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SMQ:

PHYSICIAN RATINGS OF IMPORTANT TERMS FOR DIAGNOSIS OF *CARDIAC FAILURE*

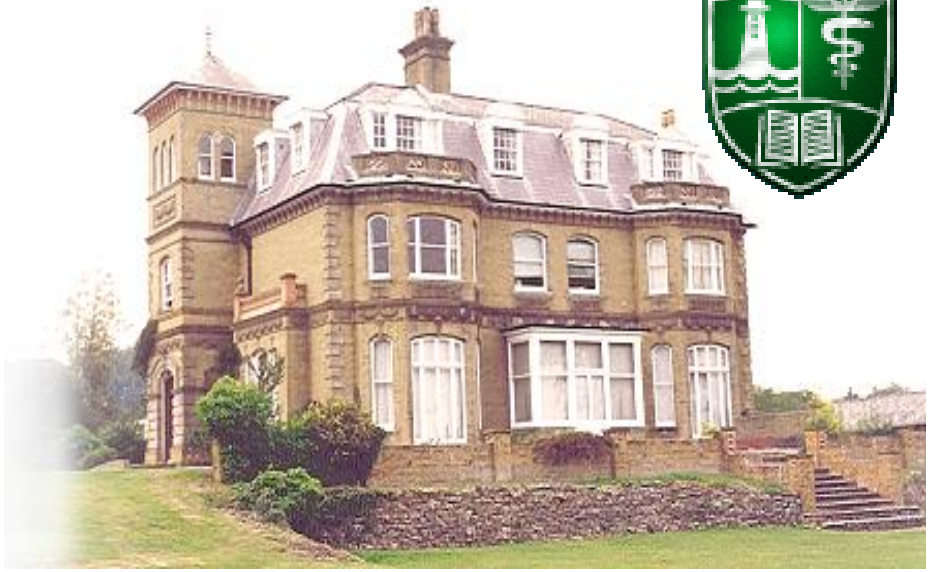
MICHELLE PERRY

SCOPE

- Background
- Research aim
- MedDRA SMQ development – Weighted SMQ
- Diagnostic Process
- Therapeutic area – Model products
- Delphi Study
- Results
- Conclusions

MHRA

Regulating Medicines and Medical Devices



University of Portsmouth

SIGNAL DETECTION IN PV

YellowCard
Helping to make medicines safer

Employed to highlight real safety concerns.

Established systems may take too long.

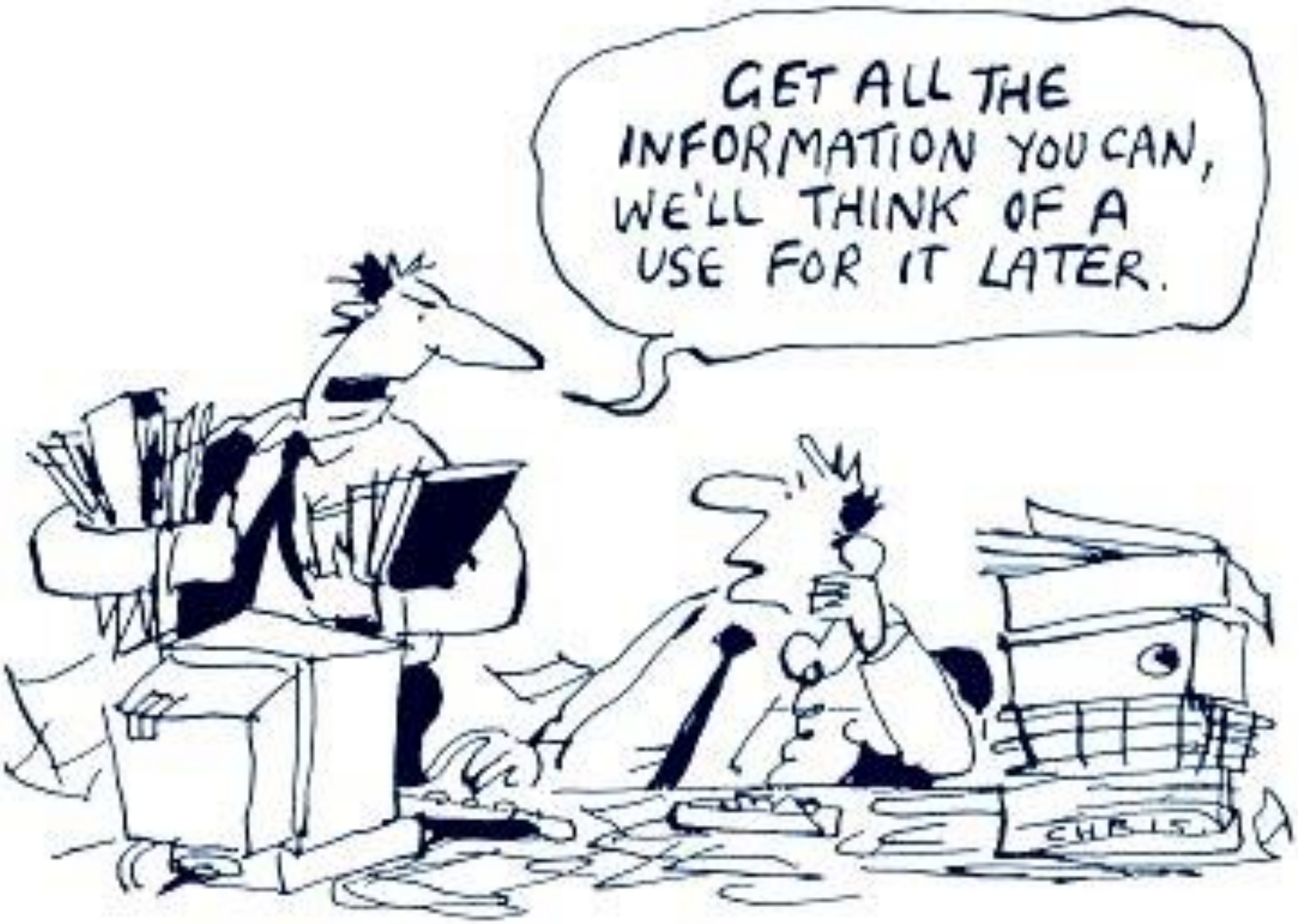
Medicinal product will have reached a large population before signals are detected.

A system is needed where signals are identified **sooner**, so that they can be investigated and any causal associations dealt with *promptly*.

RESEARCH AIM

- To review the symptoms, signs and diagnosis that may be associated with conditions considered to be ADRs, and to add a numerical value to those terms according to how discriminatory they are for the condition in question.

- Allow a symptom that is strongly associated with a condition to add more value to statistical calculations of ADR incidence than a symptom that is only weakly associated with the condition.


GET ALL THE INFORMATION YOU CAN, WE'LL THINK OF A USE FOR IT LATER.

BACKGROUND

MedDRA – medical dictionary for regulatory activities

- A comprehensive and complex medical terminology developed by ICH that is being implemented worldwide by drug regulatory authorities, the pharmaceutical and biotechnology industry, and academia for coding, reporting, analysing, and communicating regulatory information.
- Is the most widely used dictionary and has become accepted as the international standard since it was implemented in 1997.

MEDDRA SMQS

Standardised MedDRA Queries (SMQs):

- aid in identification and retrieval of potentially relevant individual case safety reports;
- SMQs are groupings of MedDRA terms, ordinarily at the Preferred Term (PT) level, that relate to a defined medical condition or area of interest.
- signs, symptoms, diagnosis, syndromes, physical findings, laboratory and other physiologic test data.

DEVELOPMENT AND USE OF SMQS IN SIGNAL DETECTION

- SMQs can be used on clinical data that are coded with PTs from a single MedDRA version.
- Volume 9A and more recent GVP guidelines recommend the use of SMQs for signal detection, validation and evaluation.
- However the advantage of using SMQs for signal detection remains unclear.
- Currently almost 100 SMQs have been created.

SMQS CAN BE USED IN VARIOUS WAYS.

- Firstly the broad search uses all the PTs in an SMQ, providing high certainty that all cases of the medical concept being investigated will be identified, including those that could have many causes.
- The narrow search limits the PTs used, providing high certainty that the cases identified are related to the medical concept.
- For some SMQs algorithms have been introduced to further aid identification of specific case reports likely to represent the medical concept in question.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

The MSSO and CIOMS have developed a weighted algorithm for one SMQ – SLE.

- great diversity in the terms reported for two drugs known to be associated with SLE.

- weight was based on the frequency of reporting of broad search terms in various categories and the probability that they relate to SLE.

WEIGHTED ALGORITHMIC SMQ

Categories	Number of PTs	Proposed Weight
Narrow search	16	
Broad search		
photosensitivity	3	1
oral ulcers	3	2
arthritis	2	3
serositis	9	3
renal disorder	8	1
neurological disorder	21	2
hematologic disorder	6	3
immunologic disorder	9	3

If the sum of the term weights is more than 6, it qualifies as a case of *SLE* in the broad search.

Narrow search terms work in the same way for all SMQs; the mention of any one of the terms from the narrow search qualifies a report as a case.

There is no literature available regarding the application and use of this weighted algorithmic SMQ in PV.

ANALYSIS OF SMQS FOR SIGNAL DETECTION

The EMA researchers in this study compared the timing of onset of a known safety signal (hyperglycaemia) for a marketed product using various MedDRA term levels (PT, HLT, HLGT) and for SMQ *Hyperglycaemia/new onset diabetes mellitus*. Proportional reporting ratios (PRRs) over time ("dynamic PRRs") for each term level and for the SMQ were calculated and used for the comparison. The researchers reported that a significant PRR was found using SMQ *Hyperglycaemia/new onset diabetes mellitus* **earlier** than for any other term level studied. The study highlighted the potential for SMQs to be used early on in signal detection for risk management, and that further research in this area would be useful.

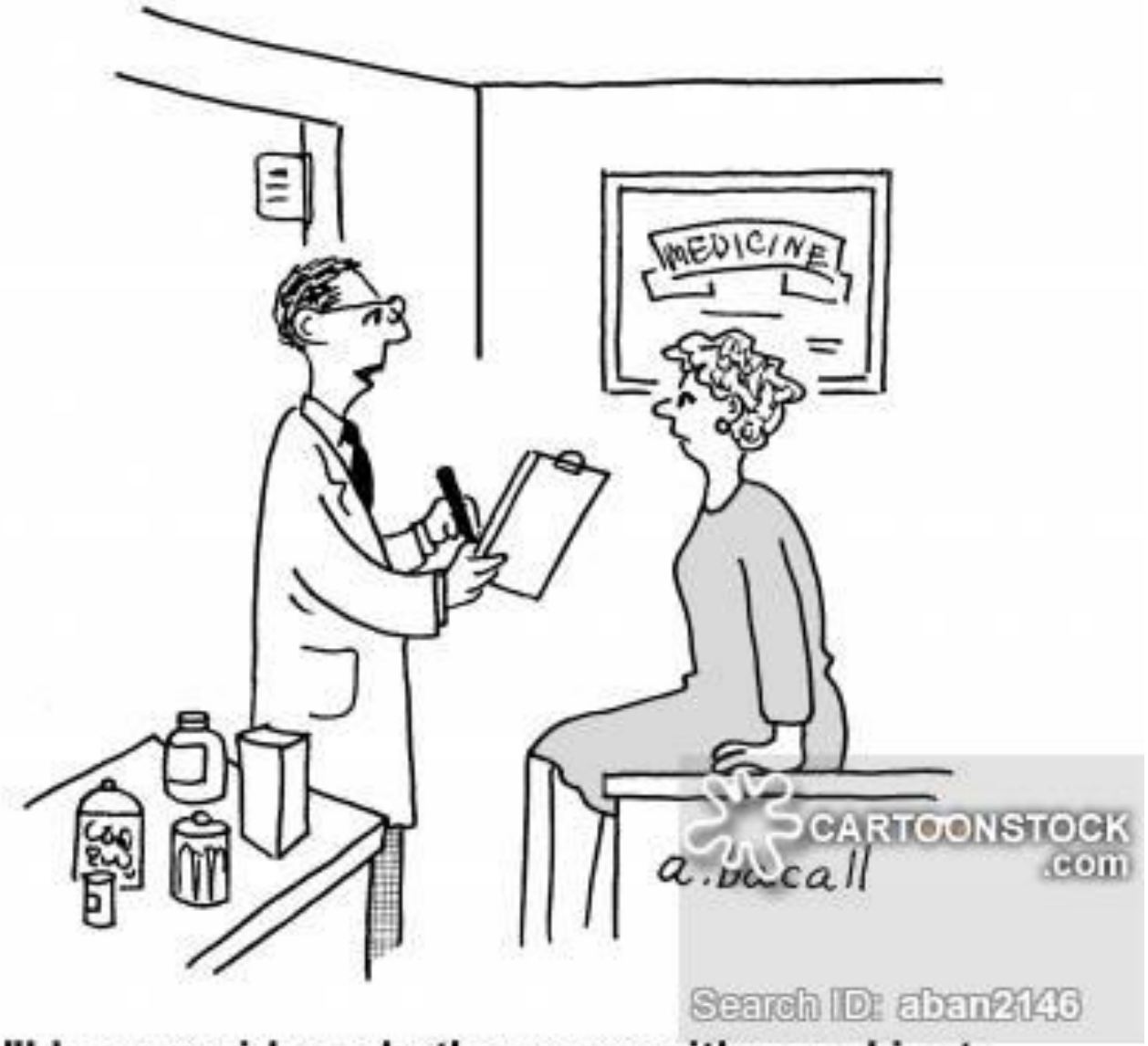
Newbould V, Halsey N, Tsintis P, Lerch M, Mozzicato P. Standardised MedDRA® Queries: Analysis of their signal detection capability. 22nd ICPE Meeting; 2006 Aug; Lisbon, Portugal; Abstract 87.

DIAGNOSTIC PROCESS

Diagnosis is defined as a "*description of a health problem in terms of known diseases*".

There are various methods and many factors involved in reaching a diagnosis. The two main aspects to the diagnostic process are: problem solving and decision making.

- "*set of actions needed to obtain a diagnosis*".
- "*complex transition that begins with the patient's individual illness history and culminates in a result that can be categorised*".



"I have no idea what's wrong with you. I just collect information. My computer makes the decisions."

DELPHI METHOD

RAND developed the Delphi method in the 1950s, originally to forecast the impact of technology on warfare. The method entails a group of experts who anonymously reply to questionnaires and subsequently receive feedback in the form of a statistical representation of the "group response," after which the process repeats itself. The goal is to reduce the range of responses and arrive at something closer to expert consensus. The Delphi Method has been widely adopted and is still in use today.

Mean scores derived from a series of judges are likely to be more reliable, and therefore useful, than those derived from a single rater.

PHYSICIANS – CHOOSING THE RATERS

Current or previous history in dealing with adverse drug reactions or PV data.

MEDICINAL PRODUCTS

- On UK market 2000-2010
- New safety signals
- No. of Yellow Card reports

CARDIAC FAILURE AND "GLITAZONES"

- Oedema/peripheral oedema/ pulmonary oedema/ fluid retention
- Cardiac enlargement/ cardiac hypertrophy/ cardiac failure

Rosiglitazone

First marketed in US 1999

MA refused in the EU – Oct 1999

MA granted in the EU with provisions – Jul 2000

Contraindicated with Congestive heart failure (CHF)

Warning added to PIL regarding the possible development of fluid retention and CHF

Treating physician – experienced in treatment of T2DM

RECORD study

DETERMINE WEIGHTING FACTORS TO BE APPLIED

- Piloting the survey – two potential respondents
- 18 physicians and one cardiac specialist
- indicate how important the felt each term was in contributing towards they diagnosis of cardiac failure.

3 = of high importance

2 = important

1 = less important

0 = not important

RESULTS OF PHYSICIAN STUDY

- 11 reviewers completed the surveys, plus the cardiac specialist.

- A number of terms were left blank.

- The mean rating for each term (by dividing by number of completed columns for that term) along with the SD were calculated.

- The list, ranked by mean (highest to lowest) and by SD (lowest to highest) was sent for second review by 4 of the original reviewers.

RATERS' COMMENTS

- A lot of terms lacked specificity
- It is still necessary to look at each case individually
- Making a diagnosis never relies on a single symptom, sign or investigation
- Take into account medical history or underlying condition

Attribute Agreement Analysis

Fleiss' kappa statistic (FKS) – the proportion of agreement after chance agreement is removed.

- Kappa = 1 = perfect agreement
- Kappa = 0 = same as expected by chance
- Negative values occur when agreement is weaker than expected by chance

ATTRIBUTE AGREEMENT ANALYSIS

Kendall's coefficient of concordance (KCC) – strength of overall agreement within a data set.

- KCC = 1 = unanimous
- KCC = 0 = no overall trend of agreement
- KCC > 0.7 (rated fair) indicate increasingly good agreement

Summary of Attribute Agreement Analysis for agreement for *cardiac failure* terms (n=69).

Response	Fleiss' kappa	Standard error	Z value	P	Agreement
0	0.045003	0.016233	2.7742	0.0028	Little
1	0.074625	0.016233	4.5972	0	Little
2	0.09846	0.016233	6.0277	0	Little
3	**0.235936**	**0.016233**	**14.5345**	**0**	**Fair**
Overall	0.130093	0.009942	13.0856	0	Slight

All raters agreed on 4 terms (5.8%) had a perfect match in all rating terms.

Kendall's coefficient of concordance was 0.3276 (Chi-square=245.067; DF=68, P<0.0001)

SECOND ROUND

4 respondents agreed with the final weightings arrived at after the first round for *cardiac failure* SMQ terms.

The improvement was expected, as in the second round, raters were presented with a list of established mean ratings that they knew had been produced after the first round.

SECOND ROUND

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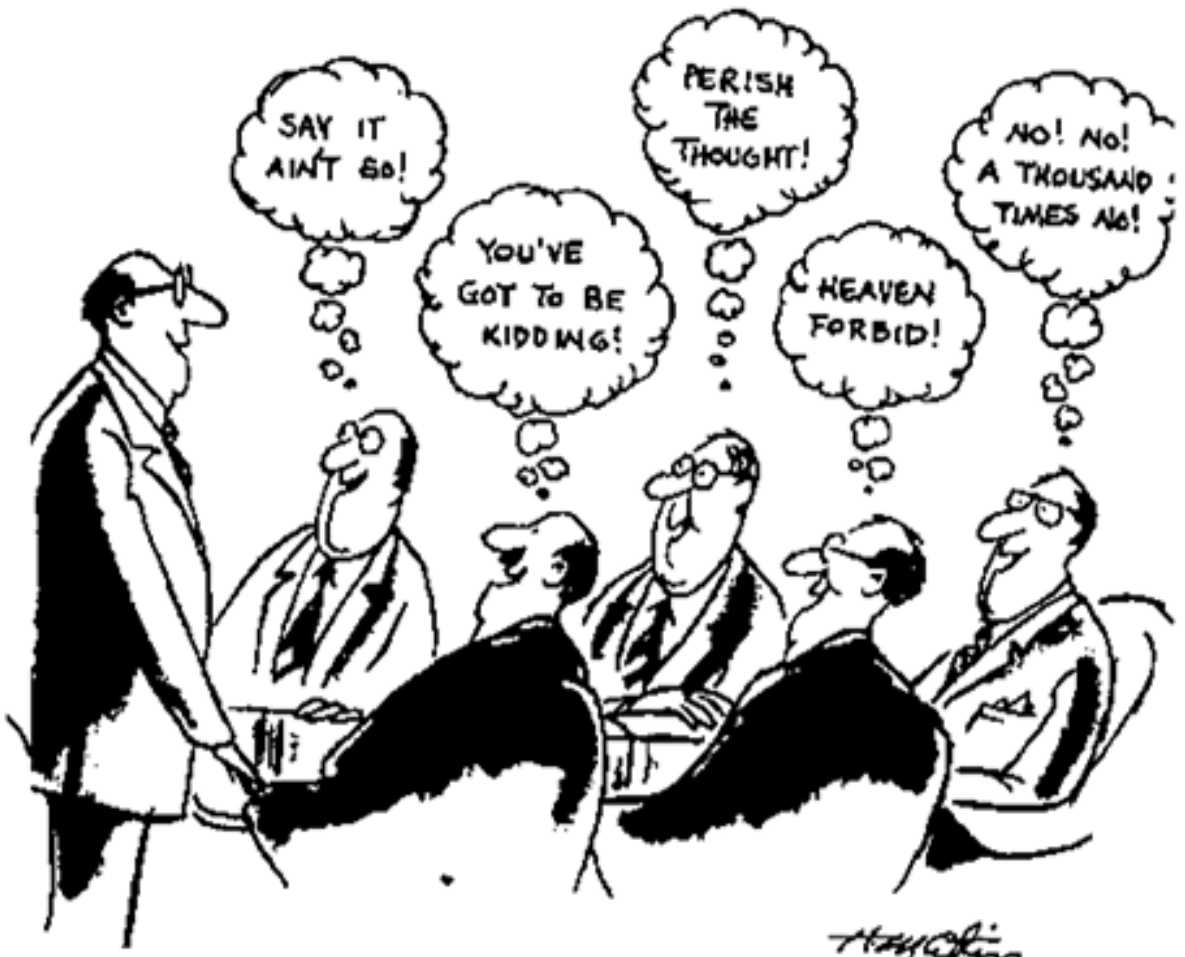

Summary of Attribute Agreement Analysis for agreement for cardiac failure terms (n=69) for clinicians engaged in PV research.

Response	Fleiss' kappa	Standard error	Z value	P value	Agreement
0	0.102852	0.0380693	2.702169	0.0034	Slight
1	0.121802	0.0380693	3.19948	0.0007	Slight
2	0.120022	0.0380693	3.15272	0.0008	Slight
3	0.184783	0.0380693	4.85384	0.0000	Slight
Overall	0.142789	0.025969	5.50100	0.0000	Slight

Raters all had the same rating match for five terms (7.25%).
Kendall's coefficient of concordance was 0.436112 (Chi-square=148.278; DF=68, P<0.0001)

Summary of Attribute Agreement Analysis for agreement for cardiac failure terms (n=69) for 11 raters compared to the independent ratings of a single consultant cardiologist.

Response	Fleiss' kappa	Standard error	Z value	P value	Agreement
0	-0.053435	0.120386	-0.44387	0.6714	None
1	0.026646	0.120386	0.22134	0.4124	Little
2	0.217391	0.120386	1.80579	0.0355	Fair
3	0.647959	0.120386	5.38235	0.0000	Moderate
Overall	0.295802	0.081375	3.63505	0.0001	Fair

Raters all had the same rating match for 38 terms (55.1%).
Cohen's coefficient of concordance* (kappa) was 0.328415 (Chi-square=29.6797; DF=15, P=0.0131)
***this effectively Kendal's coefficient of concordance, calculated when there are just two ratings to compare.**

CONCLUSION

It should be noted that the levels in the rating scale were relative to each other – not absolute and were ordinal in nature, thus limiting the level of statistical analysis that could be performed and hindering comparisons with other rating scales or exercises of a similar nature.

- Aimed to obtain expert opinion on what were considered important signs/symptoms which could be used to facilitate signal enhancement.
- The process could thus combine both clinical and scientific judgement.

CONCLUSION

Within pharmaceutical companies, all the information about a medicinal product from the initial discovery phase right through to application for marketing authorisation is available.

- specific therapeutic area
- ample information
- product fit
- ability to compare and contrast it with its competitors.

This information would be ideal for the proposed method, making the weighting model perhaps most suitable in this setting.

"The only real mistake is the one from which we learn nothing."

HENRY FORD

"Failure isn't fatal, but failure to change might be."

JOHN WOODEN

https://ie.linkedin.com/pub/michelle-perry/40/229/61b

All thoughts/questions about this presentation are welcome

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