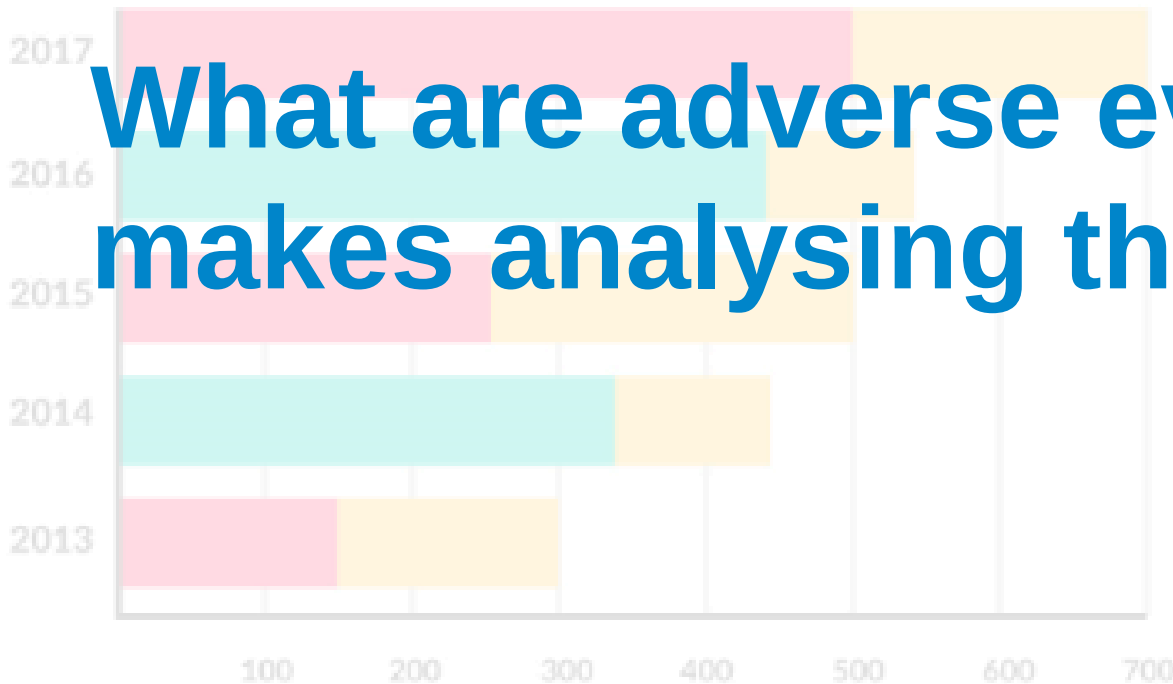


What are adverse events and what makes analysing them so challenging?



Rachel Phillips, Victoria Cornelius &
Anca Chis Ster

FUNDED BY
NIHR | National Institute
for Health Research

DISCLAIMER: This work is funded by the National Institute for Health Research (NIHR) (grant reference number DRF-2017-10-131). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health & Social Care.

- RCTs are typically designed around a primary efficacy outcome e.g. does drug A improve survival compared to drug B (standard care)
- The statistical methods to analyse these outcomes are well established
- Might have known **safety** outcomes as secondary outcomes
- **Adverse Events (AEs)** that emerge during the trial
- Methods used to analyse these outcomes are less established

Evaluating harm

- We don't know **what or how many AEs** will be reported
 - **Outcome measurement considerations:**
 - **Variable type:** single occurrence and repeated AEs, time to event, continuous
 - **Duration** of each AE
 - **Severity** of each AE
 - **Timing** of each AE
 - **Often low rates of events**
- ...all making AEs difficult to analyse**

Typically we find AE data presented in tables like this

Event	Daratumumab Group (N = 243)		Control Group (N = 237)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Common hematologic adverse event				
Thrombocytopenia	143 (58.8)	110 (45.3)	104 (43.9)	78 (32.9)
Anemia	64 (26.3)	35 (14.4)	74 (31.2)	38 (16.0)
Neutropenia	43 (17.7)	31 (12.8)	22 (9.3)	10 (4.2)
Lymphopenia	32 (13.2)	23 (9.5)	9 (3.8)	6 (2.5)
Common nonhematologic adverse events				
Peripheral sensory neuropathy	115 (47.3)	11 (4.5)	89 (37.6)	16 (6.8)
Diarrhea	77 (31.7)	9 (3.7)	53 (22.4)	3 (1.3)
Upper respiratory tract infection	60 (24.7)	4 (1.6)	43 (18.1)	2 (0.8)
Fatigue	52 (21.4)	11 (4.5)	58 (24.5)	8 (3.4)
Cough	58 (23.9)	0	30 (12.7)	0
Constipation	48 (19.8)	0	37 (15.6)	2 (0.8)
Dyspnea	45 (18.5)	9 (3.7)	21 (8.9)	2 (0.8)
Insomnia	41 (16.9)	0	35 (14.8)	3 (1.3)
Peripheral edema	40 (16.5)	1 (0.4)	19 (8.0)	0
Asthenia	21 (8.6)	2 (0.8)	37 (15.6)	5 (2.1)
Pyrexia	38 (15.6)	3 (1.2)	27 (11.4)	3 (1.3)
Pneumonia	29 (11.9)	20 (8.2)	28 (11.8)	23 (9.7)
Hypertension	21 (8.6)	16 (6.6)	8 (3.4)	2 (0.8)
Secondary primary cancer†	6 (2.5)	NA	1 (0.4)	NA

* The safety population included all patients who received at least one dose of trial treatment. Adverse events of any grade that were reported in at least 15% of patients in either treatment group and grade 3 or 4 adverse events that were reported in at least 5% of patients in either treatment group are listed. NA denotes not applicable.

† The presence of a secondary primary cancer was prespecified in the statistical analysis plan as an adverse event of clinical interest. The other adverse events of clinical interest included infusion-related reactions, infections or infestations, peripheral neuropathies, and cardiac disorders.

	Tocilizumab plus methotrexate arm (n=106)	Tocilizumab arm (n=103)	Methotrexate arm (n=108)	p value
Any AE	105 (99.1%)	99 (96.1%)	106 (98.1%)	0.32
AE rate per 100 patient-years in the study	536.7	527.0	595.1	..
Serious AEs	17 (16.0%)	19 (18.4%)	13 (12.0%)	0.44
Serious AE rate per 100 patient-years in the study	10.20	16.45	11.03	..
AEs leading to study discontinuation	9 (8.5%)	10 (9.7%)	8 (7.4%)	0.82
Serious infections	4 (3.8%)	6 (5.8%)	5 (4.6%)	0.76
Serious infection rate per 100 patient-years in the study	2.81	4.51	3.02	
Hepatic events leading to withdrawal	0	0	0	..
ALT >3 × ULN	14 (13.2%)	5 (4.9%)	12 (11.1%)	0.10
AST >3 × ULN	5 (4.7%)	1 (1.0%)	4 (3.7%)	0.37
Increase of liver enzymes leading to change in treatment	0	1 (1.0%)	2 (1.9%)	0.55
Absolute neutrophil count <1.0 × 10 ⁹ /L	7 (6.6%)	6 (5.8%)	1 (0.9%)	0.07
Platelet count <100 × 10 ⁹ /L	4 (3.8%)	3 (2.9%)	1 (0.9%)	0.37
Initiation of lipid lowering drug needed during study	16 (15.1%)	24 (23.3%)	22 (20.4%)	0.32

Data are n (%) unless otherwise specified. The strategy groups are labelled according to the randomised initial therapy. n=number of patients with at least one event. Serious adverse events were defined according to the Medical Dictionary for Regulatory Activities (MedDRA; <http://www.meddra.org/>). AE=adverse event. ALT=serum alanine aminotransferase. ULN=upper limit of normal. AST=serum aspartate aminotransferase. Additional safety data, including data for ALT and AST >ULN are in the appendix. Results of between three-group comparisons obtained with extended Fisher exact tests.

Table 3: Safety and laboratory data

Observations on current AE analysis practice in RCTs

- AE data is typically presented in frequency tables
 - Absence of analysis being performed other than inappropriate hypothesis testing
 - Dichotomisation of continuous clinical and laboratory data is frequent
 - ‘**Harm Profile**’ assessed through subjective opinion
 - Phrases like ‘well-tolerated’ often used – not always matching results in the table
-

What are we trying to do when analysing AE data?

- We're looking for **signals of harm**
 - Reporting all AE data in **tables** can be **overwhelming** to review and **incomprehensible**
 - Would **visualisations** of the data make the summaries **more digestible** and provide a **better way to review AE data**?
-