PharmaSUG 2020 - Paper SA-103

Risk-based and Exposure-based Adjusted Safety Incidence Rates

Qiuhong Jia, Fang-Ting Kuo, Chia-Ling Ally Wu, and Ping Xu, Seattle Genetics, Inc.

ABSTRACT

In clinical trials, safety event incidences are summarized to help establish the safety profiles of investigational drugs. The most common and straightforward method is the crude rate, which is the total number of subjects with at least one event of interest within a given population. However, if the average duration of exposure differs significantly between treatment groups within a trial or between trials included in an analysis due to differential drop-out rates or study design, such incidence rates may need statistical adjustment to make the comparison meaningful. The analysis of exposure-adjusted incidence rates is often found useful in such cases.

This paper introduces a simplified exposure-adjusted rate where sum of treatment duration of a population is used as the denominator, as well as a time-at-risk adjusted rate where sum of person-time-at-risk for each event of interest is used as the denominator. Person-time-at-risk for each subject is usually defined as the time from treatment start to the first onset of an event or to the end of follow-up if the event does not occur. The derivation of these adjusted rates is examined using hypothetical adverse event data, and the statistical implications are discussed in detail with comparison to the crude incidence rates. Further examples of exposure-adjusted analysis considerations such as presenting results (e.g., exposure-adjusted rate differences) in forest plots with confidence intervals will also be demonstrated.

INTRODUCTION

Most investigational drugs carry safety risk in additional to their potential efficacy benefit. Safety evaluation is crucial in clinical trials because an investigational product will only succeed if the potential benefits outweigh the risk. There are many approaches to conduct safety analysis, and one of the most common methods is to report the safety incidence rate.

Take treatment-emergent adverse events (TEAEs) as an example. Safety signals can often be detected by presenting the number of subjects with each TEAE as well as the associated percentages where the counts are divided by the number of subjects at risk, which is usually the safety population, in each treatment group. We will refer to this as the crude (incidence) rate comparison throughout this paper. The crude rate comparison is considered most appropriate between treatment groups with similar treatment duration and event collection period.

The crude incidence rate is not adequate to quantify the magnitude of the risk or its relationship to drug exposure. There are situations where safety incidence comparison is done between treatment groups with different durations at risk. This could be due to study design, comparison between multiple studies, or unequal drop-out rates and exposure duration between study treatments for long-term controlled studies. In these cases, additional exposure-adjusted safety incidence rates may be valuable to better understand the safety profile of the investigational product.

CRUDE INCIDENCE RATE

A set of hypothetical adverse event (AE) data of 400 subjects was constructed with subject number (USUBJID), treatment group (TRT01A), treatment start and end dates (TRTSDT and TRTEDT), adverse event term (AEDECOD), and event start date (ASTDT) (Figure 1). Table 1 presents the crude rates of 3 selected adverse events under treatment A and treatment B, each with 200 treated subjects. The crude rate can be calculated as:

*Number of Subjects with Events/Total Number of Treated Subjects*100*

USUBJID	TRT01A	TRTSDT	TRTEDT	AEDECOD	ASTDT
001	A	25FEB2014	20OCT2014	Diarrhoea	14MAR2014
001	A	25FEB2014	20OCT2014	Diarrhoea	15MAR2014
001	A	25FEB2014	20OCT2014	Diarrhoea	17MAR2014
001	A	25FEB2014	20OCT2014	Diarrhoea	22MAR2014
001	A	25FEB2014	20OCT2014	Anaemia	09SEP2014
002	B	03MAY2014	12JAN2015	Arthralgia	14JUN2014

Figure 1: Illustration of the Hypothetical AE Data

	Crude Incidence Rate	
	Treatment A N=200 n (%)	Treatment B N=200 n (%)
Diarrhoea	82 (41.0)	44 (22.0)
Anaemia	40 (20.0)	24 (12.0)
Arthralgia	30 (15.0)	9 (4.5)

Table 1: Crude Rate AE Table by Treatment Group

Without further qualification, this would lead any reviewer to conclude that diarrhoea and anaemia are nearly twice as prevalent in subjects on Treatment A, while arthralgia is over 3 times as prevalent. Let's see if that is actually true in our next section!

SIMPLIFIED EXPOSURE-ADJUSTED INCIDENCE RATE

Further investigation into the exposure of our hypothetical data shows that the median treatment durations are significantly different between the two treatment groups, 7.6 months vs 4.4 months (Table 2). Assuming the risk of an AE occurring is constant over time, subjects who are exposed to study treatment for a longer period of time tend to have higher chance to experience the AE. Therefore, in situations where durations of treatments are very different among treatment groups, the crude incidence rate comparison may not be sufficient to correctly interpret the safety signal.

	Treatment A N=200	Treatment B N=200
Duration of Treatment (months) Median	7.6	4.4

Table 2: Treatment Duration by Treatment Group

Simplified exposure-adjusted incidence rate takes duration of exposure into account. It is defined as the number of subjects with events per unit of exposure time. The counts used in this analysis are the same as in the crude rate calculation, namely the number of subjects who have experienced at least one event

during the event collection period. The exposure time is typically calculated in years for each subject, and if we assume the investigational drug is effective for 30 days after last exposure, the exposure period per subject in person-years is calculated as:

(Last dose date + 30 days - first dose date + 1)/365.25

The denominator of the exposure-adjusted incidence rate is total person-years, which is the sum of person-years of all subjects within the treatment group. The outcome is usually presented as exposure-adjusted subject incidence rate per 100 person-years, which is calculated as:

*(Number of subjects with events/total person-years)*100*

Using the same hypothetical AE data, simplified exposure-adjusted incidence rates of the selected AEs are presented in Table 3. In the table, n represents the number of subjects with at least one event and e is the exposure-adjusted incidence rate per 100 person-years. Total person-years was calculated for both treatment groups and is listed in the table headers, 173.6 vs 108.5 for treatment A and B, respectively.

	Simplified Exposure-adjusted Incidence Rate	
	Treatment A Person-years=173.6 n (e)	Treatment B Person-years=108.5 n (e)
Diarrhoea	82 (47)	44 (41)
Anaemia	40 (23)	24 (22)
Arthralgia	30 (17)	9 (8)

Table 3: Exposure-adjusted Incidence Rate by Treatment Group

After adjusting for the time on treatment, the risk differences of treatment A comparing to treatment B are significantly reduced from the crude rates comparison on all the selected adverse events. In Table 1, the crude rate percentages of diarrhoea and anaemia in treatment A are almost double those in treatment B. However, the exposure-adjusted incidence rates of diarrhoea and anaemia suggest that the risks of treatment A and B are fairly comparable. The same trend can be observed for arthralgia when the longer exposure time in treatment A is taken into consideration.

TIME-AT-RISK EXPOSURE-ADJUSTED INCIDENCE RATE

For acute events following close in time after start of exposure, the adjustment based on full exposure duration may underestimate the risk as it ignores the timing of the event and assumes the same time at risk of an event for subjects who have experienced an event and who have not. Also, the time at risk of a specific event in reality can be substantially different between treatment groups. In this situation, time-at-risk exposure adjustment would be another approach to more accurately evaluate the safety profile, where the time at risk for each subject is used instead of considering the full exposure period from treatment start to treatment end (Liu et al, 2006).

A time-at-risk exposure-adjusted incidence rate is defined as the number of subjects who experienced at least one event over the event observation period divided by the total person-years at risk of the event. The calculation of the denominator is different for subjects who have experienced the event and subjects who are event-free through the event observation period. Specifically, for subjects with events, the time at risk is the time from the first drug exposure to onset of the first event; for subjects with no event, the time at risk is the time from the first drug exposure to the end of event collection period, which is 30 days after the last exposure in our example.

Similar to simplified exposure-adjusted incidence rate, the time at risk is typically calculated in years. The exposure time at risk for subjects with events can be calculated as:

(Start date of the first event - first dose date + 1)/365.25 ---------- (equation 1)

And for subjects with no event, the exposure time at risk is calculated the same as simplified exposure-adjusted incidence rate:

(Last dose date + 30 Days - first dose date + 1)/365.25 ---------- (equation 2)

The denominator, total person-years at risk for each adverse event, will be the sum of person-years at risk for all subjects within the treatment group. The time-at-risk exposure-adjusted incidence rate is presented in number of subjects with events per 100 total person-years at risk:

*(Number of subjects with events/total person-years at risk)*100*

Total person-years at risk is the sum of person-years at risk of all subjects. For subjects with events, person-years at risk is calculated using equation 1, while for subjects with no event, person-years at risk is calculated using equation 2.

Using the same set of hypothetical AE data, time-at-risk exposure-adjusted incidence rates along with the total person-years at risk for each adverse event are summarized in Table 4. In the table, n represents the number of subjects with at least one event and e is the time-at-risk exposure-adjusted subject incidence rate per 100 person-years.

	Time-at-risk Exposure-adjusted Incidence Rate			
	Treatment A		Treatment B	
	Total Person-years at Risk	n (e)	Total Person-years at Risk	n (e)
Diarrhoea	102.4	82 (90)	91.7	44 (48)
Anaemia	146.6	40 (27)	99.0	24 (24)
Arthralgia	157.9	30 (19)	104.7	9 (9)

Table 4: Time-at-risk Exposure-adjusted Incidence Rate by Treatment Group

Comparing to the simplified exposure-adjusted rates in Table 3 where the same total person-years is used across all the AEs for each treatment as denominator (173.6 for treatment A and 108.5 for treatment B), the total person-years at risk for each adverse event is calculated separately here. In our example, 102.4 and 91.7 are the total person-years at risk for diarrhoea, 146.6 and 99.0 for anaemia, and 157.9 and 104.7 for arthralgia in treatment A and B, respectively (Table 4). Subjects who experienced the events had shorter person-years at risk which results in a smaller denominator and a higher time-at-risk exposure-adjusted incidence rate.

When we further investigate the onset time of these selected adverse events, the median onset time is 1.1 months for diarrhoea, 1.2 months for anaemia, and 2.6 months for arthralgia for all treated subjects. Total person-years at risk for each event is shorter compared to the total person-years from the simplified exposure-adjustment, especially for diarrhoea (102.4 vs 173.6 in treatment A and 91.7 vs 108.5 in treatment B). This is consistent with what is observed in Table 4, where time-at-risk exposure-adjusted incidence rates for both treatment groups are higher for acute adverse event like diarrhoea compared to simplified exposure-adjusted incidence rates in Table 3. On the other hand, no significant difference is observed on non-acute adverse events such as arthralgia. Looking at the risk differences between treatment groups in Table 3 and Table 4, diarrhoea is 47 vs 41 (Table 3) and 90 vs 48 (Table 4), aneamia is 23 vs 22 and 27 vs 24, and arthralgia is 17 vs 8 and 19 vs 9.The increase of the risk differences may

be due to the fact that the simplified exposure-adjusted method underestimates the risk, and this is more apparent for diarrhoea with early onset time and much shorter total person-years at risk.

RISK DIFFERENCES BETWEEN TREATMENTS USING FOREST PLOTS

To better illustrate treatment comparison of safety events, we can also produce forest plots where incidence rates are presented visually, with the risk difference and its 95% confidence interval (CI). Risk difference is defined as the difference in crude incidence rate or exposure-adjusted incidence rate between treatment groups (risk of treatment A – risk of treatment B). A risk difference below 0 favors Treatment A while those above 0 favor B. 95% CIs are computed using the normal approximation by Wald's method (Newcombe 1998).

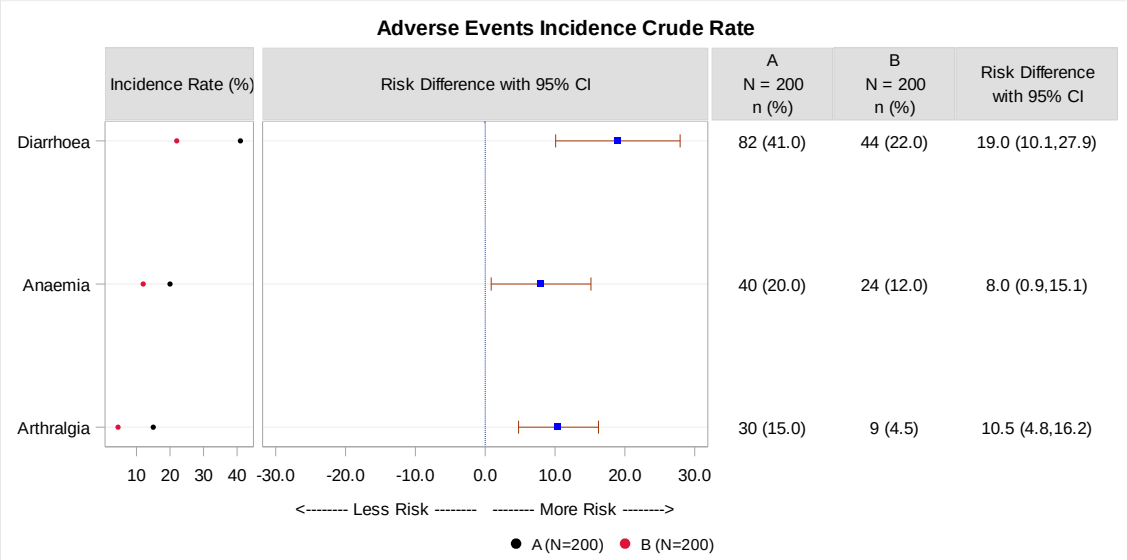

Figure 2: Forest Plot of AE Crude Rates by Treatment Group

Using the same set of AE data, a crude rate forest plot is generated in Figure 2, where the first section on the left shows the percentages of subjects who experienced at least one event, the central section displays the percentage differences with 95% CIs, and the section on the right lists detailed numbers of crude rates and risk differences with 95% CIs.

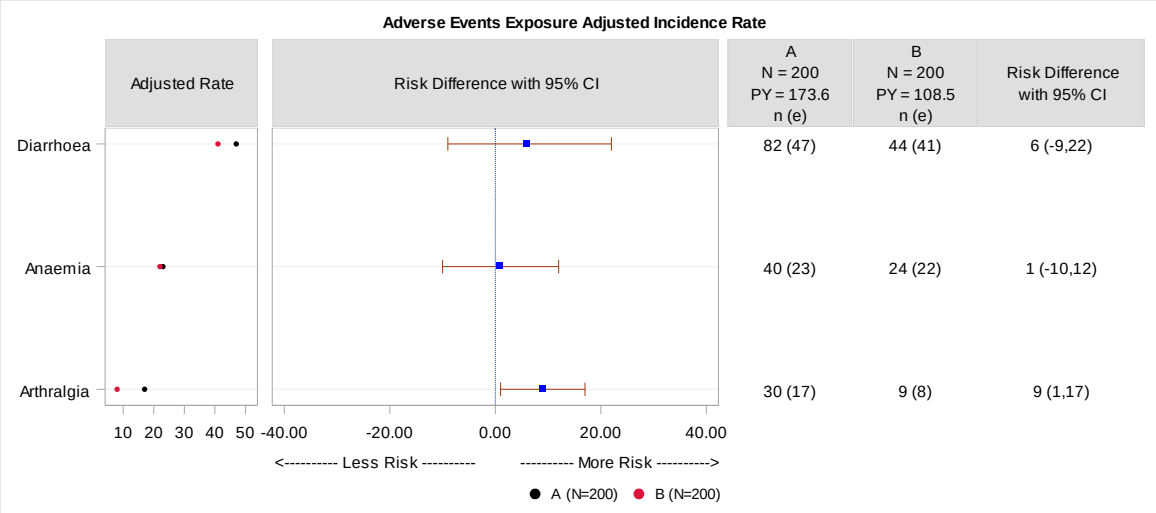

Figure 3: Forest Plot of Exposure-adjusted Incidence Rates by Treatment Group

Figure 3 shows the forest plot of simplified exposure-adjusted incidence rates, and when comparing this to Figure 2, the risk differences of all three AEs are reduced after exposure adjustment. If we look at diarrhoea and anaemia, the risk differences have shifted from more risk in treatment A to no statistical differences between treatments as the 95% CIs contain 0.

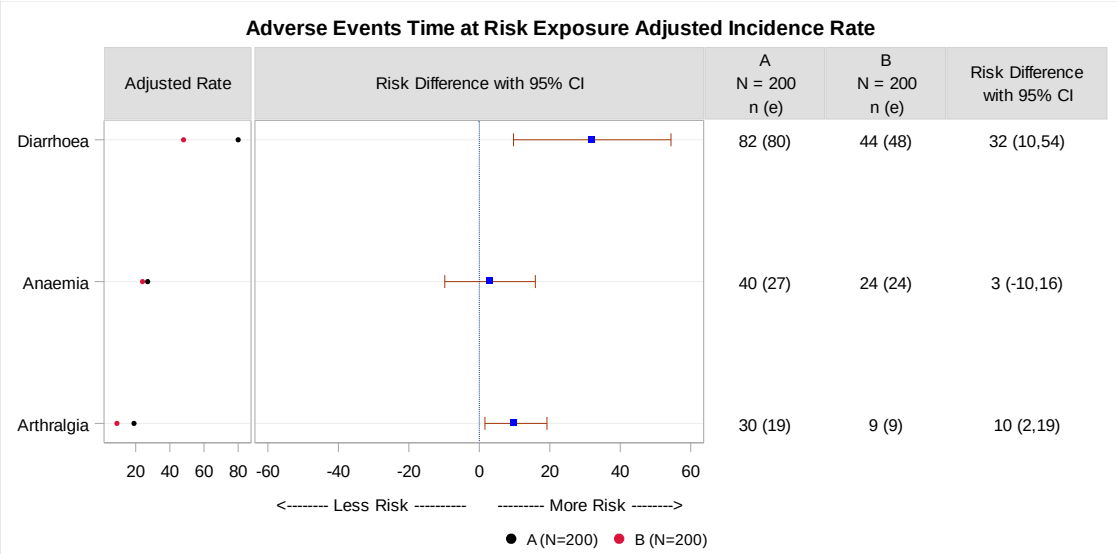

Figure 4: Forest Plot of Time-at-risk Exposure-adjusted Incidence Rate by Treatment Group

Figure 4 is the forest plot of time-at-risk exposure-adjusted incidence rates on the same AE data. Compared to the simplified exposure-adjusted incidence rates in Figure 3, the risk difference of diarrhea, the relatively early onset event, has increased from 6 to 32 subjects per 100 person-years, and this risk difference became statistically significant with the 95% CIs shifting from (-9, 22) to (10, 54). This trend is less apparent for anaemia and arthralgia where events occur comparatively later during treatment.

CONCLUSION

With the same set of data, the interpretation of a safety signal can differ a lot when we use different event incidence rates. Many aspects and assumptions should be taken into consideration to report the outcome with the most accurate representation of the data. In general, crude rate analysis is the most commonly used approach because of the straightforward calculation and the easy interpretation, and it is most appropriate when all subjects are treated for a similar period of time or for very short exposure periods per the study design (He et al, 2015).

However, when the exposure periods between treatments are significantly different, it can be appropriate to perform an exposure-adjusted analysis to account for the actual exposure duration. Furthermore, time-at-risk exposure-adjusted incidence rate is generally recommended to provide more comparable measures by adjusting for exposure time for each event of interest, since it takes into consideration the event onset time for subjects who experienced the events. Two assumptions to keep in mind when calculating both of the exposure-adjusted incidence rates are: (1) it assumes a constant risk for the event over the observational period; and (2) it assumes that any early dropout is noninformative to the event of interest, or the risk for those who dropped out being the same as those who did not (Zhou et al, 2014).

We can summarize the safety incidence rate between treatments in tabulations and forest plots using crude rate and exposure-adjusted methods. In the forest plots, we present the risk difference point estimates as well as the 95% CIs which visualize the statistical significance of differences between treatments. Each of these methods may provide biased information in some situations, so careful thought is needed for reporting and interpreting safety incidence rates in clinical trials.

REFERENCES

Liu, G. F., Wang, J., Liu, K., & Snavely, D. B. (2006). Confidence intervals for an exposure adjusted incidence rate difference with applications to clinical trials. *Statistics in medicine*, *25*(8), 1275–1286. https://doi.org/10.1002/sim.2335

Newcombe, R. G. (1998). Two-sided confidence intervals for the single proportion: comparison of seven methods. *Statistics in medicine*, *17*(8), 857–872. https://doi.org/10.1002/(sici)1097-0258(19980430)17:8<857::aid-sim777>3.0.co;2-e

He, X., Chen, L., Lei, L., Xia, H. A., & Lee, M. L. T. (2015). A Simple Method for Estimating Confidence Intervals for Exposure Adjusted Incidence Rate and Its Applications to Clinical Trials. J Biom Biostat 6: 238. https://doi.org/10.4172/2155-6180.1000238

Zhou, Y., Ke, C., Jiang, Q., Shahin, S., & Snapinn, S. (2015). Choosing Appropriate Metrics to Evaluate Adverse Events in Safety Evaluation. *Therapeutic innovation & regulatory science*, *49*(3), 398–404. https://doi.org/10.1177/2168479014565470

ACKNOWLEDGMENTS

We would like to sincerely acknowledge Avani Kaja and Michiel Hagendoorn for their valuable feedback to this paper.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the authors at:

Qiuhong Jia
Seattle Genetics, Inc.
qjia@seagen.com

Fang-Ting Kuo
Seattle Genetics, Inc.
fkuo@seagen.com

Chia-Ling Ally Wu
Seattle Genetics, Inc.
awu@seagen.com

Ping Xu
Seattle Genetics, Inc.
pxu@seagen.com