
- It is important to be confident that this data is accurate, as it is a significant component of efficacy analyses. **If the data is not accurate, the analyses will not be accurate.**
- Different types of response evaluation data.
  - **Investigator** reported :
    - In the eCRF
  - **Central Review**
    - Based on scans that were sent to central reader vendor
    - Evaluated by independent onco specialists
  - **Algorithm** derived
    - Based on tumor lesion data in eCRF
    - Response calculated by statistical programmer
- All types are based on the same response evaluation criteria
  - Ideally outcome should be consistent

Programming Design - Data Flow

SDTM

All key SDTM data containing efficacy information for deriving and comparing INV analyses.

- TU – Baseline and New Lesion Identification
- TR – Lesion Measurements and Assessments



Programming Design - Data Flow

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DOMAIN	TULNKID	TUTESTCD	TUTEST	TUCAT	TUSCAT	TUORRES	TUSTRESC	TUNAM	TULOC	TULAT	TUPORTOT	TUMETHOD	TUBLFL	TUEVAL	VISITNUM	VISIT	VISITDY
TU	NT01	TUMIDENT	Tumor Identification	TUMOR ASSESSMENT		NON-TARGET	NON-TARGET		OTHER		SINGLE	CT SCAN	Y	INVESTIGATOR	1000	SCREENING	-28
TU	T01	TUMIDENT	Tumor Identification	TUMOR ASSESSMENT	NON-NODAL	TARGET	TARGET		LIVER			CT SCAN	Y	INVESTIGATOR	1000	SCREENING	-28
TU	T02	TUMIDENT	Tumor Identification	TUMOR ASSESSMENT	NON-NODAL	TARGET	TARGET		OTHER			CT SCAN	Y	INVESTIGATOR	1000	SCREENING	-28
TU	T03	TUMIDENT	Tumor Identification	TUMOR ASSESSMENT	NON-NODAL	TARGET	TARGET		LIVER			CT SCAN	Y	INVESTIGATOR	1000	SCREENING	-28
TU	NT01	TUMIDENT	Tumor Identification	TUMOR ASSESSMENT		NON-TARGET	NON-TARGET		LIVER		MULTIPLE	CT SCAN		INVESTIGATOR	1000	SCREENING	.
TU	T01	TUMIDENT	Tumor Identification	TUMOR ASSESSMENT	NON-NODAL	TARGET	TARGET		LUNG			CT SCAN		INVESTIGATOR	1000	SCREENING	.
TU	T02	TUMIDENT	Tumor Identification	TUMOR ASSESSMENT	NON-NODAL	TARGET	TARGET		LUNG			CT SCAN		INVESTIGATOR	1000	SCREENING	.
TU	T03	TUMIDENT	Tumor Identification	TUMOR ASSESSMENT	NON-NODAL	TARGET	TARGET		LIVER			CT SCAN		INVESTIGATOR	1000	SCREENING	.
TU	NT01	TUMIDENT	Tumor Identification	TUMOR ASSESSMENT		NON-TARGET	NON-TARGET		ADREN...		SINGLE	CT SCAN	Y	INVESTIGATOR	1000	SCREENING	-28
TU	NT02	TUMIDENT	Tumor Identification	TUMOR ASSESSMENT		NON-TARGET	NON-TARGET		LUNG		SINGLE	CT SCAN	Y	INVESTIGATOR	1000	SCREENING	-28
TU	T01	TUMIDENT	Tumor Identification	TUMOR ASSESSMENT	NON-NODAL	TARGET	TARGET		ADREN...			CT SCAN	Y	INVESTIGATOR	1000	SCREENING	-28

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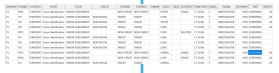

DOMAIN	TRLNKID	TRTESTCD	TRTEST	TRCAT	TRSCAT	TRORRES	TRORRESU	TRSTRESC	TRSTRESN	TRSTRESU	TRMETHOD	TRBLFL	TREVAL	VISITNUM	VISIT	VISITDY	EPOCH	TRDTC
TR	NT02	TUMSTA...	Tumor State	TUMOR ASSESSMENT		PRESENT		PRESENT	.		CT SCAN		INVESTIGATOR	80003	DISEASE EVALUATION 3	.	TREATME...	2022-12-27
TR	NT01	TUMSTA...	Tumor State	TUMOR ASSESSMENT		PRESENT		PRESENT	.		CT SCAN		INVESTIGATOR	80004	DISEASE EVALUATION 4	.	TREATME...	2023-01-21
TR	NT02	TUMSTA...	Tumor State	TUMOR ASSESSMENT		PRESENT		PRESENT	.		CT SCAN		INVESTIGATOR	80004	DISEASE EVALUATION 4	.	TREATME...	2023-01-21
TR	NT01	TUMSTA...	Tumor State	TUMOR ASSESSMENT		PRESENT		PRESENT	.		CT SCAN		INVESTIGATOR	80005	DISEASE EVALUATION 5	.	TREATME...	2023-03-11
TR	NT02	TUMSTA...	Tumor State	TUMOR ASSESSMENT		PRESENT		PRESENT	.		CT SCAN		INVESTIGATOR	80005	DISEASE EVALUATION 5	.	TREATME...	2023-03-11
TR	T05	DIAMET...	Diameter	TUMOR ASSESSMENT	NODAL	43	mm	43	43	mm	CT SCAN	Y	INVESTIGATOR	1000	SCREENING	-28	SCREENING	2022-10-27
TR	T05	DIAMET...	Diameter	TUMOR ASSESSMENT	NODAL	38	mm	38	38	mm	CT SCAN		INVESTIGATOR	80001	DISEASE EVALUATION 1	.	TREATME...	2022-12-27
TR	T01	LDIAM	Longest Diameter	TUMOR ASSESSMENT	NON-NODAL	43	mm	43	43	mm	CT SCAN	Y	INVESTIGATOR	1000	SCREENING	-28	SCREENING	2022-10-27
TR	T02	LDIAM	Longest Diameter	TUMOR ASSESSMENT	NON-NODAL	57	mm	57	57	mm	CT SCAN	Y	INVESTIGATOR	1000	SCREENING	-28	SCREENING	2022-10-27
TR	T03	LDIAM	Longest Diameter	TUMOR ASSESSMENT	NON-NODAL	77	mm	77	77	mm	CT SCAN	Y	INVESTIGATOR	1000	SCREENING	-28	SCREENING	2022-10-27
TR	T04	LDIAM	Longest Diameter	TUMOR ASSESSMENT	NON-NODAL	56	mm	56	56	mm	CT SCAN	Y	INVESTIGATOR	1000	SCREENING	-28	SCREENING	2022-10-27

Programming Design - Data Flow

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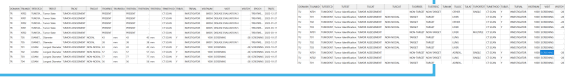

ADaM

ADRECIST (adrecist.sas)

Contains **all RECIST related data** in the database and flags over time nadir, progression, and response information in horizontal CRIT variables.

ADRECIST.sas

- Series of macro calls to build ADRECIST analysis dataset, one parameter at a time.

1. %ADPCPARAMTRGBL – Returns number of target lesions or number of target lymph nodes identified at baseline in AVAL.
2. %ADPCPARAMNTRGBL – Returns number of non-target lesions identified at baseline in AVAL.
3. %ADPCPARAMTRGSUM – Returns a by-visit parameter containing the sum of diameters of target lesions in AVAL at each post-baseline efficacy assessment. At each visit, BASE, CHG, PCHG, NDRVAL, CHGNDR, PCHGNDR are also derived to support the derivation of target lesion response. There are 5 sets of CRIT variables derived to store the visit level response assessment, one for each possible response assessment (CR, PR, SD, PD, NAE).
4. %ADPCPARAMTRGRSP – Returns target lesion response in AVAL at each post-baseline efficacy assessment.
5. %ADPCPARAMNTRGRSP – Returns non-target lesion response in AVALC at each post-baseline efficacy assessment.
6. %ADPCPARAMNEWLSN – Returns unequivocal new lesion flag (Y) in AVALC at any post-baseline efficacy assessment where one is identified.
7. %ADPCPARAMPADRCST – Uses RECIST parameter datasets as input and returns padded versions as output. For example, if a subject only has target disease at baseline, non-target disease records will be created and assigned as “Not Applicable” whenever target lesion assessments are available.
8. %ADPCPARAMOVRLRSP – Uses RECIST parameter datasets as input and returns overall response in AVALC at each post-baseline efficacy assessment.
9. %ADPCANLRCSTCNF – Uses RECIST parameter dataset, such as overall response, and applies confirmation flagging of confirmed response in ANL01FL and confirming response in ANL02FL.

- All parameters are then set together into one ADRECIST analysis dataset.

Sample ADRECIST Data

	AVISIT	PARAM	PARAMCD	AVAL	AVALC	BASE	CHG	NDRVAL	CHGNDR	CRIT1	CRIT2	CRIT3	CRIT4	CRIT5
1	Disease Evaluation 1	New Lesions (INV)	VNEWLSN	1	Y	.	.	.	.					
2	Disease Evaluation 2	New Lesions (INV)	VNEWLSN	1	Y	.	.	.	.					
3	Disease Evaluation 1	Non-target Lesions Response (INV)	VNTRGRSP	3	Non-CR/Non-PD	.	.	.	.					
4	Disease Evaluation 2	Non-target Lesions Response (INV)	VNTRGRSP	3	Non-CR/Non-PD	.	.	.	.					
5		Number of Non-Target Lesions at BL (INV)	VNTRGBL	7		.	.	.	.					
6		Number of Target Lesions at BL (INV)	VTRGBL	3		.	.	.	.					
7		Number of Target Nodes at BL (INV)	VTRGNBL	0		.	.	.	.					
8	Disease Evaluation 1	Overall Response (INV)	VOVRLRSP	2	Partial Response (PR)	.	.	.	.					
9	Disease Evaluation 2	Overall Response (INV)	VOVRLRSP	2	Partial Response (PR)	.	.	.	.					
10	Screening	Sum of Target Lesion Diameters (INV)	VTRGSUM	97		97	.	.	.					
11	Disease Evaluation 1	Sum of Target Lesion Diameters (INV)	VTRGSUM	30		97	-67	97	-67		Partial Response			
12	Disease Evaluation 2	Sum of Target Lesion Diameters (INV)	VTRGSUM	30		97	-67	30	0		Partial Response			
13	Disease Evaluation 1	Target Lesions Response (INV)	VTRGRSP	2	Partial Response (PR)	.	.	.	.					
14	Disease Evaluation 2	Target Lesions Response (INV)	VTRGRSP	2	Partial Response (PR)	.	.	.	.					

Number of Non-Target Lesions at BL (INV)
Number of Target Lesions at BL (INV)
Number of Target Nodes at BL (INV)
Sum of Target Lesion Diameters (INV)

New Lesion (INV)
Target Lesions Response (INV)
Non-target Lesions Response (INV)
Overall Response (INV)

RECIST 1.1: Response of target lesions - Example

Lesion	Baseline	DEV1	DEV2	DEV3	DEV4
Rt lung 1	30 mm	20 mm	20 mm	20 mm	30 mm
Rt lung 2	25 mm	20 mm	20 mm	20 mm	30 mm
Lt liver lobe	60 mm	50 mm	30 mm	30 mm	50 mm
Rt liver lobe	25 mm	20 mm	20 mm	20 mm	20 mm
SOD	**140**	**110**	**90**	**90**	**130**
% change from baseline	_	-21%	-36%	-36%	-7%
Nadir (lowest prior value)	_	**140**	**110**	**90**	**90**
% change from nadir	_	-21%	-18%	0%	+44% *
Target Lesion response	_	SD	PR	PR	PD

* % Change from NADIR: (130-90)/90 = 44%

- > 20% increase from NADIR and
- > 5mm absolute increase from NADIR

→ Progressive disease

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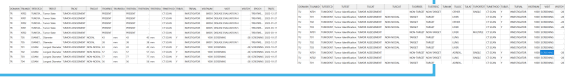
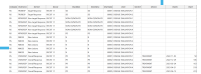


SDTM

SDTM data containing investigator reported response

RS – Investigator Response Evaluations



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Output Review Listing

Uses both **SDTM** and **ADaM** as input because this file contains information that is both highly derived (therefore coming from ADaM) and not highly derived (therefore coming from SDTM)

Provides **discordance flags** for each subject's disease assessments/evaluations present within the database for target lesions, non-target lesions, new lesions, and overall response.

Programming Design - Data Flow

SDTM

All key SDTM data containing efficacy information for deriving and comparing INV

DOMAIN	RSTESTCD	RSTEST	RSCAT	RSORRES	RSSTRESC	VISITNUM	VISIT	VISITDY	EPOCH	RSDTC	RSDY
RS	TRGRESP	Target Response	RECIST 1.1	SD	SD	80001	DISEASE EVALUATION 1	.			.
RS	TRGRESP	Target Response	RECIST 1.1	SD	SD	80002	DISEASE EVALUATION 2	.			.
RS	NTRGRESP	Non-target Response	RECIST 1.1	NON-CR/NON-PD	NON-CR/NON-PD	80001	DISEASE EVALUATION 1	.			.
RS	NTRGRESP	Non-target Response	RECIST 1.1	NON-CR/NON-PD	NON-CR/NON-PD	80002	DISEASE EVALUATION 2	.			.
RS	NTRGRESP	Non-target Response	RECIST 1.1	NON-CR/NON-PD	NON-CR/NON-PD	80003	DISEASE EVALUATION 3	.			.
RS	NTRGRESP	Non-target Response	RECIST 1.1	NON-CR/NON-PD	NON-CR/NON-PD	80004	DISEASE EVALUATION 4	.			.
RS	NTRGRESP	Non-target Response	RECIST 1.1	PD	PD	80005	DISEASE EVALUATION 5	.			.
RS	NWLES	New Lesions	RECIST 1.1	N	N	80001	DISEASE EVALUATION 1	.			.
RS	NWLES	New Lesions	RECIST 1.1	N	N	80002	DISEASE EVALUATION 2	.			.
RS	NWLES	New Lesions	RECIST 1.1	N	N	80003	DISEASE EVALUATION 3	.			.
RS	NWLES	New Lesions	RECIST 1.1	N	N	80004	DISEASE EVALUATION 4	.			.
RS	NWLES	New Lesions	RECIST 1.1	N	N	80005	DISEASE EVALUATION 5	.			.
RS	OVRLRESP	Overall Response	RECIST 1.1	PR	PR	80001	DISEASE EVALUATION 1	.	TREATMENT	2022-11-03	50
RS	OVRLRESP	Overall Response	RECIST 1.1	PR	PR	80002	DISEASE EVALUATION 2	.	TREATMENT	2022-12-29	106
RS	OVRLRESP	Overall Response	RECIST 1.1	PR	PR	80003	DISEASE EVALUATION 3	.	TREATMENT	2023-02-24	163
RS	OVRLRESP	Overall Response	RECIST 1.1	PR	PR	80004	DISEASE EVALUATION 4	.	TREATMENT	2023-04-21	219
RS	OVRLRESP	Overall Response	RECIST 1.1	PD	PD	80005	DISEASE EVALUATION 5	.	TREATMENT	2023-06-15	274

derived (therefore coming from ADaM) and not highly derived (therefore coming from SDTM)

Includes data **tracking flags** designed to draw attention to the new and changed records. If the data in a record changed, the previous value(s) is also stored in these flags.

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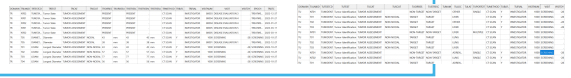

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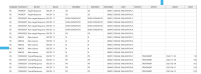

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CL_OVERALL_RESPONSE.sas

- Get RECIST related data from **ADRECIST**
- Get response evaluations data from **RS**
- Get lesion measurements and assessments data from **TR** that is not stored in ADRECIST
- Get CRF disease progression information from **CE/FA**
- **Merge** all data together
- Create **discordance flags** for target, non-target, new lesions, and overall response at each visit
- Use %compare_reports to add new and changed record flags
- Output to Excel, adding study name and database date into the file name.

Sample CL_OVERALL_RESPONSE.xls Output

	A	B	C	D	E	F	O	P	Q	AA	AB	AC	AF	AG	AH	AK	AL	AM	AP	AQ
1	Unique Subject Identifier	Visit	Response Date (Derived)	Response Day (Derived)	Response Date (INV)	Response Date Difference	Target Lesion Response (Derived)	Target Lesion Response (INV)	Target Lesion Response Diff	Non-target Lesion Response (Derived)	Non-target Lesion Response (INV)	Non-target Lesion Response Diff	New Lesion (Derived)	New Lesion (INV)	New Lesion Diff	Overall Response (Derived)	Overall Response (INV)	Overall Response Diff	Confirmed Response (Derived)	Confirming Response (Derived)
2	-100002	BASELINE	20-Feb-17	-29																
3	-100002	DISEASE EVALUATION 1	27-Apr-17	38	27-Apr-17	N	PD	PD	N	Non-CR/Non-PD	Non-CR/Non-PD	N		N	N	PD	PD	N	Y	
4	-100002	DISEASE EVALUATION 2	9-Jun-17	81	9-Jun-17	N	PD	PD	N	Non-CR/Non-PD	Non-CR/Non-PD	N		N	N	PD	PD	N		Y
5																				
6	-100005	BASELINE	28-Mar-17	-13																
7	-100005	DISEASE EVALUATION 1	19-May-17	40	19-May-17	N	NAE	NAE	N	NAE	NAE	N		Y	Y	NE	PD	Y		
8																				
9	-100006	BASELINE	7-Mar-17	-16																
10	-100006	DISEASE EVALUATION 1	2-May-17	41	2-May-17	N	PD	PD	N	NAE	Non-CR/Non-PD	Y		Y	Y	PD	PD	N		
11																				
12	-100008	BASELINE	5-Apr-17	-15																
13	-100008	DISEASE EVALUATION 1	30-May-17	41	30-May-17	N	NAE	SD	Y	Non-CR/Non-PD	Non-CR/Non-PD	N		N	N	NE	SD	Y		
14	-100008	DISEASE EVALUATION 2	21-Jul-17	93	21-Jul-17	N	NAE	PD	Y	Non-CR/Non-PD	Non-CR/Non-PD	N		N	N	NE	PD	Y		
15	-100008	DISEASE EVALUATION 3	13-Sep-17	147	13-Sep-17	N	PD	PD	N	Non-CR/Non-PD	Non-CR/Non-PD	N		N	N	PD	PD	N		

The output review listing can help the clinical review the efficacy data and query to site if any discordance.

Thank You!

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