



Adverse events: More than a mild headache for the regulatory writer

by Linda Donnini

A large clinical study can produce an overwhelming volume of adverse event (AE) data. Picking out the important findings can be a difficult task for the medical writer—most of us are not medically qualified and resort to medical dictionaries to tell dysgeusia from dysphonia, or cholesterolaemia from cholelithiasis. International Conference on Harmonisation (ICH) topic E3 [1] gives guidance on presenting AEs in a clinical study report but is mainly concerned with the summary tables attached at the end of the report. What to include within the body of the report is left largely to the discretion of the writer and reviewers. As for the discussion section, the ICH guidance—to not simply repeat the description of results—is often ignored if the writer is not sure what else to say about the data. Some points to consider in deciding what to present, and how to interpret it, can make the writing process much easier.

Common adverse events

The only in-text AE table stipulated in ICH E3 for a clinical study report is a summary of common AEs. So how do you define common? ICH suggests including AEs occurring in at least 1% of treated subjects but this frequency cut-off point is arbitrary and may not be appropriate for the size of your study population. If $N \leq 100$, then one subject equals $\geq 1\%$ and your table would include every AE rather than only the most common. Use your judgement to choose a cut-off that allows you to include all important information without compromising readability.

If your table includes an ‘overall’ column for all groups combined, make sure you apply the cut-off to each treatment group—or to the group that received study treatment rather than placebo. If you apply it only to the overall column, you may miss AEs which are frequent in the treated group but absent in the control group (such as headache in Table 1). It is important that the cut-off, and how it was applied, are clearly identified in the table title or footnote.

Table 1: Common adverse events reported in at least 10% of subjects in either treatment group

	Placebo (N=50) n (%)	Study treatment (N=50) n (%)	Overall (N=100) n (%)
Rhinitis	4 (8%)	6 (12%)	10 (10%)
Headache	0	9 (18%)	9 (9%)

Applying the 10% cut-off only to the overall column would exclude headache.

The investigator’s description of each AE, as entered on the case report form, will have been coded using a standard dictionary so that similar events can be counted together. Currently the most commonly used dictionary is the Medical Dictionary for Regulatory Activities (MedDRA); each event is given an appropriate description—the preferred term—and is grouped according to the body system or organ it affected—the system organ class. Some writers include system organ class in their common AE table while others prefer to present AEs by system organ class in a separate in-text table.

Looking at AEs by system organ class can help to reveal patterns in the data; for example, the majority of AEs may be nervous system disorders. This could be due to a particularly high incidence of headache or it could reflect a range of less common AEs that all affect the nervous system. It is important to remember that the MedDRA dictionary contains such a large number of preferred terms that the same symptoms can be coded differently depending on how the investigator described them (e.g., somnolence, sleepiness and drowsiness); the frequency of the symptoms is thereby diluted, making it less likely that they appear as common AEs. On the other hand, a system organ class will not necessarily contain all like events; in MedDRA, the preferred term ‘liver function test abnormal’ falls under the system organ class of investigations whereas ‘liver function abnormal’ is in the system organ class of hepatobiliary disorders. It is important to review the types of AEs with a critical eye and not just focus on their numbers.

Treatment group differences

Most medical writers are comfortable with summarising the most common AEs in each treatment group but they often omit what is the most important step for controlled studies—checking for differences between the treatment groups. A consistent difference across studies between the study treatment and control groups forms persuasive evidence that an AE may be treatment-related. The problem for the writer lies in deciding what constitutes a difference as there are no set rules. One solution is to set your own criteria, and summarise in the text all AEs that meet these criteria. For example, if the incidence of an AE in the treated group is at least twice that in the control group, or at least 5% higher, this may be reported as a difference. This presents difficulties at low frequencies, however; 4% could be said to be similar to 2%, or twice as high. In this case, you could seek medical opinion as to whether the AE is clinically relevant in this subject population and so worthy of

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comment in the report—a small increase in AEs of headache may be unimportant whereas an increase in pneumonia AEs may be a cause for concern. Whatever criteria you choose, make sure you are consistent in applying them not only to common AEs but also to other categories such as serious AEs (SAEs) or AEs leading to withdrawal. Too often, writers will be inconsistent, making a general statement that the incidence of each common AE is similar between the treatment groups, and then later drawing attention to a minor difference in the incidence of AEs leading to withdrawal.

The writer's job is made easier if statistical analyses have been performed to compare AE rates between the treatment groups. However, if comparisons have been conducted for each preferred term, bear in mind that you should expect some statistically significant differences simply because of the large number of tests.

Number of subjects or number of events

AEs are usually summarised by the number and percentage of subjects who have reported an event at least once. In this way, subjects are counted only once even if they had the same event multiple times. Sometimes the number of events is also summarised; this will show if subjects are repeatedly experiencing the same symptom and is useful in a long duration study or for events that are episodic, such as vomiting or diarrhoea. If the information is available, check for obvious differences between the treatment groups; a subject who experiences a single bout of diarrhoea after receiving study treatment may not be noteworthy whereas a subject who experiences repeated episodes of diarrhoea could indicate a safety concern.

Make it very clear whether you are talking about the number of subjects or number of events; this is an area that often causes confusion.

Treatment-related adverse events

The ICH definition of an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and *which does not necessarily have a causal relationship with this treatment*. Yet the purpose of collecting AE data is to identify any signs or symptoms potentially caused or worsened by the study treatment. You may, therefore, conclude that the presentation of treatment-related AEs is the most important safety aspect of a clinical study report; in reality, it is important to be aware of the limitations of causality data.

Causality can be very difficult for the investigator to assess based only on the information available at the time, such as knowledge of the subject's health, the temporal relationship of the event to when the treatment was administered

and also on which AEs are expected according to the Investigator's Brochure. The investigator will not know which treatment the subject has received if the data are blinded. Their judgement is a best estimate and so medical writers often use wording such as 'the event was considered to be treatment-related' to reflect that this is just an opinion. Consequently, do not assume that an AE can be discounted if it is considered to be unrelated to the study treatment.

Compare the common treatment-related AEs with the common AEs you identified as being more frequent in the treated group than in the control group—are they the same? Also check how many events have a missing causality assessment—these are sometimes counted as treatment-related AEs when actually the investigator has not expressed an opinion.

Causality data help the sponsor to identify the safety profile of their treatment as it develops. By the time the data are submitted as part of an application for marketing approval, the reviewer may place less importance on the investigator's assessment of causality because knowledge will have moved on. The role of subject narratives, which are written for each SAE and other significant AEs, is to provide enough background and follow-up information so that the reader can reach their own opinion as to whether the AE was treatment-related.

Severe and serious adverse events

Not all AEs are a cause for concern; even healthy volunteers receiving placebo will report AEs. The most important AEs are those which indicate poor tolerability or a detrimental effect on health. The usual criteria that are applied are intensity and seriousness.

Intensity—mild, moderate or severe—is a subjective assessment based on the degree of discomfort or limitation experienced by the subject as a result of the AE. Seriousness, on the other hand, is based on well-defined criteria relating to the threat that the event poses to the subject's life or functioning. An AE is serious if it results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, consists of a congenital anomaly or birth defect, or is otherwise considered medically significant by the investigator. A severe event may not be serious (e.g., severe headache) and a serious event may not be severe (e.g., a mild myocardial infarction that results in admission to hospital).

A summary of the most common severe AEs can be obtained by applying a cut-off frequency to the incidence of severe events for each preferred term. All SAEs, particularly fatal SAEs, should be considered important, regardless of how common they are. Detailed information about SAEs will be included in subject narratives so a summary can be sufficient in the body of the report. ICH E3 allows for SAEs that were clearly unrelated to the study treatment to be omitted or described very briefly; this may apply if there are many SAEs due to disease progression, for example in a subject population with advanced cancer.

Make clear whether you are talking about the number of subjects or number of events.

>>> Adverse events: More than a mild headache for the regulatory writer**Adverse events leading to withdrawal**

Severe or serious symptoms may cause an investigator to withdraw a subject from treatment but mild symptoms may be enough to make a subject withdraw consent. The side effects that a subject is prepared to tolerate often depend on the amount of benefit they feel they gain from the treatment. A treatment can only be effective if subjects take it as prescribed; large numbers of withdrawals in the study treatment group could spell the end of the product's development. An imbalanced withdrawal rate between a treated and control treatment group could also affect the integrity of the study; withdrawals are rarely random—often the sickest subjects are more likely to withdraw—and so the groups will no longer be comparable.

Look out for discrepancies between the percentage of subjects whose primary reason for withdrawal was an AE and the percentage of subjects who had AEs that led to withdrawal. These numbers do not always match. For example, a subject may not be willing to tolerate the rash they have developed and they tell the investigator they no longer want to continue in the study. On the AE case report form, the investigator may tick that the AE led to withdrawal. However, on the separate case report form documenting reason for withdrawal, the investigator may tick the primary reason as withdrawn consent. Subjects lost to follow-up may also have had AEs that were part of their decision to drop out of the study. The medical writer should explain in the report the reasons for any discrepancies between the two tables, if possible.

Also remember to discuss any subjects with an AE that led to a dose reduction or temporary discontinuation of treatment, if this was permitted in the protocol. An AE that resolves after dose reduction, but then recurs if the dose is escalated again, could be treatment-related.

What to write in the discussion*Identify the unexpected*

While the discussion has to contain some of the data already presented in the body of the clinical study report, try not to simply restate the results. ICH guidance recommends highlighting 'any new or unexpected findings' so first you have to determine what AEs were expected.

Were the common AEs in your study expected in that subject population? Healthy volunteers confined to the ward of a research unit for days often report headaches and fatigue, and nasopharyngitis can quickly spread within the group. Patients, on the other hand, can be expected to have symptoms that reflect their underlying disease; even though their illness was present at baseline, symptoms that worsen or change during the course of the study will be included as AEs. Events that would be uncommon in your subject population are more likely candidates for an effect of the study treatment.

If your study is controlled and you identified any AEs that were more frequent in the study treatment group than the control group, consider whether these AEs were expected. Were they identified in the Investigator's Brochure or the

protocol as possible effects of the study treatment? Was a similar treatment difference seen in previous studies? Equally importantly, did the Investigator's Brochure highlight any safety concerns that you did not observe in your study?

You are not expected to provide an expert medical opinion; get input from the medic or the safety specialist who reviews your clinical study report. Don't be afraid to suggest discussion points in your draft report, or draw attention to any AEs you think may be worthy of note. They can always ask you to amend the text but, more often than not, they will appreciate your input. They are medical experts rather than writing experts and may not be familiar with ICH requirements.

The effect of study design

If your study did not have a control group, you may wish to compare the AE rates in your study with previous studies. Here, the effect of study design can be particularly important.

Not all studies employ the same methods for collecting AE data. Most commonly, subjects are asked an open question such as 'How are you feeling?' This puts the onus on the subject to recall any signs and symptoms, and to decide whether to mention them. Other studies prompt subjects about specific symptoms using scripted questionnaires, or diaries that subjects complete at home. Not surprisingly, the prompted collection methods generally lead to a higher rate of AE reporting. Study duration affects the incidence of AEs; most subjects will experience AEs if you monitor them for long enough. Frequent study visits give subjects more opportunity to report symptoms and less time between visits to forget them. Geographical location should also be considered; some cultures are less likely to report AEs and so the AE frequency may appear lower than in studies conducted in other countries.

Signs and symptoms observed by the investigator can be recorded as AEs, including abnormal readings for vital signs, laboratory parameters or other safety assessments that the investigator considers to be clinically relevant. The higher the number of safety assessments performed, the greater the likelihood of abnormal results being detected and reported as AEs.

A poor report may come back to haunt you

Remember that, ultimately, your clinical study report and the AE data it contains may be compiled into a Marketing Authorisation Application—and that task may fall to you. So make your future work easier by using consistent styles of data presentation across clinical study reports for the same study treatment, and by making the important findings clear. One day you may be thankful you made the effort.

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Reference:

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Structure and Content of Clinical Study Reports. E3. 30 November 1995.