Utilizing R for the Graphical Reporting of Adverse Event Clinical Trial Data to Facilitate DSMB Review

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Overview

Rho serves as the Statistical and Data Coordinating Center (SDCC) for the Immune Tolerance Network (ITN) and the Inner City Asthma Consortium (ICAC) and is responsible for generating materials for Data Safety Monitoring Board (DSMB) review. Depending on the size of the clinical trial, reviewers can sometimes be presented with an expansive amount of Adverse Event (AE) incidence summary data in tabular format. Tables and supporting listings can be overwhelming and ineffective in identifying safety signals and can distract the reviewer from absorbing meaningful patterns in the data.

In order to facilitate and expedite safety data review, it is necessary to condense AE incidence into discernable chunks using graphical techniques. Utilizing R, an open-source statistical and computing language and environment, we expand on the graphical techniques prompted by Dr. Frank Harrell and summarize graphically the hierarchical classification of coded verbatim AE terms into System Organ Class (SOC) and Preferred Term (PT) using annotated dot plots. This technique combines the structural familiarity of a summary table with the visual economy of a graphic and conveys a considerable amount of information in a compact, intuitive, and readable manner. This makes it easier for the reviewer to quickly absorb meaningful patterns in the data and discern safety signals that could potentially be obscured by conventional tabular displays.

Through the use and flexibility of R graphics, this method of reporting Adverse Events can be expanded and applied to a broad range of clinical trials and reproduced for other DSMB reports.

R Graphics and Features

R is an open-source statistical and computing language and environment that has many benefits:

- Object-oriented programming
- Excellent graphing capabilities
- Thousands of user-submitted Packages available
- Large community of support
- Cross-platform
- Frequent Updates and fixes

Immune Tolerance Network

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Adverse Event Tabular Summary

Typically, Adverse Event incidence is summarized in tabular format. There are some disadvantages to displaying AE data in tabular form, including:

- Tables can be visually strenuous for reviewers to examine
- Discernable safety signals may be obscured
- Larger participant populations lead to lengthier displays

Adverse Events According to Originally Received Treatment

	Rituximab (N=99)	Cyclophosphamide /Azathioprine (N=98)
Infections and infestations	89 (89.9%)	77 (78.6%)
Upper respiratory tract infection	29 (29.3%)	25 (25.5%)
Sinusitis	16 (16.2%)	17 (17.3%)
Urinary tract infection	20 (20.2%)	7 (7.1%)
Nasopharyngitis	11 (11.1%)	14 (14.3%)
Pneumonia	10 (10.1%)	12 (12.2%)
Herpes zoster	9 (9.1%)	8 (8.2%)
Bronchitis	7 (7.1%)	8 (8.2%)
Viral upper respiratory tract infection	8 (8.1%)	5 (5.1%)
Influenza	6 (6.1%)	5 (5.1%)
Respiratory tract infection	8 (8.1%)	2 (2.0%)
Oral candidiasis	5 (5.1%)	4 (4.1%)
Candidiasis	3 (3.0%)	5 (5.1%)
Oral herpes	4 (4.0%)	4 (4.1%)
Fungal infection	4 (4.0%)	3 (3.1%)
Conjunctivitis infective	4 (4.0%)	2 (2.0%)
Laryngitis	3 (3.0%)	3 (3.1%)
Pharyngitis	3 (3.0%)	3 (3.1%)
Tooth abscess	4 (4.0%)	2 (2.0%)
Fungal skin infection	3 (3.0%)	2 (2.0%)
Gastroenteritis viral	3 (3.0%)	2 (2.0%)
Herpes simplex	3 (3.0%)	2 (2.0%)
Otitis media	3 (3.0%)	2 (2.0%)
Viral infection	1 (1.0%)	4 (4.1%)
Vulvovaginal mycotic infection	5 (5.1%)	0 (0.0%)
Diverticulitis	3 (3.0%)	1 (1.0%)
Gastroenteritis	0 (0.0%)	4 (4.1%)
Lung infection	2 (2.0%)	2 (2.0%)
Rhinitis	2 (2.0%)	2 (2.0%)
Tooth infection	1 (1.0%)	3 (3.1%)
Cystitis	2 (2.0%)	1 (1.0%)
Acute sinusitis	0 (0.0%)	2 (2.0%)
Clostridial infection	2 (2.0%)	0 (0.0%)
Clostridium difficile colitis	2 (2.0%)	0 (0.0%)
Ear infection	1 (1.0%)	1 (1.0%)
Escherichia infection	2 (2.0%)	0 (0.0%)
Eye infection	0 (0.0%)	2 (2.0%)
Infected sebaceous cyst	0 (0.0%)	2 (2.0%)
Infection	1 (1.0%)	1 (1.0%)
Lobar pneumonia	1 (1.0%)	1 (1.0%)
Lower respiratory tract infection	2 (2.0%)	0 (0.0%)
Oesophageal candidiasis	2 (2.0%)	0 (0.0%)
Oral infection	0 (0.0%)	2 (2.0%)
Otitis externa	0 (0.0%)	2 (2.0%)
Rash pustular	2 (2.0%)	0 (0.0%)
Staphylococcal infection	2 (2.0%)	0 (0.0%)
Vaginitis bacterial	1 (1.0%)	1 (1.0%)
Abdominal abscess	1 (1.0%)	0 (0.0%)
Abscess limb	1 (1.0%)	0 (0.0%)
Anogenital warts	1 (1.0%)	0 (0.0%)
Body tinea	1 (1.0%)	0 (0.0%)
Bronchitis bacterial	0 (0.0%)	1 (1.0%)
Bronchitis viral	0 (0.0%)	1 (1.0%)
Cellulitis	1 (1.0%)	0 (0.0%)
Cellulitis orbital	1 (1.0%)	0 (0.0%)
Cellulitis staphylococcal	1 (1.0%)	0 (0.0%)
Central line infection	0 (0.0%)	1 (1.0%)
Chronic sinusitis	0 (0.0%)	1 (1.0%)
Cystitis viral	1 (1.0%)	0 (0.0%)
Dacryocystitis	0 (0.0%)	1 (1.0%)
Diarrhoea infectious	0 (0.0%)	1 (1.0%)
Enterococcal sepsis	1 (1.0%)	0 (0.0%)
Escherichia sepsis	1 (1.0%)	0 (0.0%)
Folliculitis	1 (1.0%)	0 (0.0%)
Gastrointestinal infection	1 (1.0%)	0 (0.0%)

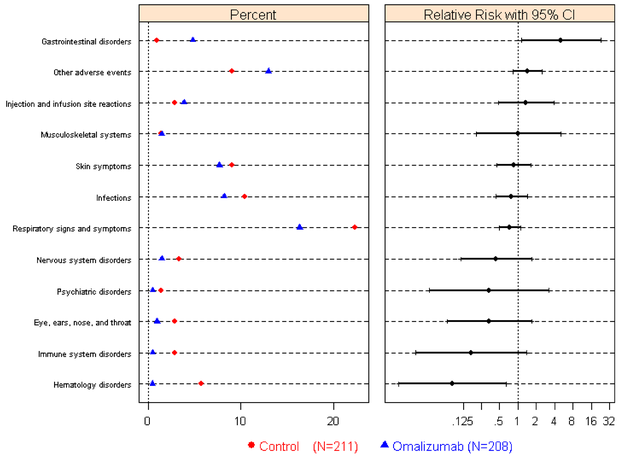
Note: Adverse events are coded according to MedDRA 11.1.

Adverse Event Dot Plots

An Adverse Event dot plot is an effective way to display incidence by treatment group through the use of dots (or symbols) plotted along the horizontal axis

- Similar to a bar chart with the bars replaced by symbols
- Each symbol represents a treatment group and is plotted on a scale
- Additional panels can display Relative Risk and associated confidence intervals

Most Frequent Adverse Events Sorted by Relative Risk



Dot plots are effective but have limitations:

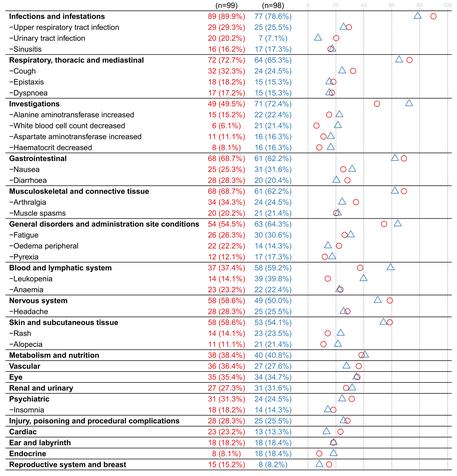
- Difficult to display higher and lower level coded AE terms simultaneously
- Only effective for displaying most frequent AEs or AEs of Special Interest
- Not comprehensive
- Typically do not include all information needed by reviewer

Annotated Dot Plots

An annotated dot plot combines summary information from a table with the visual economy of a figure. Advantages include:

- Lower and Higher hierarchical terms can be displayed together
- Facilitates safety data review
- Less strenuous
- Intuitive, readable, and exhaustive

Adverse Events (>15%)



Further Development: Interactive Displays

Rho is currently developing interactive AE graphics using the data-driven documents, D3, javascript package. This enables the user to create views based on sorting, custom filters such as AE severity, and allows the user to drill down to participant level data.

Using a variety of techniques and tools to visualize AE data expedites the review process, enhances the ability for the reviewer to detect safety signals, and allows the reviewer to ask questions of the data that traditional displays otherwise lack.

NIAID

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