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Adverse Event Data over Time

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ABSTRACT

Commonly in clinical trials Adverse Events (AEs) are captured over time and the incidence and time to first occurrence of an event are presented descriptively. The duration of the event is also often calculated in the subset of patients who have experienced the event. However, better methods are needed to combine and present AE incidence and duration information over time.

In oncology, methods for displaying tumor response and duration of response were developed by Temkin (Temkin, 1978)).

This paper will investigate the applicability, with modification as necessary, of these methods, in particular the Probability of Being in Response method, to the display and meaningful interpretation of AE data over time in clinical trials. Recommendations for the presentation of AE data in future trials will be made.

INTRODUCTION

Clinical trials evaluate the safety and efficacy of a drug. One of the methods used to evaluate patient safety within a clinical trial is to monitor and report all AEs. According to the *International Conference on Harmonization* (ICH) guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH, 1994), an AE is defined as:

Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Examples of AEs are Alopecia, Nausea and Vomiting.

AEs are captured using the AE Case Report Form (CRF). At each visit, the start date/time of the AE and stop date/time if applicable, along with the seriousness, intensity, relationship to study drug, study treatment action taken, and the outcome of the AE are recorded by the investigator. The investigator is responsible for ensuring that an investigation is performed appropriately and for protecting the rights, safety, and welfare of subjects under their care. If the adverse event meets set serious criteria in the opinion of the investigator or sponsor, then the investigator must complete a separate Serious Adverse Event (SAE) CRF and send this information to the Food and Drug Administration (FDA) and the other applicable regulators within the required time frame.

According to the ICH guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH, 1994) a SAE is defined as:

Any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is a medically important event or reaction.

The actual details of the AEs are recorded in textual or 'verbatim' terms as written in free text on the CRF. Verbatim terms are then processed through a coding dictionary such as Medical Dictionary for Regulatory Activities (MedDRA) so that similar terms are grouped together by classifying each verbatim term into a hierarchy of medical granularity. For example, if a verbatim term was recorded as 'stomach virus' on the CRF, then after coding the term using MedDRA (version 14.0), this verbatim term would be classified as having the preferred term (PT) 'Gastroenteritis viral' and the System Organ Class (SOC) 'Infections and infestations'. In addition if a verbatim term was recorded as 'viral gastroenteritis' then after coding the term, the verbatim term would also be classified as having the PT 'Gastroenteritis viral' and the (SOC) 'Infections and infestations'. The MedDRA PT is used to report AEs instead of the verbatim term.

In clinical trials AEs are typically assessed in the following ways:

- examining the incidence of the number of events and the number of subjects with AE summarized by treatment group;

- examining the time to first occurrence of AE summarized by treatment group;
- examining the duration of AE summarized by treatment group;

Usually the reporting of AEs is presented descriptively, such as when the incidence rate of the number of subjects with AE is examined. Output 1, shows an example of how the Treatment Emergent Adverse Events (TEAE's) are presented descriptively. Generally, TEAE's are events that occurred post baseline that were not present at baseline and events that worsened post baseline compared to baseline. Usually TEAE's have a cut-off date, so if there is an event which occurred over 30 days since the subject discontinued treatment, then this event will not usually be classified as a TEAE.

Output 1: TEAE's by SOC and PT

Table 14.3.2.2 1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

Category	Placebo (N=86) n (%)	Xanomeline Low (N=84) n (%)	Xanomeline High (N=84) n (%)
Subjects with any TEAE	34 (39.5)	65 (77.4)	68 (81.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
APPLICATION SITE PRURITUS	6 (7.0)	22 (26.2)	22 (26.2)
APPLICATION SITE ERYTHEMA	3 (3.5)	12 (14.3)	15 (17.9)
APPLICATION SITE DERMATITIS	5 (5.8)	9 (10.7)	7 (8.3)
APPLICATION SITE IRRITATION	3 (3.5)	9 (10.7)	9 (10.7)
APPLICATION SITE VESICLES	1 (1.2)	4 (4.8)	6 (7.1)
FATIGUE	1 (1.2)	5 (6.0)	5 (6.0)
OEDEMA PERIPHERAL	2 (2.3)	1 (1.2)	2 (2.4)
APPLICATION SITE SWELLING	0	1 (1.2)	2 (2.4)
APPLICATION SITE URTICARIA	0	2 (2.4)	1 (1.2)
CHILLS	1 (1.2)	1 (1.2)	1 (1.2)
MALAISE	0	1 (1.2)	2 (2.4)
PYREXIA	2 (2.3)	0	1 (1.2)
APPLICATION SITE PAIN	0	0	2 (2.4)
APPLICATION SITE PERSPIRATION	0	0	2 (2.4)
APPLICATION SITE REACTION	1 (1.2)	0	1 (1.2)
ASTHENIA	1 (1.2)	0	1 (1.2)
CHEST DISCOMFORT	0	0	2 (2.4)
CHEST PAIN	0	0	2 (2.4)
OEDEMA	0	2 (2.4)	0

(CONTINUED)

A Subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).
Adverse Events terms were coded using Medical Dictionary for Drug Regulatory Affairs (MedDRA) Version 17.1.
U:\sheffield\pg\tables\t_teae.sas FINAL/DATA CUTOFF: 01APR2015 15JUL2015:17:44

Output 1 shows the number and percentage of patients which had adverse events in the Placebo, Xanomeline Low and Xanomeline High treatment groups. The AEs that are shown in this table are the AEs related to the System Organ Classes General Disorders and Administration Site Conditions, and Skin and Subcutaneous Tissue Disorders.

The common way of reporting AE's descriptively within a table is predominantly due to the ICH guideline "Structure and Content of Clinical Study Reports E3" (ICH, 1995), which is adhered to by organisations conducting clinical trials. The ICH recommends in section 12.2 of the guidelines that, for the evaluation of adverse events, a detailed record of adverse events be made available to regulatory authorities such as the FDA when requested, and the regulators have guidance on the frequency, of which the AE's should be reported. The ICH also recommends that all adverse events occurring after initiation of study treatments should be displayed in summary tables. Two documents that were produced by the ICH have already been mentioned and therefore it would be helpful to know background information regarding the ICH. According to (ICH, n.d.) The ICH is an organisation that promotes international harmonisation by bringing together representatives from both regulatory agencies and pharmaceutic industry to discuss and establish common guidelines. The objective of ICH is to increase international harmonisation of technical requirements to ensure that safe, effective, and high quality medicines are developed and registered in the most efficient and cost-effective manner.

(Cao & He, 2011, p. 1) agree that currently the reporting of safety profiles including AE data is limited, especially compared to the fact that the evaluation of the efficacy of a study drug is extensive and has well developed statistical methodology. The aim of this paper is to first demonstrate the common methods which are used in clinical trials to

monitor and report AEs. Subsequently statistical methodology that is currently used to evaluate efficacy will be researched to see if the framework can be applied to the evaluation of AE dataset, and also other ways to better interpret and present AE data will be investigated. One of the methods that can be investigated as an alternative way to interpret and present AEs is the use generalised linear models to analyse the AE's and deduce the probability of a treatment group having an AE. This method is out of scope for this paper, however this paper will look at a method known as the Probability of Being in Response Function (PBRF). The PBRF is discussed in more detail on Page 5.

BACKGROUND OF THE STUDY

Data from the CDISC SDTM / ADaM Pilot Project was obtained on the CDISC website (CDISC, 2013) in order to investigate meaningful ways to present AE data. The CDISC SDTM / ADAM Pilot Project is a prospective, randomized, multi-center, double-blind, placebo-controlled, parallel-group study. The objectives of the study were to evaluate the efficacy and safety of Transdermal Xanomeline at 54 mg and 81 mg, and placebo in subjects with mild to moderate Alzheimer's disease.

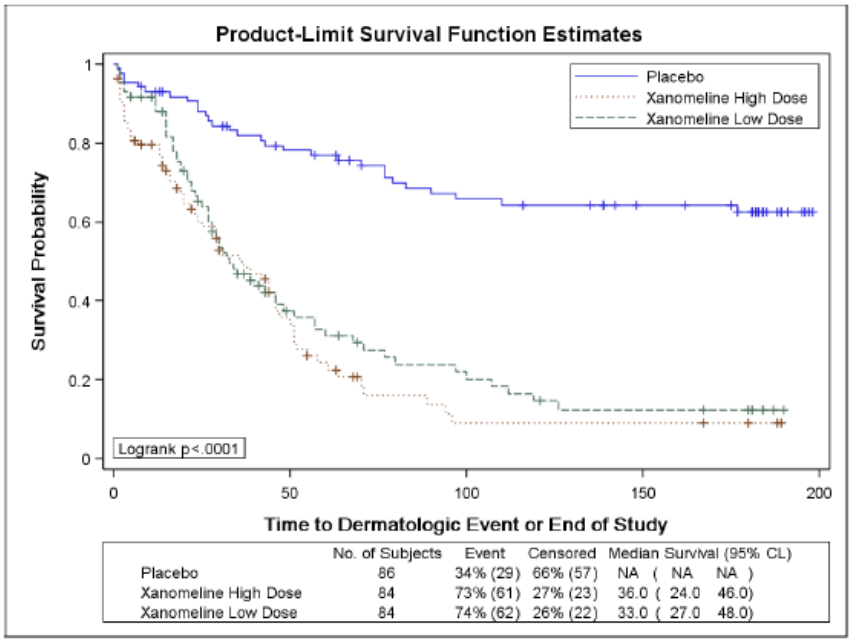
254 subjects were randomised and 86 received Placebo, 84 received Xanomeline at 54 mg (low dose) and 84 received Xanomeline at 81 mg (high dose). Subjects administered the treatments by applying 2 adhesive patches daily in the morning and subjects were followed for 26 weeks. Of the 254 subjects that were enrolled 111 (46%) were male, 143 (54%) were female. The mean age of the subjects was 75.1 years and the standard deviation of the age was 8.25 years. 218 (86%) of the subjects were Caucasian, 23 (9%) were of African Descent, 12 (5%) were Hispanic and 1 (<1%) was an American Indian or Alaska Native.

Subjects were included in the study if they were males or females of non-childbearing potential, 50 years of age or older, had probable mild to moderate Alzheimer's disease according to the NINCDS-ADRDA criteria, had an MMSE score of 10 to 23, had a Hachinski Ischemic Scale score of ≤ 4, and CNS imaging compatible with Alzheimer's disease within the past year. Subjects were excluded from the study if they had previously participated in a Xanomeline study, had used an investigational or approved Alzheimer's therapeutic medication within 30 days of prior to enrollment, serious illness requiring hospitalization within 3 months prior to screening, have certain concurrent or historical medical conditions, or were concurrently or historically using certain medications.

The reporting of adverse events, laboratory values, and vital signs were used for safety assessments. The adverse events which this paper will concentrate on were recorded for each subject at 2, 4, 6, 8, 12, 16, 20, 24 and 26 weeks post treatment. The adverse events were also recorded when there was an early termination. This paper will focus on the adverse events data, and that is the reason why the results of the adverse event data where extracted from the (CDISC Pilot Project, 2006).

Figure 1 is an extract from the CDISC Pilot Project, and is a Kaplan Meier plot. On the table below the plot, it shows that there was a disproportionate number of subjects in the Xanomeline treatment groups who experienced a special interest dermatologic adverse event with 74% (n = 62) of Xanomeline low dose and 73% (n = 61) of Xanomeline high dose subjects with at least one event of special interest compared to 34% (n = 29) of placebo subjects. The analysis of the time to the first dermatologic event indicated that the median time to first event was significantly different ($p<0.0001$) between treatment groups with a median time of 33 days in the Xanomeline low dose group (95% CI: 27 – 48 days) and 36 days in the Xanomeline high dose group (95% CI: 24 – 46 days) compared to placebo, in which the median time to first event was not estimable.

Figure 1: Time to Dermatologic Event by Treatment Group

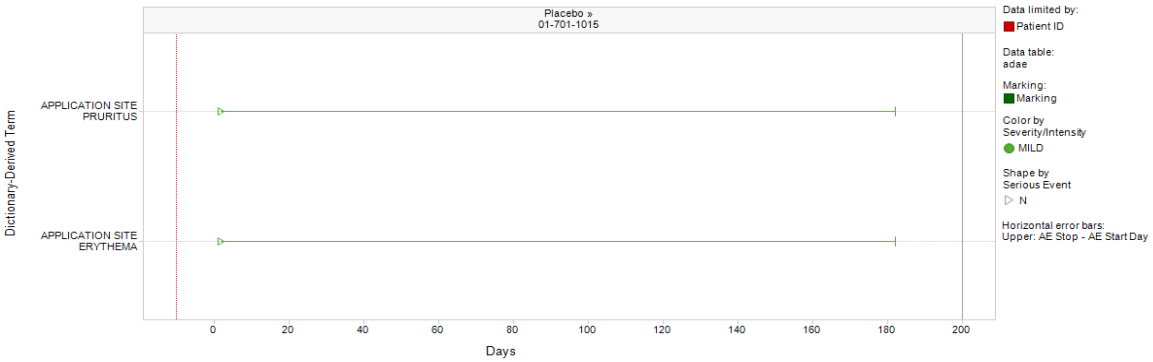


Note: Dermatologic events were identified as adverse events associated with skin conditions such as rash, pruritus, dermatitis. A full list of adverse event terms is presented in the final study report.

COMMON WAYS OF REPORTING AE'S

The common ways of reporting AE's are descriptively, or by using Kaplan Meier figures of time to first occurrence of adverse events, or by using vizualisations created by TIBCO™ Spotfire®, such as in the output below. Figure 2 shows the dermatological TEAE's that subject 1015 experienced and when the adverse events started and stopped in relation to their first dose. For example, subject 1015 was treated with Placebo on 02 January 2014, they then experienced Mild Application Site Pruritus and Application Site Erythema, the day after on 03 January 2014. Therefore the relative start day of those adverse events were on the 2nd day of treatment, calculated using adverse event start date – treatment start date + 1 (as the event was occurred post-dose). There was no end date of the Mild Application Site Pruritus and Application Site Erythema events, and so the end date was imputed to be the last date the subject was dosed, and this was 02 July 2014. Therefore the relative end dates of the TEAE's were 182, approximately 6 months after the first dose date and this is shown clearly in Figure 2, that the subject had two mild TEAE's starting just after first dose of Placebo and finished just over 180 days after treatment.

Figure 2: Treatment Emergent Adverse Event timeline for subject 1015



According to (Gillespie & Scott, 2008) the PBRF has intuitive interpretations. The rate of which it rises from 0 shows how rapid an adverse event can be attained, and then the rate at which it falls indicates how quickly the adverse event stops. The maximum height of the curve gives an estimate of the proportion of patients that had adverse event, although the proportion is usually on the low side. The height at the curve on any point of time indicates the proportion of patients that have the adverse event at any given time.

The SAS® procedure SGPLOT or Graph Template Language (GTL) can be used to plot the PBRF as shown in the PBRF figures below. Figure 3 shows the probability of having a dermatological treatment emergent adverse event at a given time point for the three treatment groups. The legend indicates that Placebo is the blue dashed line, Xanomeline Low and High Dose are the red and green dashed lines respectively. In Figure 3 the subjects in the Placebo group have much less probability of having a dermatological treatment emergent adverse event compared to the Xanomeline treated groups. In the Placebo group the curve rises slowly up to approximately 20% chance of having a dermatological TEAE from 0 to 100 days after treatment. Between 100 and 200 days after treatment the PBRF plot indicates that there probability of having an dermatological TEAE remains around 0.2. The probability of having a dermatological TEAE is between 50 and 60% approximately 60 days after being treated by Xanomeline, and for the remainder of the study the probability is similar to the probability that was seen around 60 days. After 50 days of being treated there is approximately 10% less chance of having a dermatological TEAE in the Xamomeline Low dose group, compared to the High Dose group.

There are three main steps in the computation of the PBRF. They are:

- Creating a dataset that is in the right format for the Temkin algorithm.
- Applying the Temkin algorithm (modified for treatment emergent adverse events) to the dataset.
- Plotting the Probability of having an adverse event by time.

Creating the dataset needed so that the Temkin algorithm can be applied can be done by merging together the ADaM datasets ADTTE, ADSL and ADAE. More information on the ADaM datasets is below:

- The ADTTE dataset is an Analysis Dataset of Time to Events. In this ADTTE dataset the time to event parameter is time to first dermatological event, and the dataset contains the time in days of the first dermatological event for each subject, or the time taken to discontinue or complete treatment for each subject. The ADTTE also contains a variable which identifies if the patient is censored or not. There were 254 records in the ADTTE dataset.
- ADSL is a Subject Level Analysis Dataset which is aptly named because ADSL only contains one row of data per subject. The data captured in ADSL includes treatment assignment variables, dates the subject started and finished treatment, demographic information, fatality information, reason for discontinuation, and dates of completion or discontinuation of treatments. In the ADSL provided there were data on 254 subjects.
- The ADAE dataset is an Analysis Dataset of Adverse Events, and this dataset contains information on all the adverse events that were reported during the study

Program 1, shows how to create the dataset in the format which is necessary for the Temkin algorithm. The variables to use from the datasets are:

- ADTTE.AVAL - the number of days to the event or discontinuation.
- ADTTE.CNSR - whether the subject had the event or was censored.
- ADAE.AENDY - relative day that the adverse event stopped if applicable.
- ADSL.RFENDT - the completion/discontinuation date.

Using this information, it is possible to find out the subjects that had an adverse event, and then determine the duration of event, and if the event was resolved before the subject completed or discontinued the treatment. It is also possible to find out how long the subject was in the study for before they had any adverse events.

Program 1: Ensuring Dataset is in the Right Format

```
* Read in TTE data;
data adtte;
  set ads.adtte;
  if trta = "Placebo" then trtan = 1;
  else if trta = "Xanomeline Low Dose" then trtan = 2;
  else if trta = "Xanomeline High Dose" then trtan = 3;
  rename trta = trt01a trtan = trt01an;
run;

/* Selecting the dermatological Adverse Events, so that the AE's with end days can be
determined */
proc sort data = ads.adae out = aendy;
  where AOCC01FL = "Y";
  by usubjid astdt;
run;

/* Merging on the adverse event enddate where applicable */
proc sql;
  create table adtte_endday as
  select a.*, b.aendy
  from adtte as a left join aendy as b
  on a.usubjid = b.usubjid;
quit;

/* Merging in date of discontinuation / completion */
/* This is so the censoring date can be known for subjects that have no AE end date */
proc sql;
  create table adtte_stopdate as
  select a.*, b.rfendt
  from adtte_endday as a left join ads.adsl as b
  on a.usubjid = b.usubjid
  order by a.trt01an, a.aval;
quit;

data adtte_stopdate2;
  set adtte_stopdate;
  by trt01an;

  stopday = rfendt - trtsdt + 1; /* Working out the date of discontinuation in terms
of relative day */

  if cnsr = 0 then response = 1;
  else response = 0;

  if response = 0 then do;
    censttp = 0;
    ttp = aval;
  end;
  if response = 1 then do;
    ttrespb = aval;
    ttp = stopday;
    if aendy = . then do;
      censttp = 1;
    end;
    if aendy ne . then do;
      censttp = 0;
        ttp = aendy;
    end;
  end;

  rename trt01a = TRTSEQ;
  label stopday = "Stop day";
  label aendy = "TEAE Relative End Day";
```

```
  label response = "TEAE present";
  label censttp = "Is TEAE Date Censored?";
  label ttrespb = "TEAE Relative Start Day";
  label ttp = "TEAE Relative End Day /Subject Relative End Day";
run;
```

Table 1 below shows the data from a few patients that went into the calculation of the PBRF. The 3 patients in Table 1 represent the 3 different scenarios which can happen. These scenarios are:

- The subject has a TEAE and the subject discontinues or completes the study before the TEAE has ended.
- The subject has a TEAE and the TEAE ends before the subject discontinues or completes the study.
- The subject does not get any TEAE's whilst on the study.

You can see that subject 1015 had a TEAE because the column **TEAE present** has a value of 1, and their first TEAE was on relative day 2 (indicated by the TEAE Relative Start Day column). Relative day 2 means that the TEAE started 1 day after the subject was first dosed. The column, **Is TEAE Date Censored?** tells us that the stop date of the TEAE was censored because it has the value 1. When the TEAE date is not censored then the value is 0. For subject 1015 there is no TEAE end date because it was not completed and so the TEAE end date was censored to the date the subject discontinued / completed the study, and this was at relative day 182, as seen in the **TEAE Relative End Day / Subject Relative End Day** column.

Subject 1023 had their first TEAE at relative day 3, and the TEAE ended on relative day 26, and the end date was not censored as it had resolved within the study. Subject 1047 did not have any TEAE's, and so their relative end day was captured, that is the number of days the subject was in the study for before completing or discontinuing.

Table 1: Example of Data Input for PBRF

Unique Subject Identifier	Actual Treatment	Duration of treatment (days)	TEAE Relative End Day	Stop day	TEAE present	Is TEAE Date Censored?	TEAE Relative Start Day	TEAE Relative End Day /Subject Relative End Day
01-701-1015	Placebo	182		182	1	1	2	182
01-701-1023	Placebo	28	26	29	1	0	3	26
01-701-1047	Placebo	26		46	0	0		46

Subjects that had the same profile as subjects 1015, and 1023 are known as responders because they have a TEAE. The responders in the PBRF calculations are the same subjects known to have the events in the Kaplan Meier output in Figure 1. Therefore, there were 29, 62 and 61 responders in the Placebo, Xanomeline Low Dose and Xanomeline High Dose respectively. The benefit over the PBRF over the Kaplan Meier calculations is the PBRF also takes into account the duration of the event.

The number of responders at each timepoint is indicated by the RI variable in Table 2. Table 2 shows the final format that the data needs to be in before the PBRF can be calculated. In the table T_i denotes the times of events. P_i is the number of times subjects have discontinued or completed the study without having a TEAE at T_i. R_i is the number of responses (TEAE's) at T_i. S_i represents the number of resolved TEAE's after response. Another way to look at S_i is the TEAE's with an end date (after the start date) which was not censored, at T_i. W_i represents the number of TEAE's which had censored end dates whilst on the study during $T_i;T_{i+1}$. M_i represents the number of patients in the initial state at T_i. N_i represents the number of patients observed in response state (with a TEAE) at T_i. LG_{2i}, BG_{2i}, LG_{1i}, BG_{1i} and F_i are MLE's of the component function. $P(T_i)$ is the MLE of the PBRF. For more details of the function, please see (Temkin, 1978).

In the table below a subject had a TEAE at relative day 1 within the Placebo group, and the corresponding $P(T_i)$, i.e. $P(T_1)$ is 0.0116.

According to (Temkin, 1978) to calculate the $P(T_i)$ first LG_{2i} needs to be calculated by subtracting the number that discontinued or completed treatment without an TEAE from the T_i at M_i and then dividing by M_i, i.e. (column 7 – column 2) / column 7.

LG_{1i} is calculated as $1 - (R_i/(M_i - P_i))$.

The BG_{2i} and BG_{1i} are obtained by multiplying the LG_{2j} or LG_{1j} for $j \leq i$.

F_i is calculated by subtracting the number of resolved TEAE's after response, S_i, from N_i and dividing by N_i, i.e. F_i = (column 8 – column 5) / column 8. Although when $N_i = 0$, then F_i is initialized to 1. Then, starting with $P(T_0) \equiv 0$, for each treatment, the $P(T_i)$ are calculated using the equation below:

(1)

Table 2: Subset of PBRF calculations

Actual Treatment	T_i (1)	P_i (2)	R_i (3)	L_i (4)	S_i (5)	W_i (6)	Number of subjects in Treatment Group	M_i (7)	N_i (8)	LG_{2i}	BG_{2i}	LG_{1i}	BG_{1i}	F_i	$P(T_i)$
Placebo	0	0	0	0	0	0	86	86	0	1		1	1	1	0
Placebo	1	0	1	0	0	0	86	86	0	1	1	0.9884	0.9884	1	0.0116
Placebo	2	0	1	0	0	0	86	85	1	1	1	0.9882	0.9767	1	0.0233
Placebo	3	0	2	0	0	0	86	84	2	1	1	0.9762	0.9535	1	0.0465
Placebo	7	0	1	0	0	0	86	82	4	1	1	0.9878	0.9419	1	0.0581
Placebo	8	1	0	0	0	0	86	81	5	0.9877	0.9877	1	0.9419	1	0.0581
Placebo	9	0	1	0	0	0	86	80	5	1	0.9877	0.9875	0.9301	1	0.0698
Placebo	12	1	0	0	0	0	86	79	6	0.9873	0.9873	1	0.9301	1	0.0698
Placebo	13	1	0	0	0	0	86	78	6	0.9872	0.9747	1	0.9301	1	0.0698
Placebo	14	1	0	0	0	0	86	77	6	0.9870	0.9744	1	0.9301	1	0.0698
Placebo	16	0	1	0	0	0	86	76	6	1	0.9870	0.9868	0.9178	1	0.0818
Placebo	21	0	1	0	1	0	86	75	7	1	1	0.9867	0.9056	0.8571	0.0824

The SAS procedure SGPLOT or Graph Template Language (GTL) can be used to plot the PBRF as shown in the figures below. The full code which creates the PBRF dataset and plots is found here: http://www.krissharris.co.uk/pharmasug/2017/SP06/pg/figures/f_pbr.sas. The datasets needed for the PBRF is located here: http://www.krissharris.co.uk/pharmasug/2017/SP06/data/ads/ADaMs.zip.

Figure 3 below, shows the probability of having a dermatological treatment emergent adverse event at a given time point for the three treatment groups. From the plot you can see that there is a higher probability of a TEAE in the Xan High Dose and Xan Low Dose treatment groups compared to Placebo. You can see that between 1 and 50 days after being treated, the probability of having a TEAE increases rapidly from 0 to approximately 60% in the Xan High Dose group. After 50 days since treatment start date, the probability of having a TEAE remains quite constant at approximately 60%.

Figure 3: Probability of Being in Response by Treatment Group

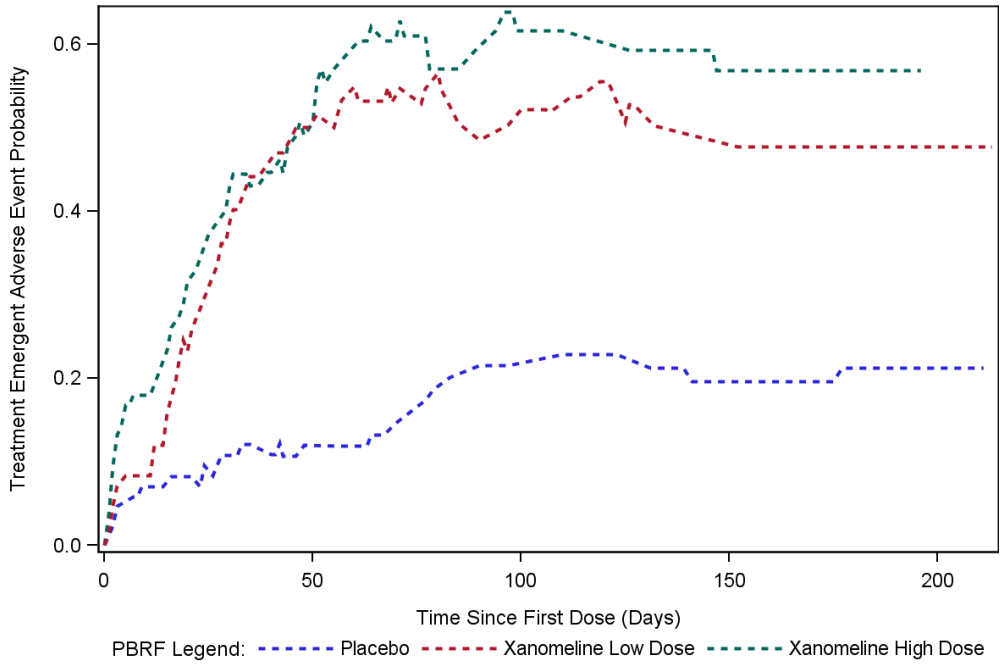
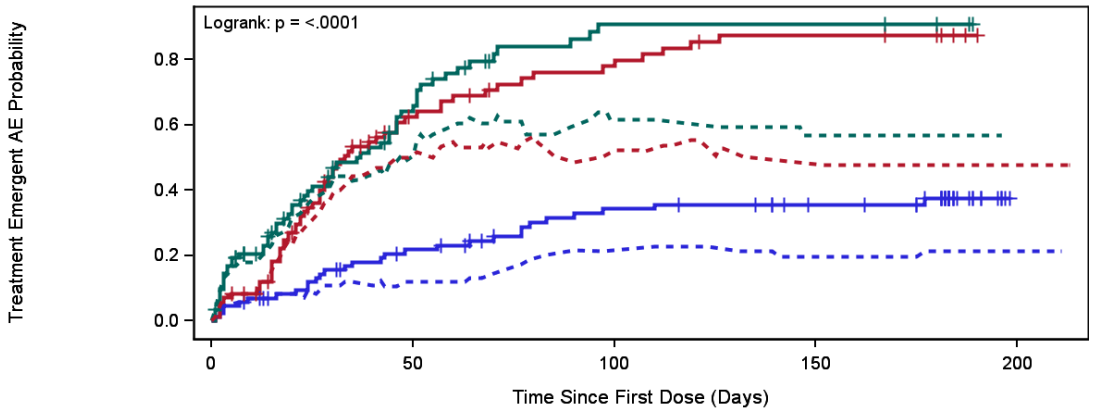


Figure 4 below shows the PBRF curves and the Kaplan Meier curves on the same plot. The PBRFs are slightly lower than the Kaplan-Meier curves at equivalent treatments.

Figure 4: Probability of Being in Response by Treatment Group and Kaplan Meier Plot



Subjects at Risk:

Placebo	86	69	59	49	45	40	35	0
Xanomeline Low Dose	84	42	20	13	8	6	5	0
Xanomeline High Dose	84	38	14	6	4	4	3	0

Arm	No. of Subjects	Events	Censored	Median AE time (95% C.I.)
Placebo	86	29 (33.7%)	57 (66.3%)	. (. - .)
Xanomeline Low Dose	84	62 (73.8%)	22 (26.2%)	33.0 (27.0 - 48.0)
Xanomeline High Dose	84	61 (72.6%)	23 (27.4%)	36.0 (23.0 - 46.0)

CONCLUSION

The aim of this paper was to investigate and display better ways of interpreting adverse event data over time, in particularly examining the methods used by Temkin (Temkin, 1978). This paper showed how adverse events are typically reported as tables of incidence rates and a Kaplan-Meier time to event figure, and this paper highlighted the reason why adverse events are typically reported the way they are, which is largely due to the ICH requirements.

TEAE rates can be compared over time using the Poisson and negative binomial models and the latter is preferred due to the over dispersion problems in Poisson. Explaining how to fit and interpret, Poisson and negative binomial models have been left out of this paper as (Allison, 2012) and (SAS Support, 2017) have great examples on how to achieve this.

Estimates of the relative event rates from the negative binomial regression can be produced with 95% CIs that can help the researcher to best understand where there might be issues in TEAE data – multiplicity however will become a real problem if many TEAEs are analysed and TEAE data themselves can be unreliable, being only subjective, spontaneous reports. Hence, very sophisticated statistical analyses may give a false impression of statistical security. And while we can compare TEAE rates we have no good way of visualising TEAE over time, albeit a Kaplan-Meier plot which only looks at time to first occurrence. This is where Temkin's approach is helpful since it allows a visual of the probability that a patient has a given TEAE at any point in time, which is given by the curve, and the area under the curve is the expected duration of an TEAE which can be also useful in comparing treatments. The paper by (Ellis, et al., 2008) shows how to compare the expected duration of an TEAE between groups statistically. Alternatively bootstrapping can be used on the area under the curve to compare the expected durations. Hence, we probably should be looking more routinely at comparing TEAE rates via negative binomial model at least as a screen for possible TEAE differences and for those TEAEs where a difference might be seen or those TEAEs of pharmacologic concern, then the PBRF is a very useful visualisation of what is happening over time and should be used more routinely, and the code is included in the appendix to make this easier.

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