

Uppsala Monitoring Centre Research Conference

# Causality Assessment in an Evolving Pharmacovigilance Landscape

## – Conference Report

May 24–25, 2012, Uppsala, Sweden





↩ Dr. Marie Lindquist Prof. Samir Okasha ↪





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THIS PUBLICATION REFLECTS THE VIEWS  
AND EXPERIENCES OF THE LECTURERS,  
AND NOT NECESSARILY THOSE OF  
THE COMPANIES.

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## Welcome address

Dr. Marie Lindquist

Director, Uppsala Monitoring Centre, Uppsala, Sweden

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In welcoming delegates to the UMC Research Conference 2012, Dr. Lindquist affirmed the critical part that causality assessment plays in the search for better science and safer use of medicines.

She referred to her childhood fascination with the great detective Sherlock Holmes and his belief that the truth, however improbable, could be discovered when the impossible had been eliminated. But was there such a thing as essential truth in criminal or medicinal investigation? Was there a risk that the search for certainty could lead to fruitless and distracting pursuits?

Bertrand Russell challenged the deterministic view that postulates that ‘whenever cause A occurs, then effect B follows’ and current thought recognises that such certainties, especially without taking account of intervening variables, are rare in real life.

Having abandoned simplistic deterministic causality, Dr. Lindquist noted that we have to face complex assessments of intricate functional relationships, often with key information missing. Scientists are now grasping at understanding situations sufficiently and with enough (but rarely sufficient) certainty to feel confident about important decisions. Although the principles of causality assessment may be relatively straightforward, the application of those principles to an individual case is a philosophical as well as a scientific challenge. Falsely attributing a harmful effect to a medicine, or a treatment, will cause a lot of damage, as was demonstrated by the MMR vaccination scare.

However, even when the truth cannot be unearthed to prove a causal relationship in the individual case, finding out as much as possible about WHY a particular

patient did not do well on a particular treatment adds to knowledge, and may help protect future patients from unnecessary suffering.

Although there might remain more questions than answers, Dr. Lindquist hoped that the conference would generate new insights through a process of open and lively exchange of views.

# Causality in sciences: a philosophical survey

Prof. Samir Okasha

University of Bristol, UK

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Prof. Okasha gave an overview of the historical development of ideas about causality in science and philosophy. Taking his starting point in the empiricism of David Hume, he discussed the ideas of 18<sup>th</sup> and 19<sup>th</sup> century philosophers, as well as later contributions regarding causality vs. correlation, randomized trials and the distinction between observational and experimental data.

The 18<sup>th</sup> century philosopher David Hume (Fig. 1) defended an empiricist view of human knowledge and articulated an elaborate theory of causation based on the notion that all human knowledge ultimately rests on experience and observation. In the first of three main theses, Hume states that causal relations are not knowable a priori. As an example, Hume asked how someone who never in life had observed a moving object colliding with another, thereby imparting motion to it, could understand the game of billiards. The second thesis states that causal relationships are never directly observable. Events can be observed to be conjoined, i.e. coupled with each other in time, but never actually connected. A brick thrown at a window, and the subsequent shattering of glass, for instance, are conjoined events, but not necessarily causally linked – something else could (theoretically) have caused the glass to break. The conclusion is that knowledge of causation can only be arrived at by inference. Hume's third thesis put forward the somewhat controversial idea that recognition of causal links is, in fact, a psychological effect. Observing a long sequence of conjoined events, such as the sun setting and rising, leads us to regard one as the inevitable accompaniment of the other, although all we actually have is a correlation pattern.

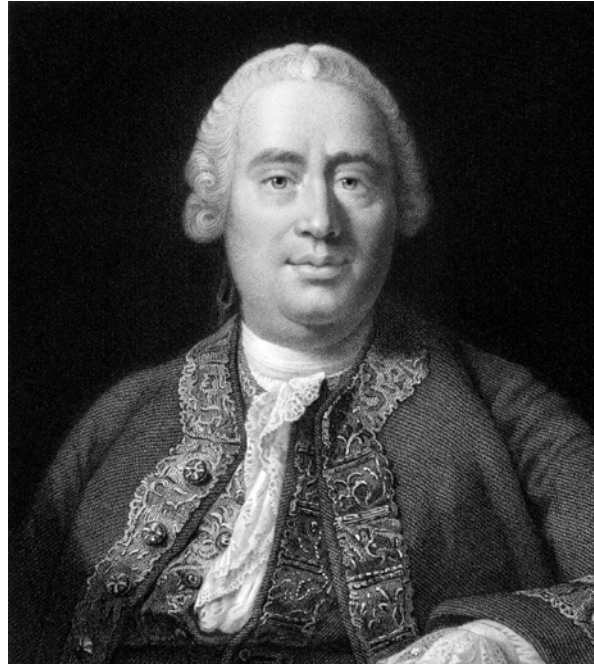
Hume's work massively influenced philosophers and scientists, particularly in the late 19<sup>th</sup> and early 20<sup>th</sup> centuries. It resulted in a certain suspicion of causality and initiated attempts to articulate the relationship

between causation and correlation. The commonly applied empiricist approach to causal inference is also an aspect of Hume's legacy. The 19<sup>th</sup> century London geneticist and statistician Karl Pearson, one of the founders of modern statistics, was heavily influenced by Hume and the empiricist tradition. Pearson maintained that the concept of causality was somehow illegitimate and should be replaced by the scientific study of correlations. In the beginning of the 20<sup>th</sup> century, Bertrand Russell stated that the word 'cause' never occurs in advanced sciences and that the notion of cause should be replaced with the mathematical notion of functional dependents. The second half of the 20<sup>th</sup> century has witnessed a lively debate among philosophers and logicians about the concept of causality, focusing on the semantic question of what we really mean by causality, and on the issue of causality vs. correlation.

The Principle of the Common Cause, stating that there cannot be any unexplained correlations in nature, attracted many philosophers in the 1920s and 1930s. This doctrine essentially says that two correlated variables, X and Y, imply either a causal link between X and Y, or a causal link between each of X and Y and a third variable, Z. X and Y could, for instance, be side effects caused by a treatment, Z. To many, the Principle of Common Cause suggested that the troubling concept of causality could be defined in probabilistic terms. However, the fact that there can be any number of different possible variables inducing the correlation between X and Y makes this less likely.

Randomised controlled trials are the gold standard for performing causal inferences – a view derived from Ronald Fisher’s work in the 1930s. Randomisation has the advantage that it guarantees the validity of the significance test and ensures that any differences between control and treatment groups are due to the treatment. In the strict sense, however, this may not be true. Some Bayesian philosophers argue that two treatment groups are absolutely certain to differ in some respects, any of which might be causally implicated in the trial outcome. Randomisation cannot therefore guarantee that the groups will be free from bias. Although this may be true from a logical standpoint, it may have little practical significance.

It is often argued that there is a methodological divide between experiments and observation; experimentation, i.e. intervention, is assumed necessary in order to make reliable causal inferences. The history of some sciences gives support to this view. The difference between experiments and observation, however, becomes less obvious when considering the Bayesians’ view, in which a set of beliefs is continually updated based on new information.



↑ *Fig. 1. David Hume, 1766.*

*Photo: Georgios Kollidas/Shutterstock*

# Determining causality case by case

Prof. Robin E. Ferner

University of Birmingham, UK

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Prof. Ferner's presentation was based on the assumption that drugs can cause adverse drug reactions (ADRs) in some patients, and that it may be possible to distinguish disorders that represent ADRs from others. In clinical terms, therefore, it is possible to diagnose an ADR in the same way as it is possible to diagnose pneumonia.

The practice of diagnosis has evolved and today we recognize four distinct diagnostic strategies: gestalt (pattern recognition), algorithmic, exhaustive and hypothetico-deductive.

Some ADRs present a classical clinical pattern, in the way that other disease syndromes do. For example, designated medical events such as toxic epidermal necrosis and bone marrow aplasia are distinct entities that commonly represent ADRs. The strategy of pattern recognition sometimes breaks down, as illustrated by the fact that nine children born to members of the group Thalidomide UK, had genetic thalidomide-like deformities, although their parents' phenotype had initially been attributed to thalidomide.

Diagnosis by algorithm offers a clear path to follow, albeit one from which it is difficult to deviate. Algorithms also present other difficulties. The Naranjo algorithm, for example, recommends challenge, dechallenge and rechallenge, which presents obvious difficulties if the event was serious or fatal. The final assessment produced by a given causality algorithm depends strongly on the relative weight of each criterion, which is usually fixed more or less arbitrarily.

The third diagnostic method – the exhaustive one – where everything possible is taken into consideration, is impossible in practice. The final method – hypothetico-deductive – is iterative. A theory is formulated, data are acquired to support that theory, and a conclusion is

drawn. This method, however, requires considerable experience and direct contact with the patient.

Statistical methods of diagnosis exist. Logistic regression programmes can take many issues into account (time to onset, challenge, dechallenge, rechallenge, risk factors, etc.) to calculate a causal probability to three significant figures: they are more sensitive but substantially less specific than algorithmic methods. Bayesian methods are also relevant and conform more closely to clinical decision-making.

As uncertainty is always present in diagnosis, be it for ADRs or other diagnoses, it makes sense to consider what information will help us be more definitive. Here, three important aspects of ADRs – dose response, timing and susceptibility (DoTS) – can help. It is helpful to remove the rare cases where causality is definite or impossible, leaving the middle ground. Here DoTS can help make a coherent picture.

In summary, every case requires exploration of the diagnostic space. This calls for experience, diagnostic imagination, and consideration of the prior probabilities. These probabilities can be adjusted according to a simple DoTS scheme. But in order to be just in your judgement, you always need to keep your eyes open.

# Causality assessment from clinical trials

Dr. Sonia Hernández-Díaz

Harvard School of Public Health, USA

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Dr. Hernández-Díaz compared randomized clinical trials and observational studies, and discussed some of the shortcomings of the intention-to-treat approach. In discussing alternative methods, she emphasised the problems of loss to follow-up and adherence, and suggested that some methods currently reserved for observational data could also be useful in clinical trials.

Randomized clinical trial (RCT) is the preferred design for causal inference. The main difference between RCTs and observational studies is that RCTs allow for randomization and blinding. However, in most other respects, e.g. defining objectives and study population, sample size, statistical power, etc., the two are, or can be made, similar in both function and result. In fact, RCTs with long follow-ups that result in deviations from protocol are very similar to observational studies with baseline randomization (Toh S, Hernán MA. *Int J Biostat* 2008; 4: Article 22). In a study where data from a published observational study were analysed in exactly the same way as an existing clinical trial – using the same inclusion criteria, analysis, follow-up, exposure definitions and outcome definitions – the main conclusions were identical (Hernán MA et al. *Epidemiology* 2008; 19: 766–79, Toh S et al. *Epidemiology* 2010; 21: 528–39).

In intention-to-treat (ITT) analyses, subjects are classified based on the initial randomized treatment assignment, and the treatment eventually used is ignored. Groups are thus exchangeable, and any differences in outcome between them are interpreted as being caused by the treatment. However, due to incomplete follow-up and adherence, ITT often underestimates the treatment effect, and is therefore less suitable in safety studies. Furthermore, ITT measures the effectiveness of a medication in a (partly non-adhering) population, rather than the effect in an adhering individual. Adjustments for incomplete

follow-up can be made using methods like per protocol analysis, but this assumes that loss to follow-up occurs at random. The ‘per protocol’ approach restricts the analysis to those subjects that follow treatment, assuming that the treatment effect in perfect followers is comparable to that in the study population.

In ‘as treated’ analyses, subjects are classified according to actual treatment. This implies a time-varying exposure, which might break the randomization. Moreover, it requires that the effect to be estimated must be defined (e.g. the effect of continuous treatment). The ‘as treated’ approach is valid only if bias from non-adherence and loss to follow-up can be appropriately adjusted for.

In randomized trials with substantial loss to follow-up or poor adherence, we need to consider methods that today are reserved for observational studies; methods that allow for compensation of poor compliance, incomplete follow-up and time-varying confounders (Hernán MA, Hernández-Díaz S. *Clin Trials* 2012; 9: 48–55). Inverse probability weighting, g-estimation, and instrumental variable estimation can reduce the bias introduced by non-adherence and loss to follow-up.



# Assessing causality from observational studies

Prof. Miriam Sturkenboom

Erasmus University Medical Center, The Netherlands

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Assessing causality from observational data is obviously problematic due to the poor control of confounding factors. Prof. Sturkenboom discussed ways of handling these problems and presented results from studies using recent methods that can remove some of the uncertainties and potentially clarify questions about causality.

Is there a causal relation between smoking and lung disease, or is the relation merely an association? This is the type of question dealt with in epidemiological association studies based on observational data.

Unlike clinical trials, studies of observational data do not, strictly speaking, allow assessment of causality. The reason for this is that confounding factors may influence the results – a factor can be said cause an event only if there are no concomitant alterations in any other factor.

Counterfactual models of causality are commonly used in epidemiology. In such models, a typical question would be: “In a group of people that were exposed, what would have happened if they had not been exposed?” Counterfactual models do not, however, allow for keeping factors constant and do not, therefore, solve the problem of confounding variables. The well-known Hills criteria have been used extensively in attempts to assess causality from observational data. Lack of evidence for some of these criteria, such as plausibility and coherence, may be a matter of time and should be taken as evidence against potential causality; they may not be supportive, but rather due to lack of data. On the contrary, other criteria, e.g. strength, consistency and temporality, are very important.

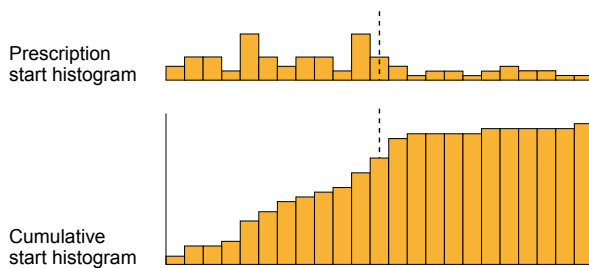
The FDA divides the drug safety surveillance process into three ‘pillars’: signal generation (essentially data mining), signal refinement (more

specific analyses), and signal evaluation (including traditional epidemiological studies). In all three, data could come from active surveillance of large linked healthcare databases, a fact that raises questions about validity and verification between the pillars. A more realistic approach may be to regard the process as a continuum rather than divisible into pillars.

New methods for signal generation on longitudinal records allow for ‘cleaning’ of false positive associations, i.e. eliminating some of the confounded associations and potential biases. One example is a novel pattern discovery methodology for event history data published by Niklas Norén (Norén GN et al. *Data Min Knowl Disc* 2010; 20: 361–87). The EU-ADR project ([www.alert-project.org](http://www.alert-project.org)) has applied and developed several methods – producing signals for specific drugs and events based on data from multiple healthcare databases. Performance comparisons of these data against a reference set of true positive and negative drug-event associations show that the longitudinal GPS method followed by LEOPARD performs best (Schuemie MJ et al. *Pharmacoepidemiol Drug Saf* 2011; 20: 292–9). LEOPARD plots drug usage over time in the form of a cumulative curve, in which the changing slope can be interpreted in terms of, for instance, protopathic bias (Fig. 1). In EU-ADR, not only temporality and strength of associations are analysed, but also biological plausibility and whether the event is a known side effect.

Although we cannot assess causality from observational data, these new high-throughput methods allow us to find more associations, faster and on a larger scale, and novel methods help us eliminate some of the uncertainties surrounding the estimates of associations.

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↑ *Fig. 1. Transformation of prescription data to cumulative form. In this particular case, the flat appearance of the cumulative curve after the prescription event may be interpreted to indicate that there is no protopathic bias (Schuemie MJ et al. Pharmacoepidemiol Drug Saf 2011; 20: 292–9).*

# Automated causality assessment for longitudinal observational databases

Dr. Patrick Ryan

Johnson & Johnson Pharmaceutical Research and Development, USA

Dr. Ryan explored opportunities for a systematic analytical framework to expand the use of observational data to further our understanding of the causal effects of medical products, and highlighted areas for future research and development.

Traditionally, pharmaco-epidemiologic studies have been used to test the strength of association between exposure to medical products and subsequent health outcomes. Recent initiatives, such as the Observational Medical Outcomes Partnership (OMOP, [omop.fnih.org](http://omop.fnih.org)), are currently exploring the potential of using networks of observational databases to monitor and identify risk. OMOP has conducted a series of experiments to measure the performance and predictive accuracy of various observational study designs. Furthermore, a suite of standardized analytics has been developed to characterize observational data and explore patterns in drug utilization and disease occurrence.

The data used by the OMOP network are very extensive and include both administrative claims and electronic health records. They allow for results beyond those gained by analysing spontaneous data, e.g. they also suggest new associations and permit inferences for cases where diagnosis is made long after exposure. With the huge amount of data and all the new methods available, most of Hill's criteria should be possible to assess.

A possible future application could be a 'causal dashboard' (Fig. 1) – an interactive software package, such as a mobile phone app for causal inference – where specific questions regarding drugs and outcomes are answered with reference to each of the Hill criteria. For example, strength could be indicated by the relative risk estimates based on observational studies to date; consistency could be assessed based on results from different data sources, algorithms and design decisions; and temporality should include analyses

using the new methods that also take time before exposure into account.

Such an app would compliment what we already know from clinical trials, pre-clinical animal studies, spontaneous adverse event reports and formal pharmaco-epidemiology studies. It would encourage exploration – both drugs and events could be easily replaced – and would provide means for achieving a deeper understanding of associations, beyond that of simple relative risks. It should, however, be regarded as one more piece of the puzzle of causal assessment rather than a final answer.

Although the app is still a vision, it definitely seems feasible, and many of the pieces are already in place. Further development will, however, require bringing together a variety of different skills and expertise.



↑ Fig. 1. Components of a possible 'causal dashboard' reflecting Hill's criteria (Patrick Ryan 2012).

# Accommodating causality considerations in benefit–risk assessment

Ola Caster, Ph.Lic.

Uppsala Monitoring Centre, Sweden

Ola Caster discussed the close link between benefit–risk assessments and decisions, and suggested a probabilistic decision-analytical approach to address the problem of uncertain causality in benefit–risk assessment.

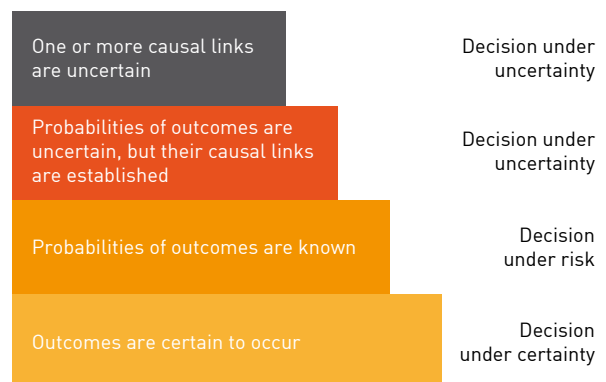
Causality considerations are important in benefit–risk assessment, particularly when post-marketing signals are involved. Benefit–risk assessments should jointly evaluate a drug’s positive and negative effects, and are by nature closely linked to decision-making: for example, regulators need to decide on initial or sustained licensing of drugs, and the patient/physician dyad may need to choose from several available therapies. Indeed, many recent approaches to quantitative benefit–risk assessment are based on decision analysis.

A hierarchy of complexity for benefit–risk assessment can be built using concepts from decision theory (Fig. 1). In this structure, ‘Decision under certainty’ constitutes the base. This corresponds to a hypothetical scenario where the outcome following a given drug is equal for all patients and known with certainty. However, certainty does not necessarily imply simplicity: even if the outcome of each alternative is known, fundamental clinical judgements are unavoidable in the comparison of those outcomes. On the next level, ‘Decision under risk’, a drug is allowed several possible outcomes, whose associated probabilities are assumed to be precisely known. While still hypothetical, this level requires many more outcomes to be considered, and ordinal comparisons are in general insufficient. At the next level in the hierarchy, ‘Decision under uncertainty’, probabilities of outcomes are allowed to be uncertain. This is more realistic, but implies a huge increase in analytic complexity. Probabilistic modelling is one feasible approach.

At the top of the hierarchy reside benefit–risk assessments that face uncertain causality. Multiple and

inherently different factors could contribute to such uncertainty, e.g. the risk of unidentified confounders in observational studies, the availability of only few strongly informative case reports, or the lack of experimental evidence for a plausible mechanism. It is reasonable to explicitly separate the uncertainty with respect to the probability of a causal link between a drug and an adverse effect from the uncertainty with respect to the size of the association between the two.

A probabilistic approach requires the uncertainty around the probability of a causal link to be represented by a probability distribution. Expert judgement may be a viable way of constructing simple distributions for this purpose. This presentation contained one made-up example, in which the nature of the expert judgement influenced the overall result hugely more than the shape of the distribution used to model the expert judgement.



↑ Fig. 1. A complexity hierarchy for benefit–risk assessments, based on established decision-theoretic concepts (Caster, 2012).

# Societal challenges – the patients’ perspective

Dr. Mary Baker MBE

President, European Brain Council and Patron, European Parkinson’s Disease Association

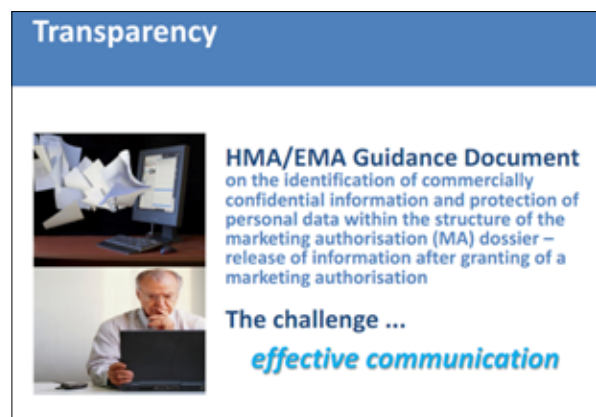
Dr. Baker highlighted the challenges of an increasingly aging population and the burden that this places on our healthcare system. She also emphasised the need for closer communication between patients, physicians and industry regarding medicines and their effects.

Perhaps 2/3 of all the people who have ever reached the age of 65 are still alive, and today a young girl born in Japan has a 50/50 chance of living to be 100 years of age. This is a wonderful achievement and well worth celebrating. However, it represents an enormous challenge to society and our healthcare system – the longer we live, the more diseases we acquire. Additional factors that add to this challenge include patients having less time with their doctors, the threat of counterfeit medicines, and a society that expects and hopes for a ‘quick fix’.

The way forward to overcoming these challenges requires several counter-measures, but effective communication is one key issue; there has to be a far closer understanding between all parties about medicines, their side effects, and their adverse effects. Furthermore, it is equally important for patient-reported outcomes to be fed back to industry. Several initiatives designed to promote better communication are now in place. They include a European directive about transparency (Fig. 1) and a Patient Academy Summer School set up between the European Federation of Neurological Associations and the London School of Economics to bring patient advocacy groups up to speed about how to communicate with authorities and speak in a language that is understandable to both sides. Patients have a voice and need to be listened to and involved!

Causality assessment is for many people an unfamiliar and perhaps misunderstood term. But whenever

a medicine is removed from the market or its use restricted, often amid huge publicity, public trust in the pharmaceutical industry declines. If there is cause and effect, patients need to be told about it in a way that they can understand and at a time that is right. Partnership and constant dialogue between industry and patients using the well-established doctor/patient relationship is essential for managing health in an effective and responsible manner.



↑ Fig. 1. Greater transparency should bring key aspects of medicines and their use more into the public domain.

# Causality assessment in practice – pharmaceutical industry perspective

Dr. Lachlan MacGregor

Senior Safety Scientist, F. Hoffmann-La Roche Ltd., Basel, Switzerland

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Dr. MacGregor focused on how individual case reports are handled, and the ways in which information on causality is captured and utilized.

‘Case processing’ is the name given to the activities that start with a fax or phone call from a patient, pharmacist or physician, through to the final, complete case report. A major challenge faced when processing individual cases (whether spontaneous or from clinical trials), is to quickly identify the most informative reports, i.e. those providing compelling evidence of new adverse drug reactions.

Spontaneously reported events are all considered causally ‘related’ to the drug for initial triage purposes unless explicitly considered by the reporter to be unrelated. For adverse events submitted from trials, an initial decision regarding relatedness is more important. Adverse event reports captured in the company Drug Safety database are heterogeneous in terms of the reporter’s level of concern regarding a causal role of the drug. Figure 1 shows results of a survey of reported adverse events over a 12-month period for one drug. In this example, fewer than half of the events were explicitly considered by the reporter to be causally related to the drug. All reports of serious adverse events from clinical trials must be recorded, irrespective of the reporter’s causality assessment.

Although a binary yes/no approach to causality assessment is convenient, and is needed for regulatory reporting purposes, such an approach does not necessarily reflect the process that occurs in clinical practice, where diagnoses are often made with

degrees of certainty. Two points are worth noting. First, the recommendation of a regulatory working group (CIOMS VI) to use a binary yes/no causality assessment; second, the concern expressed recently by the FDA about the number of adverse event reports from clinical trials assigned as ‘related’ due to precaution rather than positive information to indicate a causal relationship.

The Naranjo algorithm was used at Roche between 2001 and 2009 to assist in the triage of certain types of case during case processing, but proved to be generally unhelpful and was subsequently withdrawn.

Expressing causality in words is not without problems, and the challenge of communicating probability should not be underestimated – possible has many shades of meaning.

There is much to take into account when assessing a new safety signal, although the focus of each investigation depends on the drug–event pair in question. For example, in some instances, one or two case reports may provide compelling evidence of causality. In others, pre-clinical or epidemiological data may be the focus of attention. It is important to remember that having decided that a causal relationship exists, simply adding a new adverse event to the product label is not enough. The prescriber and patient must also be informed about the probability and clinical importance of the event.

## Reporter's causality assessment

*Example: One drug, 12 month period 2010–2011*

- **Events from study cases:**

568/2155 (26%) 'not related' (2 re-assigned 'related' by the company)

944/2155 (44%) 'related'

643/2155 (30%) no reporter causality assessment

- **Events from spontaneous cases:**

199/2681 (8%) 'not related'

1191/2681 (44%) 'related'

1291/2681 (48%) no reporter causality assessment

*Note: All spontaneous events are considered 'related' by the company for reporting purposes*

↑ *Fig. 1. In this example, fewer than half of the adverse events from study and spontaneous cases (44% for both) were explicitly attributed by the reporter as related to the drug. No reporter causality assessment occurs frequently, but is partly explained by the additional 'events' created by the company from symptoms/signs or other information recorded in the original report in an attempt to capture as much information as possible concerning potential new adverse drug reactions. All reports of serious adverse events from clinical trials must be recorded, irrespective of the reporter's causality assessment.*

→ The opinions expressed in this presentation are those of the author, and do not reflect those of F. Hoffmann-La Roche Ltd.

# Challenges of assessing causality within regulation

Dr. Pia Caduff-Janosa

Swissmedic, Switzerland

Dr. Caduff-Janosa reviewed the place of causality assessment decision-making within the EU's legal framework of pharmacovigilance following legislative modifications, aimed at increasing transparency, improving efficiency and strengthening the post-authorisation regulation of medicines.

The main EU legislative modifications covering pharmacovigilance reached by Regulation 1235/2010 amending Regulation 726/2004 and Directive 2010/84/EU amending Directive 2001/83/EC define the objectives listed above. As regulatory agencies are mandated by governments to implement medicinal product legislation in general, this places considerable expectations on them. Among other things, governments expect agencies to monitor the safety of medicinal products and issue authorization based on robust and consistent data assessment. Industry wants agencies to authorize their products quickly, prescribers expect transparent and timely information on drug safety, and patients/consumers need safe and effective drugs at their disposal.

Agencies also have the power to take action, but withdrawing a drug from the market is usually the last step. Many other things can be done beforehand, e.g. inform about new knowledge, work on the product information leaflet, limit drug use to special populations, etc. However, taking a decision on what to do and when to do it requires evidence; the question is how much evidence and of what kind. One of the most important tools to gain evidence is to ascertain if a certain medication may have caused a specific reaction or clinical picture.

Causality assessment is thus a central issue of pharmacovigilance. It can help qualify a relationship likelihood on a scale from 'excluded' to 'very likely',

it can reduce discrepancy between assessors, and it can improve the scientific basis of individual assessments. Methods of causality assessment can be categorised as those that rely on expert judgement or global introspection, algorithms or Bayesian approaches, all of which have their pros and cons.

The utility of causality assessment as applied at the individual level or triggered by signal detection (population level) remains a matter of discussion. Many agencies dealing with large databases have abandoned individual assessment, while others have kept it partly as a means of ensuring quality of data and a homogeneous evaluation of cases. It appears, therefore, that the best way forward is the combined use of different techniques to enable a transparent, efficient, fair and timely evaluation of safety issues and the decision-making that follows.

→ All views expressed within this presentation are those of the presenter. They do not in any way represent an official position of any organization.



# The drug relief system in Taiwan

Wen Chen, Pharm. D.

Chief, Division of Drug Safety, Taiwan Drug Relief Foundation

The Taiwan Drug Relief System is a unique, no-fault compensation-based scheme for injuries caused by legal medication use. Dr. Chen described how the scheme complements national adverse drug reaction (ADR) reporting and outlined both its aims and investigation principles, including causality assessment.

The Taiwan Drug Relief System operates under the Taiwan Drug Relief Foundation (TDRF), which also runs the other major activity for post-marketing drug safety regulation, the ADR Reporting Centre. TDRF is funded by the Taiwan FDA and the drug relief system itself is supported by levies collected from license holders. Both programs are separate from national health insurance. The main purpose of the drug relief system is to alleviate the pain and anger of victims suffering from drug injuries in a timely and friendly manner. It provides assessable consumer protection without the burden of a costly and time-consuming lawsuit. Relief is only given when none of the parties involved is liable for the harmful event.

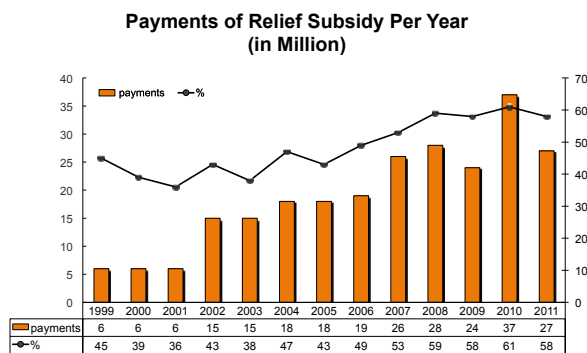
The drug relief investigation follows a set process flow and its causality assessment is similar to standard ADR case evaluation. Assessment is based on clinical knowledge or experience. Regarding case approval, other issues are also considered, as are certain exclusion criteria, including immunization (a vaccine injury compensation program already exists), and if the ADR is sufficiently common or foreseeable or not serious enough.

ADR management and the appropriateness of drug usage are also key aspects of the investigation and also the most clinically challenging. Negative examples of the improper use of drugs include wrong indication or contra-indication, improper dosage, interaction and improper practice. The latter, for

example, covers neglect of allergy history, insufficient diagnosis and not dealing with the ADR in time.

Figure 1 shows the approval percentage for the drug relief system over the last decade. The most common approved ADRs over this period relate to skin and subcutaneous tissue disorders (66%), which makes sense since skin lesions can be easily observed by patients.

In conclusion, a case-based drug relief investigation has many similarities with signal-generated ADR causality assessment, but also some interesting differences. It is not intended for legal or regulatory purposes, but rather to protect consumers.



↑ Fig. 1. Approval percentage for the Taiwan Drug Relief System. The recent increase is due to a policy change related to exclusion criteria so that more patients can benefit from the program.

# Legal claims

Michael Napier CBE QC

(former chairman Irwin Mitchell LLP, UK)

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Mr. Napier, a solicitor with forty years' experience of representing patients making compensation claims against pharmaceutical companies, made a strong case for no-fault compensation for drug side effects, but noted that such a system should be introduced only if its structure can guarantee fair and proper levels of compensation.

The case for no-fault compensation for drug side effects is overwhelming. Yet after a quarter of a century of active litigating, it is sad to report that little or no progress has been made, except probably in Taiwan (see previous presentation) and the Nordic countries. The medicolegal community and the pharmaceutical industry should thus not lose any more time in seeking answers to these two very important questions. Firstly, in the fifty years after the thalidomide disaster, what has been learned about the relationship between (a) the scientific proof of causality for adverse reactions to drugs and medical products and the legal proof of liability and causation for defective products, and (b) the role of regulatory/licensing authorities? Secondly, how can legal claims be resolved in a less attritional, less costly and more efficient way that guarantees speedier and fairer outcomes for everyone involved?

The law of negligence places on a pharmaceutical manufacturer a duty of care to the consumer of its products. Lawyers handling adverse drug reaction claims such as Distaval, Prednisolone, Practolol and Benoxaprofen, as well as defective medical devices

such as the Dalkon Shield, face enormously complex legal issues of knowledge and causation alongside complex expert medical evidence on causality. It is necessary to establish a duty of care breach involving an act or omission and the causal link to the injury in respect of which compensation is sought. All of these issues require expert testimony.

A claim brought under the 'strict liability' regime of the European inspired Consumer Protection legislation on defective products will fail if a manufacturer can show that all reasonably practicable steps were taken in producing the product, with the result that strictness of liability will be severely diluted. Even if this defence is defeated, the claimant will still have to overcome issues of medical causation to establish that the harm caused justifies compensation. To the best of the presenter's knowledge, in the twenty-five years since the Consumer Protection Act was introduced in the UK, no court judgment has been given in favour of a claimant in a pharmaceutical case where strict liability was pleaded.

Regarding redress mechanisms, rules exist to facilitate grouping together claimants with a common cause.



The UK requires that claimants must proactively come forward (opt-in). Claimants also risk having to pay the other side's costs if they lose. In contrast, the US class action system applies an opt-out mechanism without risk of adverse costs. A EU hybrid 'collective redress' procedure adopts an opt-out mechanism, but still retains the risk of adverse costs.

The most difficult hurdle that group action claimants have to overcome is funding, which in pharmaceutical litigation cases is always astronomical. In the UK, where legal aid is no longer available for most civil cases, it is virtually impossible to bring a group action using the only available alternative of the 'no win-no fee' model. In the USA, where contingency fees operate without the risk of adverse costs, each side pays its own costs win or lose. The US model is thus more favourable to claimants. Nevertheless, the problems of causation, procedure, funding and costs that face consumers in actions against pharmaceutical companies collectively present an almost insurmountable hurdle.

Can anything be done about this situation that presents such challenges to access to justice for

those injured by medical products? The proposal of no-fault compensation should be taken seriously by the pharmaceutical industry seizing the moral high ground to remove the cost and attrition of litigation. However, to assure the accountability of manufacturers of defective products, the powers of regulators and licensing bodies should be increased to include punitive action when standards are breached. It is noteworthy that the Nordic countries have operated no-fault compensation schemes for many years, and that causation is decided using the flexible 'preponderant probability' test.

In the public interest, the pharmaceutical industry needs to work with governments to remove the many barriers of injustice that we still see today 50 years after the thalidomide disaster. At the very least, all European countries should hurry to introduce the opt out collective redress system that at least gives claimants some hope of obtaining funding, which is the biggest barrier of all.

→ The opinions in the presentation are entirely the author's own.

# Media viewpoint

Mads Ellesøe

Mads Media, Copenhagen, Denmark

As an award-winning freelance journalist specialized in investigative reporting, Mr. Ellesøe gave a brief journalistic view of causality assessment and highlighted some of the issues that define a news story and decide whether or not it appears in the media.

Journalism is not science. It is based on completely different issues and there are no definite news criteria. Nevertheless, a story about conflict is always good, as is identification with victims.

Contrary to popular belief, journalists do want to tell the truth, but each medium defines the truth in different ways, stretching from tabloid media at one end of the scale to medical press at the other.

Few journalists have the time to investigate a ‘causality’ story and many do not understand medical reports. We thus depend on independent experts. So when we get scent of something, we call someone and ask what’s going on. But once we’re on the trail, we’re not so stupid that we can’t understand an adverse effects report. We also know to look at funding and conflict of interest among authors. In other words, journalists talk to people, collect information from sources and raw data, and then see if their editors think they have a story to run. The best scenarios are a ‘smoking gun’ or strong indication, but if you want to tell a story – especially on TV – there has to be a human consequence, a dead or injured person. Otherwise it’s not a story – it’s just somebody saying something.

Most journalists will thus never open a medical report. The few who do will likely interpret causality assessment together with an independent expert. Most probably, however, other factors will determine if the story is aired or not.





Prof. Ralph Edwards ↩



Prof. Miriam Sturkenboom ↗



Ola Caster ↗



↙ Prof. Robin E. Ferner

Dr. Sonia Hernández-Díaz ↘







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