Statistics•Collaborative

design and analysis for biomedical research

Advice for a More Readable IDMC Safety Report

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BASS XXV, Savannah, GA

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Goal of session

- Provide simple examples of how Sponsors & IDMC members can instruct reporting statistician to make the IDMC's job easier.

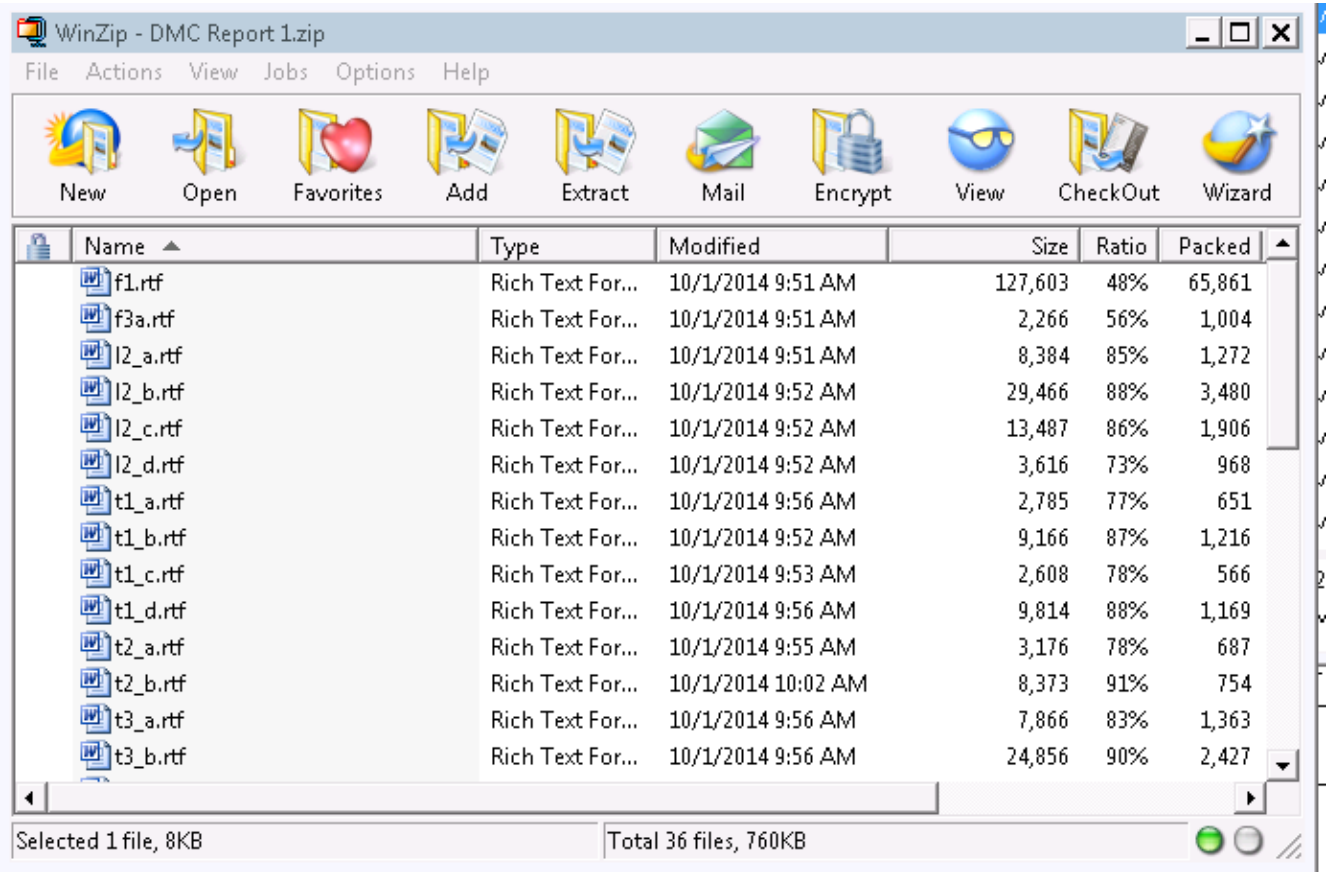
- The 3 C's: Reports that are
  - Clear,
  - Concise, and
  - Comprehensive

What's wrong with most IDMC reports?

- 'Where's Waldo' of safety signals
- Seems as though CROs must charge by the page?
- IDMC members' time is valuable
  - time should be spent gaining insights into data, rather than looking for data

What's wrong with most IDMC reports?

An actual IDMC electronic "report"!



1) Report organization

- Single, organized report, rather than e-file of 50 cryptically named files
- Plane-trip ready
- My view: A role of the reporting statistician is editor
  - Report needs to be organized
  - Report evolves over time
  - What supportive data are better presented in appendices?

1) Report organization

Contents

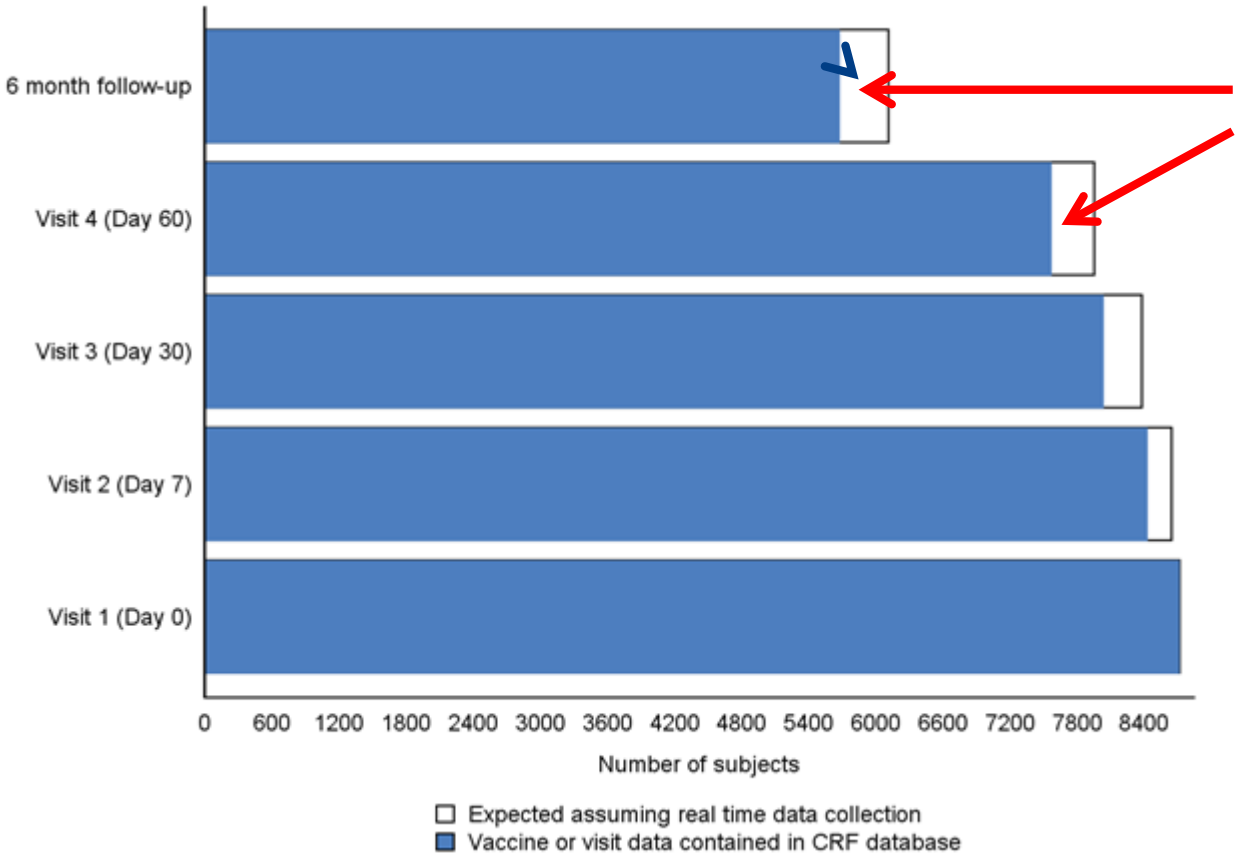
1) Report organization

Tables

2) Data currentness

- Tension in IDMC reporting between accuracy and timeliness
- Surest way to anger a IDMC is to present data that are several months old
- So… let's not anger the IDMC by having them realize their data are so stale

2) Data currentness



Blank portion of bar represents data that are in the field but not in IDMC's report

2) Data currentness

	Group A	*Group B*
Newly reported AEs with onset on or before 23DEC2016, n/N (%)	**334/1454 (23)**	**337/1433 (24)**
Onset date for newly reported AEs	**N=334**	**N=337**
2015		
January to July	4 (1)	1 (<1)
August to December	2 (1)	4 (1)
2016		
January	5 (1)	6 (2)
February	5 (1)	4 (1)
March	9 (3)	4 (1)
April	9 (3)	16 (5)
May	4 (1)	14 (4)
June	13 (4)	15 (4)
July	13 (4)	13 (4)
August	27 (8)	25 (7)
September	45 (14)	30 (9)
October	61 (18)	53 (16)
November	61 (18)	64 (19)
December	76 (23)	88 (26)

AEs that occurred before last report's data extraction date, but had not yet been reported in the last report's database

For events that had not yet been reported, when had they occurred

3) False precision adds noise

Death by a thousand decimal points

Table 2-99 (Page 1 of 12)
Number of patients requiring dose interruptions and/or reductions of study treatment
(Safety set)

	Study drug			Standard of care therapy		
	Group A N=307 n (%)	Group B N=362 n (%)	All patients N=669 n (%)	Group A N=307 n (%)	Group B N=365 n (%)	All patients N=672 n (%)
- Reductions						
Number of reductions						
0	252 (82.1)	298 (82.3)	550 (82.2)	307 (100.0)	365 (100.0)	672 (100.0)
1	36 (11.7)	49 (13.5)	85 (12.7)	0 (0.0)	0 (0.0)	0 (0.0)
2	19 (6.2)	15 (4.1)	34 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)
Number of patients with at least one dose reduction by reason						
Adverse event	48 (15.6)	55 (15.2)	103 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)
Dosing error	3 (1.0)	5 (1.4)	8 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Subject/guardian decision	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Physician decision	4 (1.3)	3 (0.8)	7 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	7 (2.3)	4 (1.1)	11 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)

Better

Table 2-99 (Page 1 of 12)
Number of patients requiring dose interruptions and/or reductions of study treatment
(Safety set)

	Study drug			Standard of care therapy		
	Group A N=307 n (%)	Group B N=362 n (%)	All patients N=669 n (%)	Group A N=307 n (%)	Group B N=365 n (%)	All patients N=672 n (%)
- Reductions						
Number of reductions						
0	252 (82)	298 (82)	550 (82)	307 (100)	365 (100)	672 (100)
1	36 (12)	49 (14)	85 (13)	0	0	0
2	19 (6)	15 (4)	34 (5)	0	0	0
Number of patients with at least one dose reduction by reason						
Adverse event	48 (16)	55 (15)	103 (15)	0	0	0
Dosing error	3 (1)	5 (1)	8 (1)	0	0	0
Subject/guardian decision	0	1 (<1)	1 (<1)	0	0	0
Physician decision	4 (1)	3 (1)	7 (1)	0	0	0
Missing	7 (2)	4 (1)	11 (2)	0	0	0

Even better

Table 2-99 (Page 1 of 12)
Number of patients requiring dose interruptions and/or reductions of study treatment
(Safety set)

	Study drug		Standard of care therapy	
	Group A N=307 n (%)	Group B N=362 n (%)	Group A N=307 n (%)	Group B N=365 n (%)
- Reductions				
Number of reductions				
0	252 (82)	298 (82)	307 (100)	365 (100)
1	36 (12)	49 (14)	0	0
2	19 (6)	15 (4)	0	0
Number of patients with at least one dose reduction by reason				
Adverse event	48 (16)	55 (15)	0	0
Dosing error	3 (1)	5 (1)	0	0
Subject/guardian decision	0	1 (<1)	0	0
Physician decision	4 (1)	3 (1)	0	0
Missing	7 (2)	4 (1)	0	0

4) Recap the last report

- IDMC will not necessarily remember trends seen in its last report
- Executive summaries can be helpful here
- As can copies of previous meeting minutes

Exec summary

Executive summary (Current report: December 2014)

	Group A n (%)	Group B n (%)	
Randomized and treated (Table 6)	**2900**	**2900**	
Off treatment (Table 7)	498 (17)	594 (20)	←
Off study at time of treatment discontinuation (Table 7)	74 (3)	75 (3)	
Deaths (Table 18)	81 (2.8)	82 (2.8)	
Subjects with adjudicated CV events			
MACE (Table 24)	119 (4.1)	143 (4.9)	←
CV death (Table 24)	41 (1.4)	44 (1.5)	
MI (Table 30)	57 (2.0)	58 (2.0)	
Stroke (Table 31)	46 (1.6)	53 (1.8)	
Heart failure (Table 32)	36 (1.2)	54 (1.9)	←

Include prior exec summary

Executive summary (Prior report: June 2014)

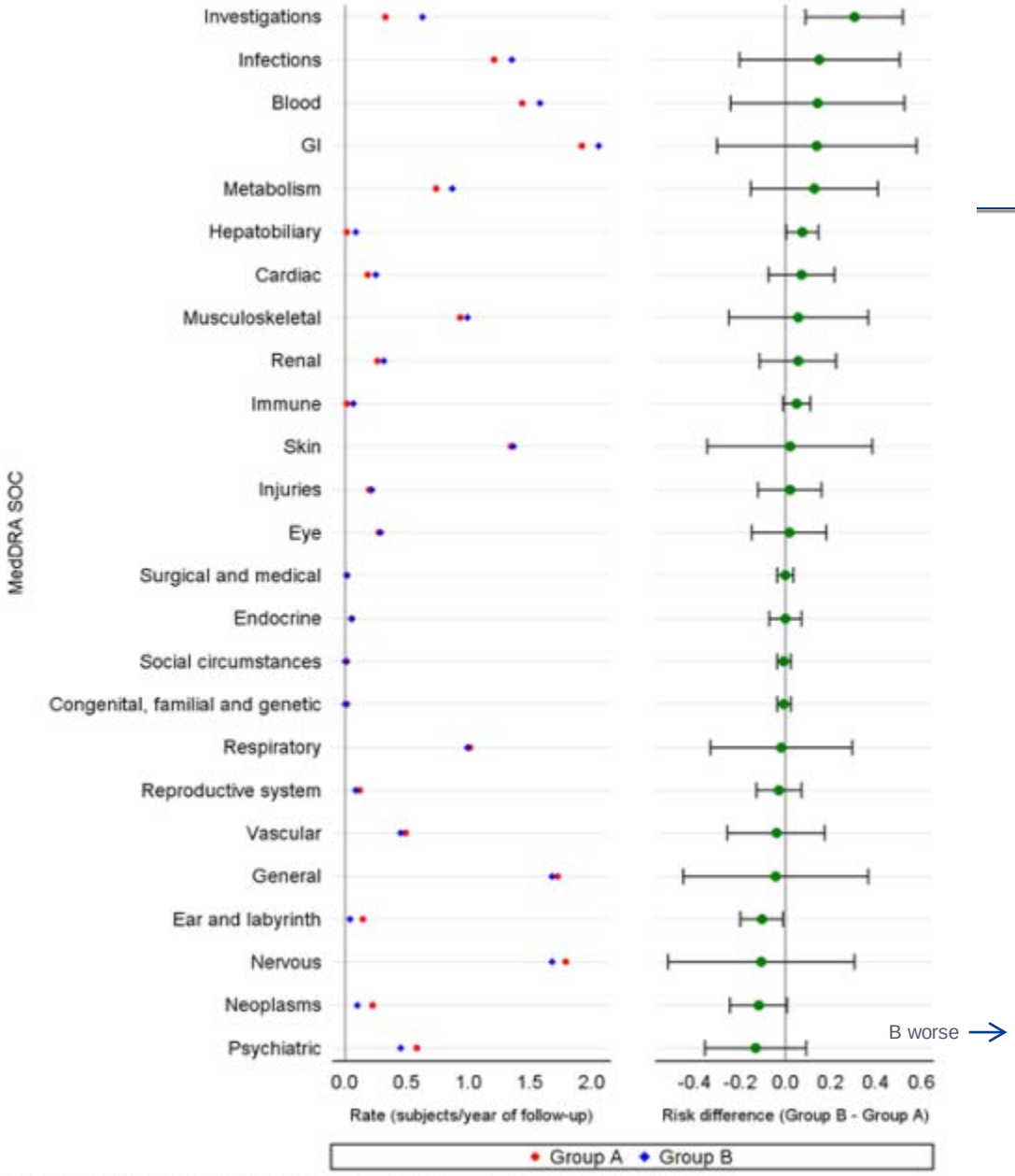
	Group A n (%)	Group B n (%)
Randomized and treated	**2900**	**2900**
Off treatment	316 (11)	384 (13)
Off study at time of treatment discontinuation	45 (2)	51 (2)
Deaths	53 (1.8)	54 (1.9)
Subjects with adjudicated CV events		
MACE	81 (2.8)	91 (3.1)
CV death	23 (0.8)	26 (0.9)
MI	38 (1.3)	41 (1.4)
Stroke	32 (1.1)	36 (1.2)
Heart failure	23 (0.8)	29 (1.0)

5) Forest, to tree, to leaf
(and maybe to chlorophyll)

- For especially dense sections (i.e., AEs), begin with overview of data and then drill to details

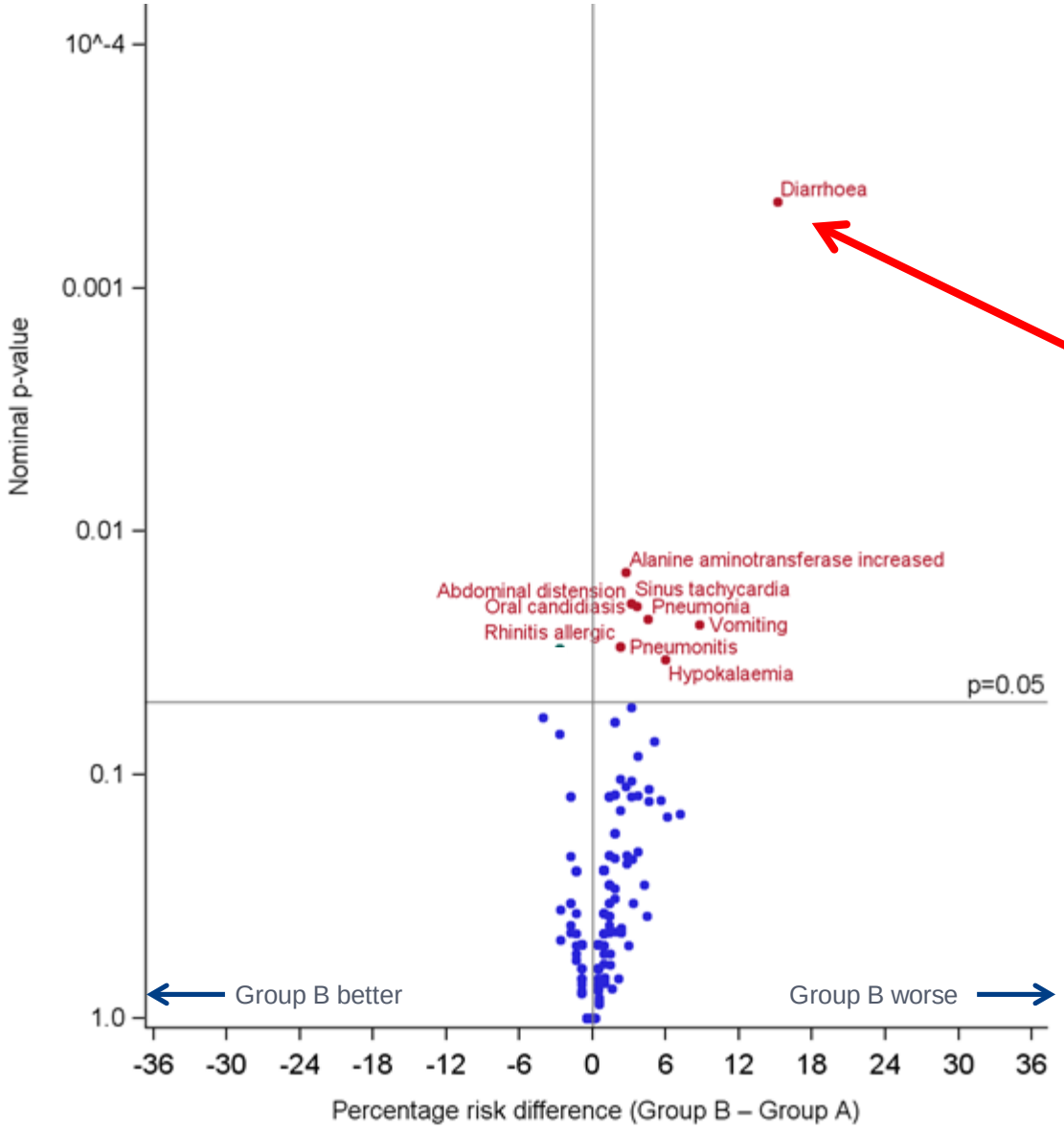
- Helps navigate multi-page tables and figures that follow

Dotplot



Rates are calculated as the number of subjects with events divided by subject-years of follow-up.
Subject-years of follow-up: Group A = 77.15, Group B = 79.73

Volcano plot



Diarrhea
45 (20%) in Group A and
78 (35%) in Group B

Fisher's exact p = 0.0004

Volcano plot

- But what about multiple comparisons?
- Free SAS code available online
  http://www.ctspedia.org/do/view/CTSpedia/ClinAEGraph003

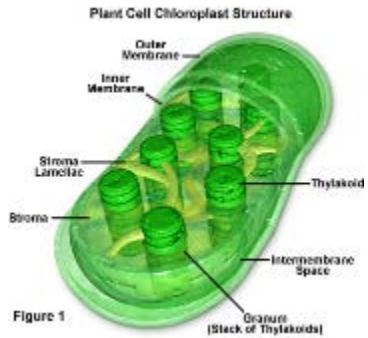
Overview AE table

Subjects with any	*Group A N=197 n (%)*	*Group B N=197 n (%)*	*Total N=394 n (%)*
Death	3 (2)	4 (2)	7 (2)
SAE	49 (25)	45 (23)	94 (24)
SAE related to study drug	18 (9)	19 (10)	37 (9)
Grade 3+ AE	36 (18)	43 (22)	79 (20)
Grade 3+ AE related to study drug	13 (7)	17 (9)	30 (8)
AE leading to study drug discontinuation	19 (10)	23 (12)	42 (11)
AE leading to study drug interruption	36 (18)	37 (19)	73 (19)
Depressive episode	19 (10)	23 (12)	42 (11)
Grade 3+ depressive episode	36 (18)	37 (19)	73 (19)
Bleed	36 (18)	43 (22)	79 (20)
Grade 3+ bleed	13 (7)	17 (9)	30 (8)

- Volcano plot
- Dotplot

- AE overview table

- Table of SAEs
- Table of Grade 3+ AEs
- Table of AEs leading to tx discontinuation
- Etc.



- By-subject listing
- SAE narratives

6) Be a lumper, not a splitter

- MedDRA preferred terms can split related events
- In next slide, how many participants had a UTI?

MedDRA system organ class / preferred term	*Group A N=1440 n (%)*	*Group B N=1440 n (%)*
Infections	**1315 (91)**	**1324 (92)**
Nasopharyngitis	147 (10.2)	155 (10.7)
Urinary tract infection	139 (9.7)	160 (11.1)
Upper respiratory tract infection	104 (7.2)	83 (5.8)
Bronchitis		
Influenza	46 (3.2)	48 (3.3)
Sinusitis	35 (2.4)	41 (2.8)
Cystitis	34 (2.4)	33 (2.3)
Gastroenteritis	29 (2.0)	24 (1.7)
Vulvovaginal mycotic infection	24 (5.0)	26 (5.2)
Cellulitis	18 (1.2)	22 (1.5)
Pneumonia	13 (0.9)	23 (1.6)
Lower respiratory tract infection	20 (1.4)	14 (1.0)
Pharyngitis	21 (1.5)	11 (0.8)
Vulvovaginal candidiasis	21 (4.3)	15 (3.0)
Localized infection	7	13 (0.9)
Vaginal infection	15 (3.1)	16 (3.2)
Respiratory tract infection	9 (0.6)	9 (0.6)
Gastroenteritis viral	8 (0.6)	10 (0.7)
Genital infection fungal	9 (0.6)	20 (1.4)
Onychomycosis	11 (0.8)	10 (0.7)
Herpes zoster	12 (0.8)	7
Pyelonephritis chronic	5	4
Pyelonephritis	9 (0.6)	0
Ear infection	9 (0.6)	6
Tooth infection	10 (0.7)	5
Furuncle	7	4
Tinea pedis	8 (0.6)	9 (0.6)
Tooth abscess	9 (0.6)	5
Osteomyelitis	10 (0.7)	6
Pyelonephritis acute	0	2

Denominators and column header counts include all treated subjects. Only percentages ≥ 0.5% are shown.

MedDRA System Organ Class/ High Level Term/ Preferred Term	*Group A N=1440 n (%)*	*Group B N=1440 n (%)*
Infections	**1315 (91)**	**1324 (92)**
Upper respiratory tract infections	442 (31)	402 (28)
Nasopharyngitis	224 (16)	203 (14)
Upper respiratory tract infection	157 (11)	135 (9)
Sinusitis	57 (4)	65 (5)
Pharyngitis	42 (3)	25 (2)
Rhinitis	19 (1)	17 (1)
Tonsillitis	14 (1)	5
Laryngitis	12 (1)	3
Acute sinusitis	5	4
Pharyngotonsillitis	3	5
Tracheitis	3	3
Chronic sinusitis	2	3
Tracheobronchitis	6	1
Epiglottitis	0	2
Peritonsillar abscess	0	2
Thornwaldt disease	1	0
Urinary tract infections	175 (12)	191 (13)
Urinary tract infection	139 (10)	160 (11)
Cystitis	34 (2)	33 (2)
Pyelonephritis chronic	5	4
Pyelonephritis	9 (1)	0
Pyelonephritis acute	0	2

Denominators and column header counts include all treated subjects.

6) Be a lumper, not a splitter

- Standardized MedDRA Queries (SMQ) can also help when AEs of interest fall into several body systems
- Bleeding events
  - Hemorrhagic stroke → Nervous system
  - Hemoptysis → Respiratory
  - Melena → GI
  - Ecchymosis → Skin

List of SMQ Topics for Development by CIOMS Working Group for SMQs
(as of 1 March 2017)

SMQs in Production

- Accidents and injuries
- Acute central respiratory depression
- Acute pancreatitis
- Acute renal failure
- Agranulocytosis
- Anaphylactic reaction
- Angioedema
- Anticholinergic syndrome
- Arthritis
- Asthma/bronchospasm
- Biliary disorders
- Breast neoplasms, malignant and unspecified
- Cardiac arrhythmias
- Cardiac failure
- Cardiomyopathy
- Central nervous system vascular disorders
- Chronic kidney disease
- Conjunctival disorders
- Convulsions
- Corneal disorders
- Dementia
- Demyelination
- Depression and suicide/self-injury
- Drug abuse, dependence and withdrawal
- Drug reaction with eosinophilia and systemic symptoms syndrome
- Dyslipidaemia
- Embolic and thrombotic events
- Eosinophilic pneumonia
- Extrapyramidal syndrome
- Extravasation events (injections, infusions and implants)
- Fertility disorders
- Gastrointestinal nonspecific inflammation and dysfunctional conditions
- Gastrointestinal perforation, ulceration, haemorrhage or obstruction
- Generalised convulsive seizures following immunisation
- Glaucoma
- Guillain-Barre syndrome
- Haematopoietic cytopenias
- Haemodynamic oedema, effusions and fluid overload
- Haemolytic disorders
- Haemorrhages
- Hearing and vestibular disorders
- Hepatic disorders
- Hostility/aggression
- Hyperglycaemia/new onset diabetes mellitus
- Hypersensitivity
- Hypertension
- Hypoglycaemia
- Hyponatraemia/SIADH
- Hypotonic-hyporesponsive episode
- Interstitial lung disease
- Ischaemic colitis
- Ischaemic heart disease
- Lack of efficacy/effect
- Lacrimal disorders
- Lactic acidosis
- Lens disorders
- Lipodystrophy
- Malignancies
- Malignant lymphomas
- Medication errors
- Myelodysplastic syndrome
- Neuroleptic malignant syndrome
- Noninfectious diarrhoea
- Noninfectious encephalitis
- Noninfectious encephalopathy/delirium
- Noninfectious meningitis
- Ocular infections
- Ocular motility disorders
- Optic nerve disorders
- Oropharyngeal disorders

http://www.meddra.org/sites/default/files/page/documents/list_of_smq_topics_for_website_march_2017_0.pdf

Study specific class/preferred term	*Treatment 01 N=330*		*Treatment 02 N=330*	
	All grades n (%)	*Grade 3-4 n (%)*	*All grades n (%)*	*Grade 3-4 n (%)*
Hemorrhages	**30 (9)**	**1 (<1)**	**51 (15)**	**2 (1)**
Epistaxis	6 (2)	0	15 (4)	0
Contusion	2 (1)	0	7 (2)	0
Rectal haemorrhage	5 (2)	0	4 (1)	0
Haemorrhoids	2 (1)	0	5 (1)	0
Vaginal haemorrhage	2 (1)	0	5 (1)	0
Haemoptysis	2 (1)	0	3 (1)	0
Haematuria	2 (1)	0	4 (1)	0
Gingival bleeding	2 (1)	0	2 (1)	0
Haematochezia	1 (<1)	0	2 (1)	0
Haematoma	2 (1)	0	1 (<1)	0
Conjunctival haemorrhage	1 (<1)	0	1 (<1)	0
Ecchymosis	1 (<1)	0	1 (<1)	0
Haematemesis	0	0	2 (1)	0
Haemorrhoidal haemorrhage	1 (<1)	0	1 (<1)	1 (<1)
Breast haemorrhage	1 (<1)	0	0	0
Haemarthrosis	0	0	1 (<1)	0
Haemorrhage intracranial	1 (<1)	1 (<1)	0	0
Periorbital haematoma	0	0	1 (<1)	0
Petechiae	0	0	1 (<1)	0
Post procedural haemorrhage	0	0	1 (<1)	1 (<1)
Pulmonary haemorrhage	0	0	1 (<1)	0
Uterine haemorrhage	1 (<1)	0	0	0
Vitreous haemorrhage	1 (<1)	0	0	0

7) Traffic light your output

MedDRA system organ class/ high level term/ preferred term	*Apollo* *n (%)[a] N=152*	*Apollo* *# (rate)[b] Yrs=147*	*Gemini* *n (%)[a] N=158*	*Gemini* *# (rate)[b] Yrs=167*
Any AE	**125 (82)**	**852 (5.8)**	**124 (78)**	**1086 (6.5)**
Cardiac	**69 (45)**	**165 (1.1)**	**69 (44)**	**230 (1.4)**
Heart failures NEC	40 (26)	71 (0.5)	42 (27)	95 (0.6)
Cardiac failure	20 (13)	30 (0.2)	23 (15)	38 (0.2)
Cardiac failure congestive	17 (11)	24 (0.2)	20 (13)	33 (0.2)
Cardiac failure acute	8 (5)	10 (<0.1)	9 (6)	19 (0.1)
Cardiogenic shock	4 (3)	4 (<0.1)	2 (1)	2 (<0.1)
Cardiac failure chronic	3 (2)	3 (<0.1)	2 (1)	2 (<0.1)
Cardiorenal syndrome	0		1 (1)	1 (<0.1)
Ventricular arrhythmias and cardiac arrest	25 (16)	34 (0.2)	24 (15)	89 (0.5)
Ventricular tachycardia	20 (13)	27 (0.2)	18 (11)	43 (0.3)
Ventricular fibrillation	2 (1)	3 (<0.1)	6 (4)	33 (0.2)
Ventricular extrasystoles	3 (2)	3 (<0.1)	2 (1)	2 (<0.1)
Cardiac arrest	1 (1)	1 (<0.1)	2 (1)	5 (<0.1)
Cardio-respiratory arrest	0		2 (1)	2 (<0.1)
Ventricular arrhythmia	0		2 (1)	2 (<0.1)
Pulseless electrical activity	0		1 (1)	2 (<0.1)
Ischaemic coronary artery disorders	11 (7)	16 (0.1)	14 (9)	18 (0.1)
Angina pectoris	7 (5)	11 (<0.1)	10 (6)	12 (<0.1)
Acute MI	2 (1)	2 (<0.1)	2 (1)	2 (<0.1)
MI	1 (1)	1 (<0.1)	2 (1)	2 (<0.1)
Angina unstable	1 (1)	1 (<0.1)	1 (1)	1 (<0.1)
Acute coronary syndrome	1 (1)	1 (<0.1)	0	
Myocardial ischaemia	0		1 (1)	1 (<0.1)

7) Traffic light your output

MedDRA system organ class/ high level term/ preferred term	*Apollo*		*Gemini*	
	n (%)[a] N=152	*# (rate)[b] Yrs=147*	*n (%)[a] N=158*	*# (rate)[b] Yrs=167*
Any AE	**125 (82)**	**852 (5.8)**	**124 (78)**	**1086 (6.5)**
Cardiac	**69 (45)**	**165 (1.1)**	**69 (44)**	**230 (1.4)**
Heart failures NEC	40 (26)	71 (0.5)	42 (27)	95 (0.6)
Cardiac failure	20 (13)	30 (0.2)	23 (15)	38 (0.2)
Cardiac failure congestive	17 (11)	24 (0.2)	20 (13)	33 (0.2)
Cardiac failure acute	8 (5)	10 (<0.1)	9 (6)	19 (0.1)
Cardiogenic shock	4 (3)	4 (<0.1)	2 (1)	2 (<0.1)
Cardiac failure chronic	3 (2)	3 (<0.1)	2 (1)	2 (<0.1)
Cardiorenal syndrome	0		1 (1)	1 (<0.1)
Ventricular arrhythmias and cardiac arrest	25 (16)	34 (0.2)	24 (15)	89 (0.5)
Ventricular tachycardia	20 (13)	27 (0.2)	18 (11)	43 (0.3)
Ventricular fibrillation	2 (1)	3 (<0.1)	6 (4)	33 (0.2)
Ventricular extrasystoles	3 (2)	3 (<0.1)	2 (1)	2 (<0.1)
Cardiac arrest	1 (1)	1 (<0.1)	2 (1)	5 (<0.1)
Cardio-respiratory arrest	0		2 (1)	2 (<0.1)
Ventricular arrhythmia	0		2 (1)	2 (<0.1)
Pulseless electrical activity	0		1 (1)	2 (<0.1)
Ischaemic coronary artery disorders	11 (7)	16 (0.1)	14 (9)	18 (0.1)
Angina pectoris	7 (5)	11 (<0.1)	10 (6)	12 (<0.1)
Acute MI	2 (1)	2 (<0.1)	2 (1)	2 (<0.1)
MI	1 (1)	1 (<0.1)	2 (1)	2 (<0.1)
Angina unstable	1 (1)	1 (<0.1)	1 (1)	1 (<0.1)
Acute coronary syndrome	1 (1)	1 (<0.1)	0	
Myocardial ischaemia	0		1 (1)	1 (<0.1)

8) Code defensively

- By definition, "dirty" interim data will have more data quality issues than a clean and locked final database
- Limiting IDMC safety reporting only to clean data causes unacceptable lag in reporting
- IDMC programming needs to account for dirty data, warts & all
  - Measurements incompatible with life (e.g., height of 150 inches)
  - Nonsensical measurements (e.g., post-tx dosing dates before randomization)

8) Code defensively

Not coded defensively

Category	Statistic	Treatment A N = 30	Treatment B N = 26
Duration of Exposure (weeks) [a]	n	17	14
	Mean	6.70	1.90
	SD	3.837	13.392
	Median	8.20	4.10
	25th, 75th percentiles	4.10,8.40	4.00,8.10
	Min,Max	1.1,16.1	-43.9,8.8

Recommend setting obvious errors to missing in presentation

9) Harmonize data sources

- Frustrated IDMC member: "Table 5 shows **10** subjects discontinued from the treatment due to death, but the AE table shows only **9** events with fatal outcomes. Now you tell me **11** subjects have died; you need to get your story straight."

- Possible explanation:
  - 2 deaths were not reported as AEs because they were beyond safety reporting period (therefore, 9 fatal AEs and not 11)
  - One subject who died had already discontinued from treatment for other reasons (e.g., investigator decision), which accounts for why 10 and not 11 d/c treatment due to death

- Alternative explanation – interim data are dirty and various sources of information are not yet fully reconciled

9) Harmonize data sources

Subjects who were hospitalized

	Group 1 *N=9,000* *n (%)*	*Group 2* *N=9,000* *n (%)*
Any hospitalization from the following CRFs	**2,712 (30)**	**2,586 (29)**
From adverse events records	2,435 (27)	2,374 (26)
From clinical event adjudication CRF	2,128 (24)	1,994 (22)
From thrombotic event assessment	399 (4)	279 (3)

Each event category is counted once per subject, but subjects can be counted in multiple categories.

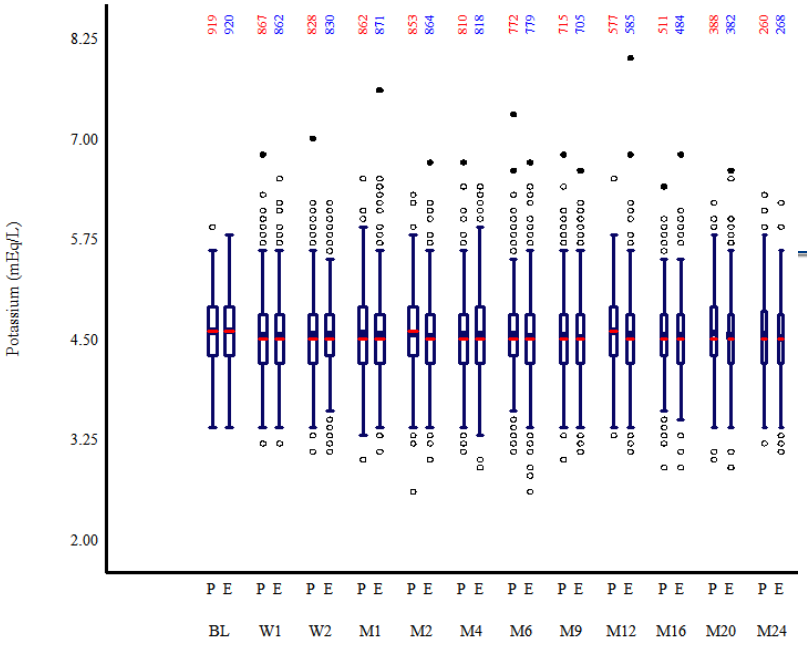
10) Get graphic

- Lab and vital sign summaries can go on… and on… and on.

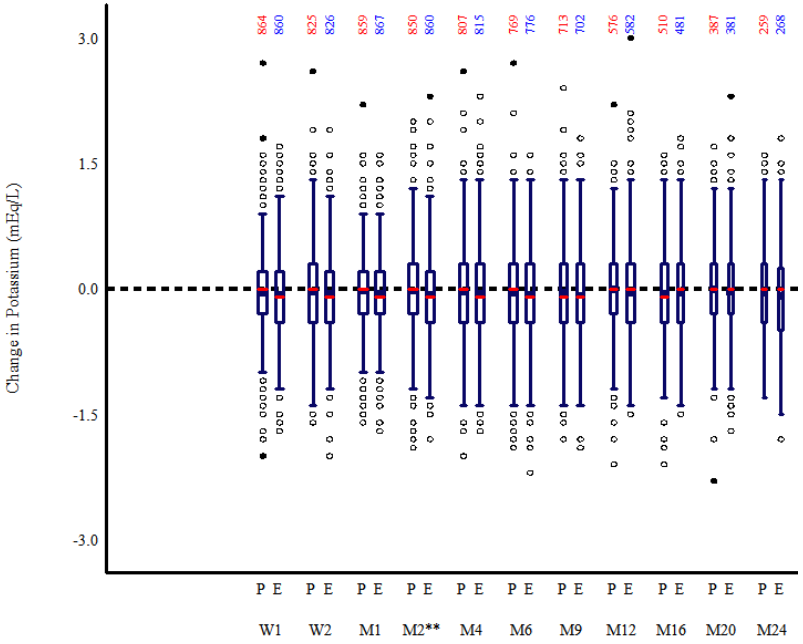
- Suggestion
  - Identify laboratory thresholds of interest
    - e.g., doublings in serum creatinine
    - e.g., LFTs increasing to > 5×ULN

  - Boxplots or scatterplots of post-baseline shifts to identify potential changes of interest
  - Appendix tables can provide univariate statistics and frequencies for any signals identified in the plots

Sample lab boxplot

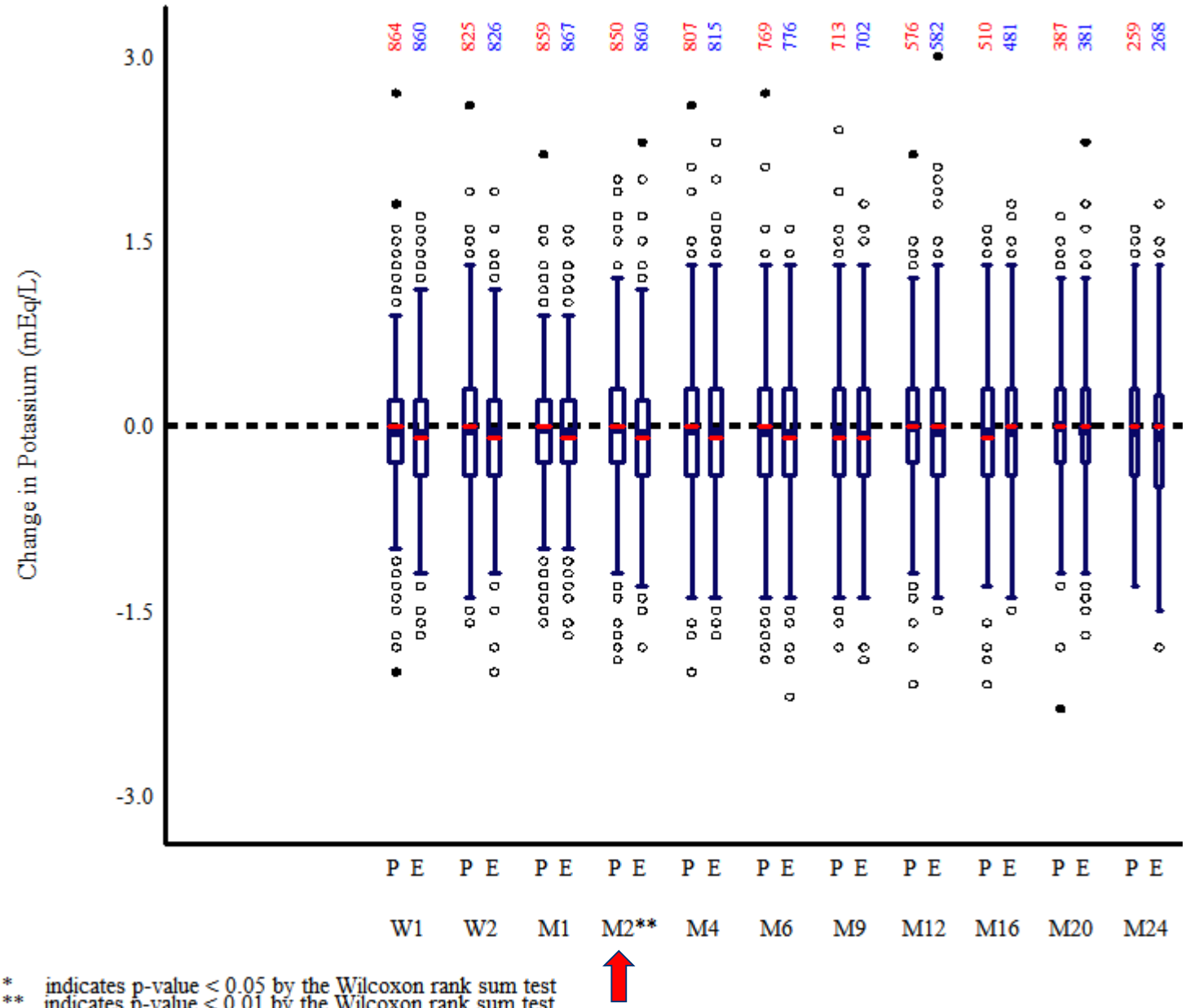


Lab value over time by group



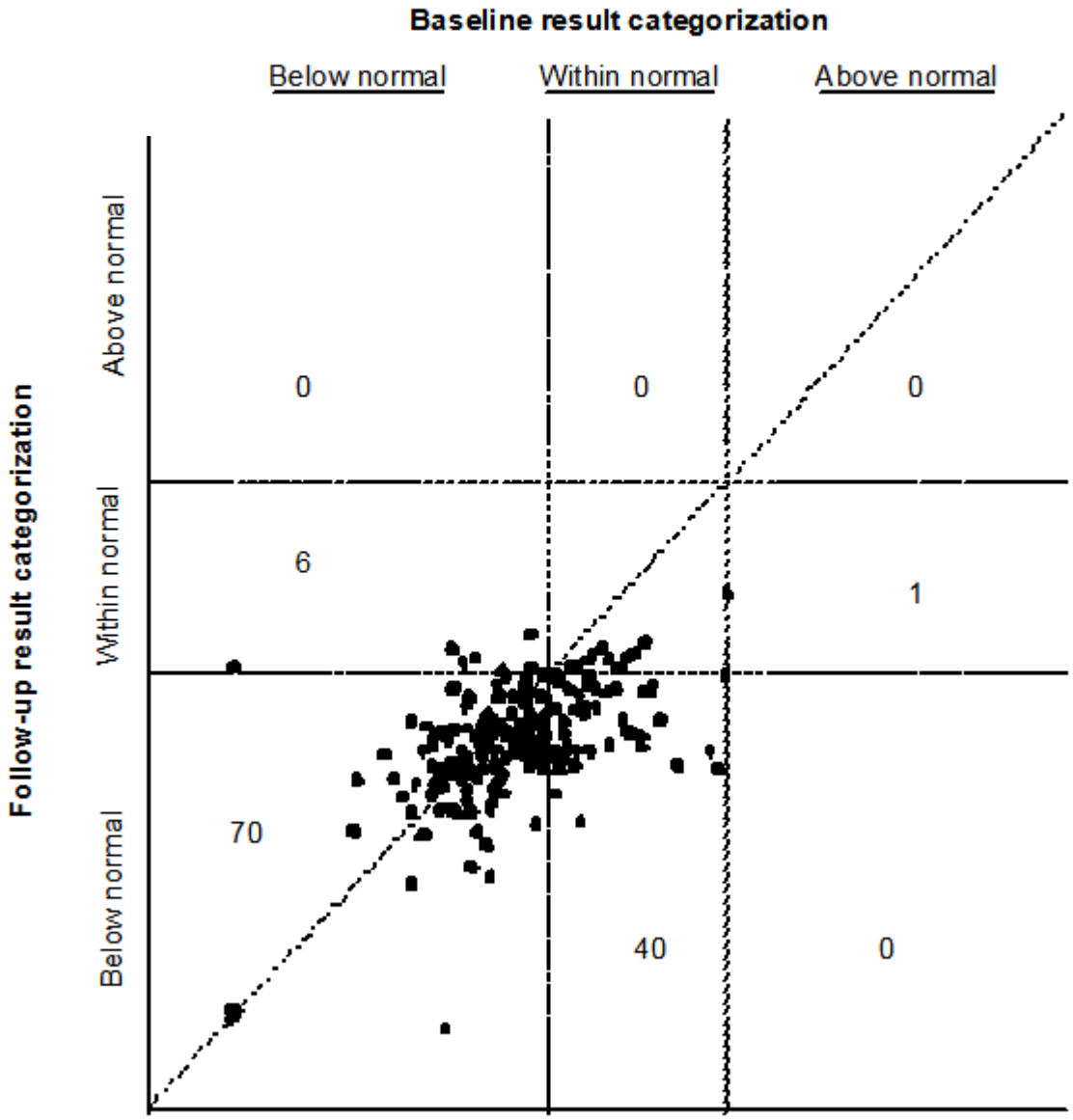
Changes from baseline in lab value over time by group

* indicates p-value < 0.05 by the Wilcoxon rank sum test
** indicates p-value < 0.01 by the Wilcoxon rank sum test
*** indicates p-value < 0.001 by the Wilcoxon rank sum test



* indicates p-value < 0.05 by the Wilcoxon rank sum test
** indicates p-value < 0.01 by the Wilcoxon rank sum test
*** indicates p-value < 0.001 by the Wilcoxon rank sum test

Interpretation of laboratory shift plots



Quadrants of interest enumerated

Higher concentration of points below diagonal reference line indicate reduction in parameter relative to BL

Higher concentration of points above diagonal reference line indicate increase in parameter relative to BL

The tips…

1. Organize the report
2. Summarize data currentness
3. Eliminate false precision
4. Recap the last report
5. Go from general to more specific
6. Be a lumper, not a splitter
7. Traffic light output
8. Code defensively
9. Harmonize data sources
10. Encourage graphical presentations

Thank you!

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