EDITORIAL

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# First, Catch Your Signal!

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## 1. The Trouble with Definitions

Over the years there have been many attempts to define what we mean by a signal. We have come to the view that attempts to provide a single, concise definition cannot succeed because a signal in pharmacovigilance is not an entity. There are several signal endpoints possible that depend on a multiplicity of factors, defying a deconstructural approach. It is a little like defining 'love', which is very subjective and, even allowing for that, it seems that there are different kinds of love. No definition allows us to understand the range of love and its attributes! This does not mean that the definitions are wrong, only that they do not give a full picture.

One might start by saying that a signal in pharmacovigilance is any new information about a drug or its use that is interesting/important, and which may have some impact on the way the drug will be used. This simple concept is incorporated in all definitions, which are then expanded in a variety of ways. But the difficulty with this starting point is that a signal is part of a process that starts with an observation that arouses interest or concern. This is a value judgement by the observer, leading him or her to more thought, investigation and activity around the observation to the point where the observer feels they have a hypothesis to share with others. That point seems intuitively right to designate a 'signal' in the sense of information worth passing on to others, for them to know about and to consider further action. But all this is vague and subjective: what is 'interesting' or 'important'? What kinds of 'thought' and activity' are required? How does one decide whether one has sufficient information and argument to warrant telling others?

There is another problem arising from the wide use of 'signal' and 'alert'. Some would say that a signal is the point at which one individual starts to do more investigation, and an alert is the point at which one tells others about the result (who the others are is not clear, but seems to be usually used for the wider health professional audience). Some people use 'signal' and 'alert' in the opposite sense, but we will not complicate matters by mentioning 'alert' further!

We propose that a signal can only be understood by answering the following questions: What do I think is an important observation affecting drug use and patient safety? How do I find these observations and consider them? How do I know when I have found enough for a signal? What should be done with the signal? These questions can be considered both generally and in relation to an individual case.

## 2. What Do I Think Is an Important Observation Affecting Drug Use and Patient Safety?

A useful guide is to consider whether an observation might improve the use of a drug for some patients, and how the new information should be developed to make it optimal.

It is important to take into account how different stakeholders might need to use the information. One challenge is that there are many potential useful bits of information and little time to consider them all, but the above consideration is surely helpful in making priorities.

The context of the signal reviewer's situation and experience are critical and, if we are concerned with case reports, this also applies to

the reporter. Only those factors they feel are of interest and importance to them will stand out, and no signalling system can be free of such outset bias. These personal preferences may range from medical or pharmaceutical specialization or attitudes to their job and whether they view it from a company or public health perspective.

We have tended to emphasize the qualitative aspects of signal detection in the past, since case reports cannot be easily used quantitatively because of under-reporting and lack of knowledge about numbers exposed to the drug, but we have always been concerned about large numbers of reports. Now quantification of suspected adverse drug reactions is easier, using longitudinal databases or disproportionality in large databases as part of the signal process. Whether the observed rates in a dataset are of concern is still largely a matter of judgement, even when quantitative methods are used.

We also need to consider signals of systematic medical error, of overdose, of those due to counterfeit products and adverse effects due to drug interactions as important. These medical disasters have not been considered as a main part of pharmacovigilance in the past, but information on such safety matters has always been gained during the process of pharmacovigilance, and cannot be ignored. Now, there are other groups of professionals working in these areas and cooperation with them is vital.

It might well be that a reviewer who is unconcerned about an apparently minor clinical event may change their view if there is a large number of reports that are of good quality and without obvious alternative causation. Conversely, poor quality and probable confounding, even when there are many reports or even a comparative study, may lead to reluctance by the most enthusiastic reviewer to believe they have a signal. In this respect, the process from finding an interesting observation to turning it into a useful hypothesis, and therefore a signal, is iterative. This may involve waiting and searching for better data or other supportive information.

It is possible to set rules and standard operating procedures for finding signals, but we believe they may be limiting and harmful. If one is setting out to find the unknown, to cling only to the predictable is a mistake.

It seems clear that neither one person nor one process can be sure to detect useful new signals, and the only way forward is an eclectic approach that can only be fully realized using the best communication possible of hypotheses and data between all those interested in signals. We should be open about hypotheses and contemplate other colleagues' opinions during their development. This means that we should allow normal scientific development to operate, sharing ideas, and not work only within closed bureaucratic systems.

## 3. How Do I Find These Observations and Consider Them?

All signals depend upon data and how to look at it, but even the first registration of data is likely to be a poor record of the clinical event and all the surrounding factors that lead a patient to make their concern known to health professionals. Further information is lost in the clinical diagnosis and its transcription to medical description or diagnosis, and ultimately to the terse abbreviation of the event into its stored form using predetermined, hierarchical terminology. This multiple translation is bound to distort and omit information contained in the first record of suspicion of a problem in a patient. Sometimes information may be added during this process of recording, which may certainly be a helpful observation, although we should also consider the possibility that it may be wrong, misleading and unhelpful. We should also bear in mind that various kinds of people may be involved in rendering a patient's complaint into stored information in a database, that parts of the process may involve auto-encoding, and that sometimes the data may be merged from different sources by data linkage. Some diagnoses are more likely than others to be distorted: depression or perhaps a syndrome, where one is not sure that all the criteria for the diagnosis have been met, are more likely to be misrepresented than spina bifida, an awful condition, but also a diagnosis with stark clarity.

Hypotheses come from this heterogeneous mess of data, and the imperfections apply to all observational data from case reports, through published case series, to registers of longitudinal data. The different methods we may apply to sifting through this variable data start with individual case report review and reappraisal of accumulated similar cases. It may be that it will take quite a lot of reports linked to a new drug from a known class before new information attracts anyone's attention, such being the effect of expectancy on one's alertness. In the same way, reports with events having a high background incidence in unexposed people may also not attract attention.

What applies to human review is also true of the use of knowledge finding (data mining) by computer algorithms using disproportionality, depending, as the process does, on a distinction from the background of reports on other drugs in the database. Well known adverse reactions to common drugs may mask the same common reaction linked to a new drug for a long time. Neither humans looking at the data nor unsupervised signal detection are reliable in these situations.

Obviously this problem can be overcome by screening for common drug-related adverse reactions as a routine. Those that argue for a solely epidemiological approach with large prospective cohorts or observational studies on longitudinal data still need to decide what to look for: choosing a preselected set of commonly occurring drug-related events will be a large limitation to finding new and important safety concerns. Those that argue for unsupervised data mining (knowledge detection) can only find quantitative disproportionality of events linked to a particular drug or drugs against a variable background incidence of the event. This is also limiting, particularly if change in events over time is not factored in, and if the nature of the background data is not understood.

With some reservation, it seems reasonable to suggest that clinical events related to drugs are more likely to be signals if they are seen in different datasets, compiled in different ways, and identified by different people and tools: that is really the strength of pharmacovigilance, even though it is possible that biases and confounding may affect them all.

## 4. How Do I Know When I Have Found Enough for a Signal?

This is to decide whether the data is 'worthy' of constituting a signal and whether a hypothesis of a causal relationship between drug and event is plausible. This is the major area for debate about signals, and includes considerations around data quality, the presence of reporting biases, confounding, and more factors that influence the strength of association between a drug and a clinical event. Then there is the seriousness of the event to consider, which forms a backdrop to all our thoughts on signals, essentially influencing us to be less dismissive as we do our evaluations. No signal is complete without a complete analysis and description of the strengths and weakness of the data and methodology.

We have discussed the vagaries and varieties of those who review data and then the data itself. Even though the signal process has many problems, it does carry advantages. Those who have an inquisitive and critical attitude and look at data in different ways, and, using all the tools they have available, will spot patterns and discrepancies in data and use their experience and skills to propose a hypothesis. Moreover, collecting data about new adverse or positive outcomes from drug use in clinical practice is a sound way to make progress in drug development, and certainly to improve therapy. To look at data as it is acquired and to make hypotheses thereon is a suitably humanitarian, ethical and active approach to caring for the sick. In this respect, we should tolerate signals that may ultimately prove false. On the other hand, unlikely signals cause extra work in considering them and may damage the reputation of a drug to the detriment not only to the commercial market but to some or all patients who may benefit from it.

One never really knows when one has found a first signal other than by knowing that the data and logic involved in it are sound enough for debate and further action, and we emphasize that a hypothesis is the endpoint of the signal process.

A good signal is a hypothesis with all the elements that contribute to it mentioned, so that another observer may debate with the proposer and agree or not that a case has been made for a signal.

Signals are only 'proved' later if they are upheld by other investigation; this is simply a normal part of science.

## 5. What Should Be Done with the Signal?

Signals are, in various degrees, compelling in their data and logical arguments, but they are never endpoints. In some serious situations they may lead to regulatory action because delay may compromise patient safety if the proposed adverse reaction is serious and seems frequent. In these situations, the nature of the hypothesis and reasons for action must be made clear to those who make, prescribe, dispense and use the drug involved. More often a signal should lead to further prompt action to confirm or refute it by other work. The new work should be undertaken in a way, and with data, that deals with problematic parts of the signal, which implies that the hypothesis should ideally be framed in a way that allows further study: a non-disprovable hypothesis has little value other than causing a scare.

It is surprising how infrequently definitive studies are carried out to investigate signals, but this probably reflects on the less serious nature of many signals and also that adverse reactions are generally uncommon, which makes epidemiological confirmation, at least, more difficult. It is a shame that, for the most part, we do not know the overall predictive value of our signals, and with new methodology and data available for signal detection this is an area for critical examination in the near future.

We are often asked by others 'what is a signal'. This brief description of some attributes of signals, particularly the signalling process, will be unsatisfactory to those who need clarity in their lives, since there is naturally uneasiness in dealing with the new and untested, but if we do not find new signals (make new hypotheses) progress is impossible. We hope you will be successful in 'catching' useful signals.

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