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Defining 'Signal' and its Subtypes in Pharmacovigilance Based on a Systematic Review of Previous Definitions

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Abstract

Having surveyed the etymology and previous definitions of the pharmacovigilance term 'signal', we propose a definition that embraces all the surveyed ideas, reflects real-world pharmacovigilance processes, and accommodates signals of both harmful and beneficial effects.

The essential definitional features of a pharmacovigilance signal are (i) that it is based on one or more reports of an association between an intervention or interventions and an event or set of related events (e.g. a syndrome), including any type of evidence (clinical or experimental); (ii) that it represents an association that is new and important and has not been previously investigated and refuted; (iii) that it incites to action (verification and remedial action); (iv) that it does not encompass intervention-event associations that are not related to causality or risk with a specified degree of likelihood and scientific plausibility.

Based on these features, we propose this definition of a signal of suspected causality: ''information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to justify verificatory and, when necessary, remedial actions.''

This defines an unverified signal; we have also defined terms – indeterminate, verified, and refuted signals – that qualify it in relation to verification.

This definition and its accompanying flowchart should inform decision making in considering benefits and harms caused by pharmacological and nonpharmacological interventions.

''Everybody can make distinctions: it is the lexicographer's business to make broad definitions which embrace them.''

— Dean Liddell

1. The Importance of Clear Definitions in Pharmacovigilance

The importance of clear and consistent communication in drug therapy, so that patients, prescribers, manufacturers and regulators can understand each other, has been emphasized,[1-3] and terminology can have profound impacts according to the interpretations of legislators, judges and juries. In addition, lack of clear and agreed definitions is an impediment to formulating conceptual frameworks necessary for process improvement. In the absence of clear definitions, expert working groups and others may spend considerable time and resources in repeating or initiating activities that may not achieve clear resolutions.

Considerable definitional ambiguity remains in the use of the term 'signal' in pharmacovigilance,[4] and vigorous debate about it continues, as one of the authors of this paper (MH) has observed when participating in various expert working groups. As signal detection is a front-line activity, this is of concern. The purpose of this review is to clarify the definition of terminology for signals. To do so, we have reviewed existing definitions, extracted the essential features that they have expounded, and synthesized those features in a way that maps on to real-world pharmacovigilance processes. In this way we hope that all those who have to confront the problems of assessing adverse drug reactions, particularly those who are not experts in the field, can understand the nature of different types of signal and their practical relevance.

Formulating simple definitions in pharmacovigilance can be difficult. Firstly, pharmacovigilance involves probabilistic and subjective aspects. This means that different individuals, faced with the same information, may come to different conclusions. Secondly, pharmacovigilance relies on qualitative and quantitative information,[5] the former from spontaneous reports and the latter from secondary calculations that typically homogenize the data and potentially ignore unique clinical information.[6] Thirdly, it involves stochastic and non-stochastic phenomena. For example, three reports of a serious medical event could reflect either a chance reporting spike in the absence of causality or a true underlying causal relationship. Apparently identical safety messages or 'signals' may thus reflect stochastic noise, non-stochastic information with safety implications, and non-stochastic information without safety implications. Any definition of 'signal' in pharmacovigilance should take these problems into account.

Before starting, we note that the term 'safety signal', although widely used, is misleading – traditionally, signals in pharmacovigilance imply *lack* of safety, and there is in any case no satisfactory definition of 'safety'.[7] Furthermore, as we shall show, a pharmacovigilance signal is evidence of a suspected causal association sufficient for hypothesis formulation. 'Suspected' means ''that one suspects to exist, or to be such; imagined possible or likely'' (*Oxford English Dictionary*)[8] Thus, 'suspected' links subjective and evidential elements without implying proof. Therefore, we prefer the term 'signal of suspected causality'. This term makes no assumptions about what is caused (i.e. accommodating signals of both beneficial[9] and harmful effects) or by what type of intervention. It could be used to refer to any intervention-event pair, where the intervention is not a drug or a biologic but, for example, a device, cell therapy, gene therapy, or a surgical or other procedure, and the event is a benefit or a harm. Thus, the definition that we propose in the context of the methods that we shall describe is generalizable to other contexts.

2. The Process of Definition

Lexicographers have striven repeatedly to produce clear, unambiguous and accurate definitions for even the simplest definienda, despite

great difficulties,[10] and sometimes with highly controversial results.[11] In the 18th century, definition was regarded as stemming solely from etymology, but by the time James Murray and his colleagues were ready to begin work on the *New English Dictionary* (later to be called the *Oxford English Dictionary*) it was recognized that it was also important to take into account the history of the usage of the definiendum,[12] a principle that was enshrined in the lexicographic rules that they devised, reflected by Richard Chenevix Trench's epigrammatic observation that "every word should be made to tell its own story."[13] In doing so, they took their cue from Aristotle, who had observed in the *Topika* that "a definition should refer to what is prior and better known."[14]

Since, as Aristotle also pointed out, a definition is intended to inform, a definition that is formulated by considering what is already known will not inform those who are ignorant of that knowledge.[14] Therefore, in attempting to formulate a definition of 'signal', by which we mean 'signal of suspected causality', we shall review its etymology and the ways in which it has previously been defined, leaning in particular on definitions that are commonly cited or contained in major pharmacovigilance reviews or guidance documents of major pharmacovigilance organizations, and keeping in mind the needs of specialists in the field. This lexicographic method follows that adopted by Aronson and Ferner in their assessments of drug safety terminology[1] and medication errors.[2]

3. 'Signal': Etymology and Definitions in Standard English Dictionaries

The word 'signal' comes from the Latin word 'signum'. It originally derived from the hypothetical Indo-European root SEK, to cut, which also gave words such as venesection, sickle, scratch and perhaps even sex, which divides men from women. A signum for the Romans was a mark cut or impressed into a surface, e.g. by a signet ring. It then came to mean any sign in general, and in military use it meant a sign, usually prearranged, for the initiation of an action.

It is not irrelevant to add that the word 'risk', although of obscure origin, may be a member of the same family, possibly deriving from the Latin word resecare, which meant to cut back and was used to describe, among other things, a ship's being cut asunder by rocks.

'Signal', used as a noun, is defined in Webster's online dictionary[15] as:

1. Any communication that encodes a message; "signals from the boat suddenly stopped."
2. Any incitement to action.

If the first of these definitions was applied to pharmacovigilance, it would make every report a signal. But a pharmacovigilance signal is more than just a message ("an oral, written, recorded, or electronic communication sent from one person, group, etc., to another", *Oxford English Dictionary*), as we shall see when we examine principles and existing definitions. The second definition reflects the key idea that Aronson and Ferner[1] have identified as defining a signal – the incitement to formal action, like the Latin military signum. The *Oxford English Dictionary* ratifies this idea and adds the idea that a signal can contain a warning:

3. A sign agreed upon or understood as the occasion of concerted action, esp. one ordering the movement of troops or ships; also fig., an exciting cause.

4a. A sign or notice, perceptible by sight or hearing, given especially for the purpose of conveying warning, direction, or information.

And when it sets the word in the context of an electrical signal, the *Oxford English Dictionary* also includes the idea that a signal contains information about its source:

4c. … a current or wave whose presence is regarded as conveying information about the source from which it comes.

A signal therefore conveys specific information about its source and spurs one to action or even demands it (e.g. a traffic signal).

We are aware of the use of the term 'signal' in other fields, such as information theory,[16] electrical engineering, consumer product safety and meteorology. However, none of these uses adds anything of importance to this exposition.

4. Existing Definitions of 'Signal' in Pharmacovigilance

4.1 The WHO

The WHO has defined 'signal' as ''Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented.''[17]

A limitation of this definition is that it potentially admits as a signal any report that does not violate known scientific laws or principles. The definition is not self-contained, being followed by a qualifier that stipulates that ''usually more than one case is required….'' This qualifier is important, because it implies that the information content of the signal must sufficiently reduce uncertainty to justify some action, and therefore partially mitigates the former limitation. This should be part of the definition.

It is not clear from the statement that ''the relationship [should be] unknown or incompletely documented'' whether this refers to the local analyst, organizations formally charged with safety surveillance, or the current state of collective scientific knowledge. Since no knowledge is ever completely documented, this is probably one aspect of the definition that may not be nailed down with absolute precision, and probably should not be included. However, originality is an important part of a signal of suspected causality and should be included in any definition.

Lindquist has appended three qualifying 'notes' to the WHO definition of signal,[3] of which note number one is new, specifying that the reported association ''is considered important to investigate.'' This is ambiguous, because it does not specify whether it refers to the clinical importance of the signal *per se*, or the weight of evidence that supports it, both of which are relevant, or to other possibilities. The note emphasizes the extent to which subjectivity is involved in assessing the importance of a signal.

In summary, there are two key features of this definition: the information that is reported and the possibility that there is a causal relationship (the relationship being [previously] unknown or completely documented). It could be argued that virtually any information would be considered a signal under this definition, including every spontaneous report, even though experts in the field know that this is not the intent.

4.2 Meyboom et al.

Meyboom et al.[18] have written that ''A signal in pharmacovigilance is more than just a statistical association. It consists of a hypothesis together with data and arguments, arguments in favour and against the hypothesis. These relate to numbers of cases, statistics, clinical medicine, pharmacology (kinetics, actions, previous knowledge) and epidemiology, and may also refer to findings with an experimental character.''

This is not, strictly speaking, a definition, but a description. One useful aspect of this formulation is that it emphasizes that signal detection incorporates a strong subjective element (hypothesis and arguments) that transcends a mechanized process. However, although a signal may be identified because of data and arguments, it does not itself consist of ''a hypothesis together with'' data and arguments, as their statement says it does. The formulation does not address ''incitement to concerted action'' as a distinguishing feature, and the requirement for both data and arguments implies that not all signals establish a suspected risk that requires formal verification. However, we believe that a signal should be associated with a degree of probability that warrants further action.

4.3 Council for International Organizations of Medical Sciences (CIOMS) IV and CIOMS VI

In the report of the Fourth Working Group of the Council for International Organizations of Medical Sciences (CIOMS IV),[19] the following definition of 'signal' was given: ''A report (or reports) of an event that may or may not have a causal relationship to one or more drugs; it alerts health professionals and should be explored further.'' This definition adds the

possibility of a multiplicity of drugs in a single signal, implying drug interactions or non-decidability about attribution. It also formally includes incitement to action and recognizes the need for verification as a part of the definition. CIOMS VI[20] included other explanatory text: "A signal … can refer not only to a new (unexpected) and potentially important event, but also to an unexpected finding for an already known event … A signal is not a confirmed finding but is generally referred to as an hypothesis-generating situation that must be validated ('signal strengthening') or disproved." These points, not part of the definition itself, should be included.

4.4 The US FDA

The following statement appears in the US FDA's guidance on *Good Pharmacovigilance Practices and Pharmacoepidemiological Assessment*:[21] "A safety signal refers to a concern about an apparent excess of an adverse event compared to what would be expected. Signals can arise from post-marketing data and other sources, such as preclinical data and events associated with other products in the same pharmacologic class. It is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use. Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event."

This description incorporates the qualitative notion of a 'concern', which acknowledges a subjective aspect of signal detection. It acknowledges the possibility that a signal may emerge from a single report and highlights the need for further investigation. However, it does not explicitly acknowledge that signals may be identified from qualitative clinical information; it does not specify who expresses the concern; nor is it clear how quantitative expectedness is defined. Finally, as with other formulations, it does not accommodate signals of unanticipated therapeutic benefits.

4.5 The Medicines and Healthcare Products Regulatory Agency

A signal is defined in Metters'[22] report for the Medicines and Healthcare products Regulatory Agency (MHRA) on access to the Yellow Card reporting system in the UK as "an indicator or reported information that suggests a possible causal link between an adverse event and a medicine, when the postulated link was previously unknown or poorly documented." This is similar to the WHO definition quoted in section 4.1.

4.6 The New Zealand Intensive Medicines Monitoring Programme

The New Zealand Intensive Medicines Monitoring Programme (NZIMMP) definition states: "In practice, events are treated as signals if they arouse a strong suspicion of a hitherto unrecognized adverse reaction. This may be the result of a single case report of high quality with a positive dechallenge and rechallenge ("definite" relationship), regarded as an index case, or a cluster of cases where the relationship that can be established may be of lesser strength. The number of reports and the strength of the relationship may be such that causality can be confirmed with the data on hand."[23] Here we see another expression of the subjective element in pharmacovigilance, in this case arousal of suspicion, which leads to the perceived need for formal action. Conversely, this process might lead to the conclusion that a signal does not exist. This definition also acknowledges the possibility that a single anecdote may constitute a signal.

5. Progressing From Message to Signal

At some point there is a transition from regarding a piece of information as simply a message about harm/unexpected benefit to information qualifying as a signal of suspected causality that corresponds to a hypothesis. Figure 1 illustrates the processes whereby pharmacovigilance messages are transmuted into signals.

After certain objectively defined procedures (which in spontaneous reporting systems would

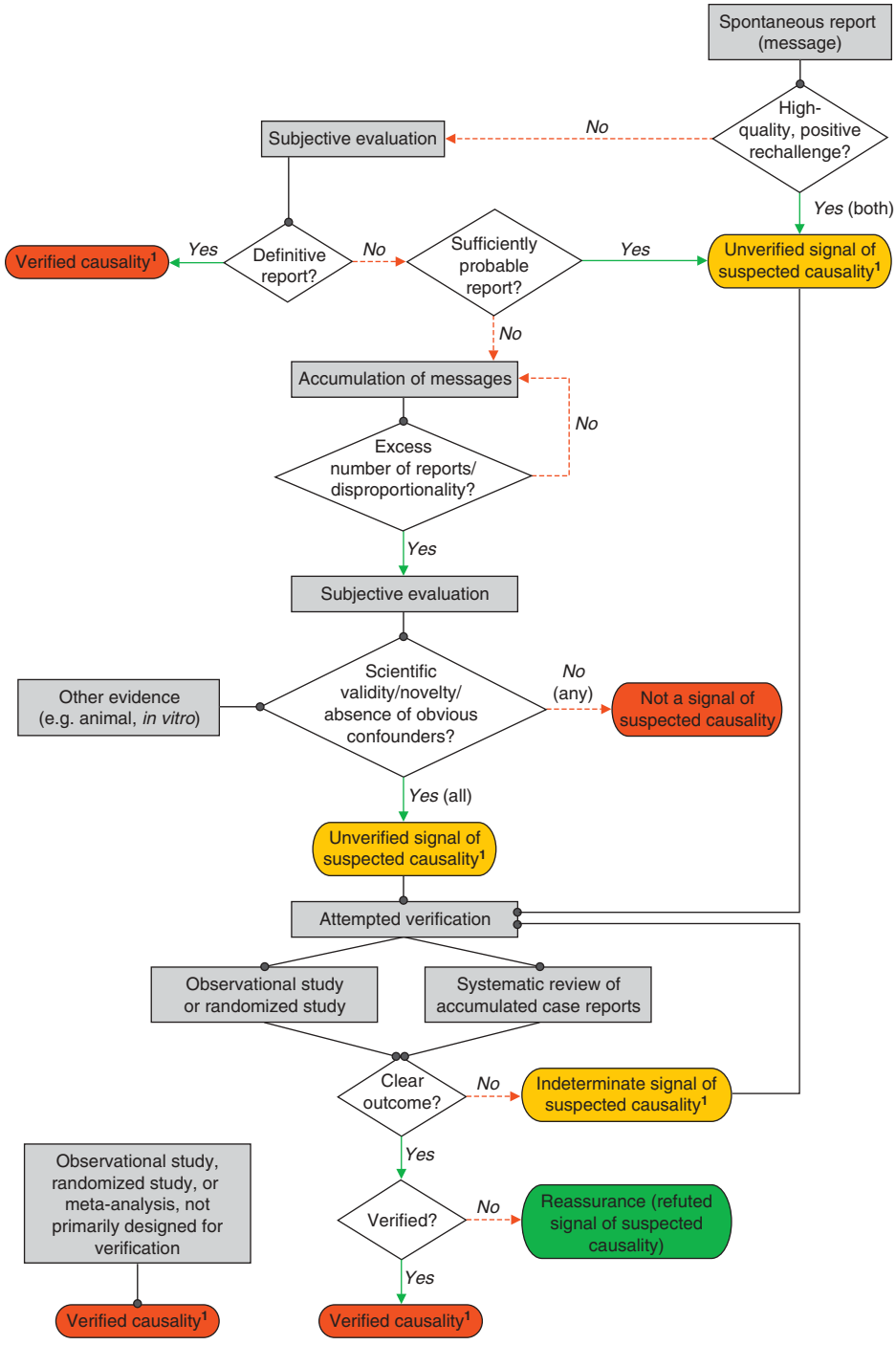

Fig. 1. The ways in which different types of signals of suspected causality emerge from real-life pharmacovigilance processes or other methods. The unconnected parallel track (bottom left) represents a signal that may emerge from an independent study (observational or experimental) that was not originally intended to investigate an adverse reaction. **1** Remedial action may be taken in any of these cases.

include registration/logging in, triage and data entry), subjective judgements are often required in assessing potential causality and then deciding about amendments to labels and revocation of licences, although in recent years attempts have been made to bring more objectivity into these procedures.

It is important to note that a single report or a few reports (messages) can sometimes constitute a signal of suspected causality. Firstly, an event that has been subjected to well documented, high-quality, positive rechallenge, involving objective signs that are distinct from the natural history or complications of the disease being treated and that are unlikely to have competing explanations, can constitute a signal, but one that requires verification.[24,25] Alternatively, a definitive ('between-the-eyes') reaction (e.g. species- and/or strain-specific systemic infection after live immunization) would also constitute a signal, but a verified signal of causality;[26] in such a case, simple evaluation of the event leads to verification. A single report can even lead to disproportionate reporting.[27]

For other reports, various factors can be considered, including the clinical and epidemiological characteristics of the event and case-specific information that is commonly used in assessing causality. For example, some designated medical events that are rare and serious and have a high drug-attributable risk that has been attributed to several pharmacological therapeutic classes may be considered to be signals after only one or a few reports (e.g. toxic epidermal necrolysis, torsade de pointes), i.e. they have a relatively high *a priori* or 'pre-test' probability of a causal drug-event association. In some cases they may be near pathognomonic events.

If none of these applies, accumulation of messages is required, after which further subjective assessment will be required to determine whether the association is scientifically valid, novel, important and without clear confounders. Some of these factors will increase the probability that a drug-event pair represents a suspected adverse drug reaction, allowing the elevation of a message or set of messages to the status of a signal of suspected causality. Alternatively, a signal may emerge from an independent study (observational or experimental) that was not originally intended to investigate an adverse reaction; this is indicated by the unconnected parallel track in figure 1 (bottom left).

6. Pharmacovigilance Actions to be Taken After the Identification of a Signal

The quality and quantity of information contained in a signal (its value) determines the nature of the appropriate action to be taken. This should be either some type of formal investigation intended to verify or refute the signal, or a decision not to perform further verification, if initial evaluation suggests that there is already a high degree of certainty. Verification is followed by remedial actions (e.g. a change in formulation, a change in labelling or withdrawal of the drug). Note that precautionary remedial action may be taken even if the signal remains indeterminate and has not been fully verified (e.g. because to do so would be impractical) [figure 1]. Furthermore, although many remedial actions are instituted by regulatory authorities, not all are; for example, a remedial action may take the form of a decision to publish a less formal warning (e.g. in a letter to prescribers) and to continue monitoring.

7. Sources of Information in Pharmacovigilance

The data sources that comprise the substrate for identification of signals of suspected causality include individualities (i.e. single anecdotes or case series), observational studies (such as case-control studies) and experimental studies (randomized trials or meta-analyses). Information from nonclinical sources, such as animal and *in vitro* studies, can also contribute (figure 1). These different sources of signals need to be recognized in any definition of 'signal'.

7.1 Individualities

We define individualities as single reports or accumulations of such, including anecdotal reports or case series, whatever their source. About 30% of the world literature on adverse drug reactions is in the form of such reports.[28]

Occasionally, a single anecdotal report, or no more than a handful of such, can be sufficiently

definitive to be regarded as a signal of suspected causality, as discussed in section 5.

When a sufficient number of individual reports have accumulated, disproportionate reporting may be detected, and this in turn may subsequently lead to the identification of a signal of suspected causality. An example is illustrated in figure 2, which shows the application of one specific data-mining metric/threshold combination to reports of the drug + event association of topiramate + glaucoma, resulting in disproportionate reporting.[29] At a certain point the messages (reports) that had accumulated and resulted in disproportionate reporting were considered to require formal investigation/remedy, given the probability of a causal relationship and the nature of the event, which was novel and of clinical importance. It was also scientifically plausible, being attributable to inhibition of carbonic anhydrase and/or ciliary body swelling, in the absence of obvious confounders. In other words, it was a signal of suspected causality.

However, not all cumulative associations of this sort should be regarded as signals of suspected causality requiring formal investigation or remedy. Some may be scientifically implausible, e.g. leukaemia occurring the day after exposure to a drug. Others may lack novelty or be of no importance to the patient or public, or may not even command regulatory or clinical attention. Yet others may have arisen because of potential confounders. For example, when the drug-event association minoxidil-alopecia emerged (figure 3) it was clear that this was unlikely to be a true signal, since it had been confounded by the association between the drug and its indication, a common scenario in pharmacovigilance. The alternative explanation, that minoxidil caused paradoxical alopecia, was highly unlikely. Any definition of signal must take confounders of this sort into account, so that cumulative messages are not necessarily elevated to the status of signals of suspected causality, requiring formal investigation or remedy.

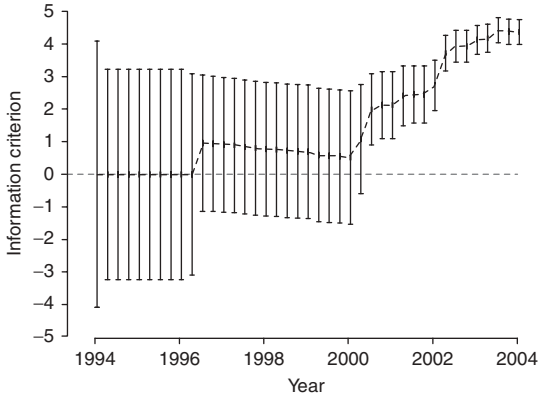

Fig. 2. A data-mining/disproportionality analysis of topiramate and glaucoma in the WHO database, using the Bayesian Confidence Propagation Neural Network; the information criterion, shown as mean ± 2 standard deviations, crossed the disproportionality threshold of 0 during the second quarter of 2000 (reproduced from Bate et al., Uppsala Monitoring Centre,[29] with permission).

7.2 Observational Studies

Signals of suspected causality can emerge from observational studies. For example, the reported observation that paracetamol (acetaminophen) potentiates the effect of warfarin first emerged from a case-control study.[30] Such signals may or may not need further verification.

7.3 Randomized Studies

In some cases the signal first emerges from a randomized controlled trial (RCT). For example, evidence that rofecoxib causes an increased risk of cardiovascular disease first emerged from an RCT,[31] and could not have done otherwise. Such signals will often be considered to need no further verification.

8. A Proposed Definition of a Signal of Suspected Causality

From this analysis of previous definitions and principles, essential features emerge that should inform a definition of the term 'signal of suspected causality', whether beneficial or harmful, pharmacological or nonpharmacological. These features are listed in table I, in which we also show which features have been covered by the previous definitions or descriptions listed in section 4. None of the previous definitions contains all of the important features. Although the definition in

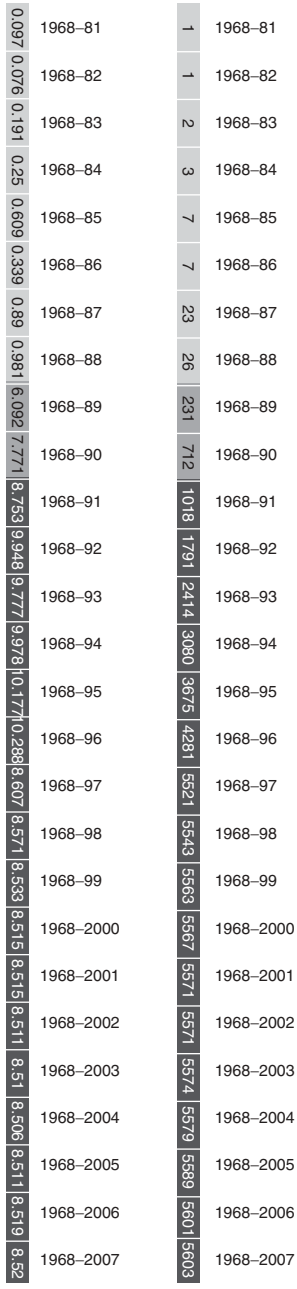

Fig. 3. A data-mining/disproportionality analysis of minoxidil and alopecia in the US FDA Adverse Event Reporting System (AERS) database using the multi-item gamma-Poisson shrinker; a minoxidil formulation was first approved in the US to treat male-pattern baldness in 1988 and by 1989 there were 231 drug-event reports (right panel), which crossed a disproportionality threshold of 2.0 at the fifth percentile (left panel).

CIOMS IV plus the notes in CIOMS VI together come very close, they do not explicitly accommodate signals of unanticipated therapeutic benefit. In addition to these features, any definition should not encompass drug-event associations that are not judged to be of sufficient likelihood.

Based on these features, we propose the following eclectic definition of a signal of suspected causality:

''Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to justify verificatory and, when necessary, remedial actions.''

9. Subtypes of Signals of Suspected Causality

This definition implies that a signal of suspected causality is unverified (figure 1). However, a single type of signal of suspected causality is not adequate if we are to have a close mapping between definition and processes in pharmacovigilance. Figure 1 illustrates how different subtypes of signals of suspected causality arise as outcomes of the usual processes in pharmacovigilance. Based on this analysis, we propose the following modifiers:

- indeterminate: a signal of suspected causality that has been subjected to attempted verification and has been neither verified nor refuted;
- verified: a signal of suspected causality that has been verified either by its nature or source (e.g. a definitive anecdote or a convincing association that has arisen directly from an RCT) or by formal verification studies;
- refuted: a signal of suspected causality that has been subjected to attempted verification and has been refuted.

10. Signal of Disproportionate Reporting

Finally, we mention a specific distinct use of the word 'signal' in the term 'signal of disproportionate

Table I. Features that should inform a definition of the term 'signal of suspected causality' and their inclusion in previous definitions

Feature	1	2	3[a]	4	5	6
1. A signal can be generated by a single report, but more often requires several reports of an association between an intervention (e.g. a drug) or interventions and an event or set of related events (e.g. a syndrome)			✓	✓		✓
2. Such reports include any types of evidence, ranging from anecdotes to the results of randomized studies and including animal and *in vitro* evidence; although a single anecdote can occasionally constitute a signal, usually more than one case is required			[✓]	✓		
3. A signal represents an association involving an intervention or interventions and an event or connected set of events, which has not been previously investigated and refuted, and which, if verified, would represent a new causal association or a new aspect of a known association	✓		[✓]		✓	✓
4. The event or events should be of importance to the patient and/or the public	✓		[✓]			
5. A signal may include a scientifically plausible hypothesis about the source of the signal (i.e. mechanism), as part of the subjective processes that elevate a collection of messages to a signal of suspected causality		✓	[✓]			
6. A signal incites to action, namely verification plus remedial action			✓	✓		
7. Signals of unanticipated potential therapeutic benefits,[b] as well as harms, are explicitly accommodated						

a The bracketed items refer to the notes in the Sixth Working Group of the Council for International Organizations of Medical Sciences (CIOMS VI), not to the CIOMS IV definition of a signal.

b Examples of adverse events that have subsequently led to therapeutic benefits include hirsutism due to minoxidil, hypoglycaemia due to sulfonamides and penile erection due to sildenafil.

1 = WHO;[17] **2** = Meyboom et al.;[18] **3** = CIOMS IV/VI;[19,20] **4** = FDA;[21] **5** = MHRA;[22] **6** = NZIMMP.[23]

reporting' (SDR),[32] a term used to refer to the numerical outputs of disproportionality analysis, which has been frequently used in the published literature and incorporated by one major regulatory authority, the European Medicines Agency (EMEA), into guidelines on the use of statistical approaches to signal detection.[33] Because the observation of an SDR may depend on the algorithm/model used, assumes that the highlighted terms accurately reflect the suspicions of the reporters, as opposed to a local coding convention, and may be due to causality, statistical noise, or reporting artefacts, alone or in combination, this is not a signal of suspected causality as defined here, but evidence of possible increased reporting of an intervention-event association, without explicit consideration of detailed patient-level clinical information. As the minoxidil-alopecia example in section 7.1 shows, an SDR does not necessarily constitute a signal of suspected causality.

We are aware that there is potential for confusion between what we have defined here as a signal of suspected causality and what has been called an SDR. This is related to the tradition of using the term 'signal' in pharmacovigilance without further specification. This difficulty could be avoided by replacing the term 'signal of disproportionate reporting' with another term, such as indicator, measure, sign, or statistic of disproportionate reporting (IDR, MDR, or SDR). We have no personal preference; each of these terms would acknowledge the lack of an objective and universal definition of the level at which reporting becomes disproportionate and would maintain logical consistency by differentiating what is observed (a numerical output) and what that output suggests (disproportionate reporting).

11. Conclusions

By considering the etymology and previous definitions of 'signal' in pharmacovigilance and other fields, and the desirability of a definition that maps closely to real-life pharmacovigilance processes, we have offered a definition of 'signal of suspected causality' and subtypes of such signals. We believe that our proposed definitions and the flowchart that accompanies them (figure 1)

should help in making decisions about signals in pharmacovigilance and in other areas in which non-pharmacological interventions can cause benefits or harms.

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