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OMICS Group is an amalgamation of Open Access Publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 500 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 500 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

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OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

COMBINING QUANTITATIVE AND QUALITATIVE METHODS IN SIGNAL DETECTION AND EVALUATION IN PHARMACOVIGILANCE.

MICHELLE PERRY

SCOPE

Background

Method

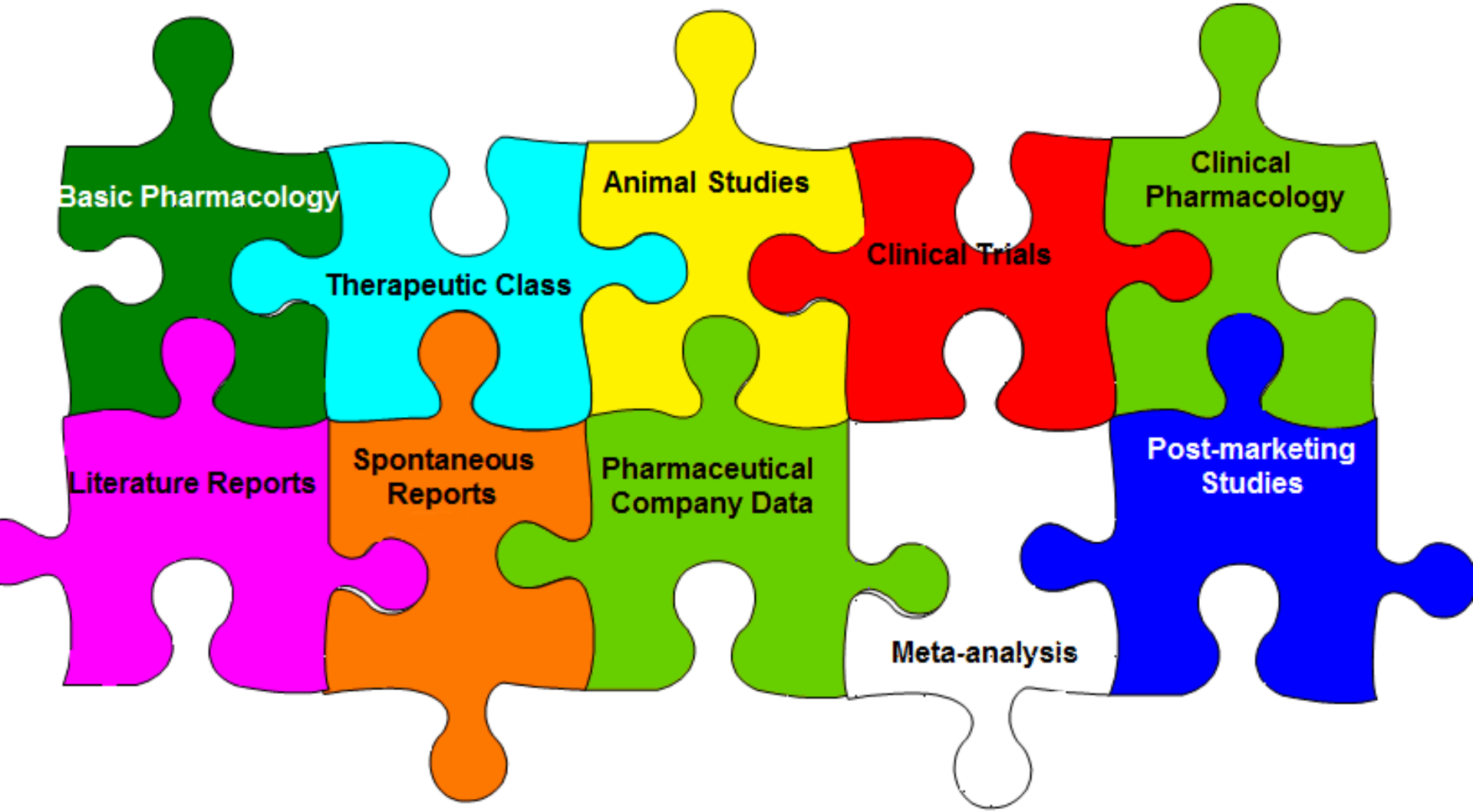
Results

Conclusion

Further research

THALIDOMIDE CHILDREN- BORN WITH VARIOUS LIMB DEFECTS

IN AN IDEAL WORLD…



SPONTANEOUS REPORTING DATA

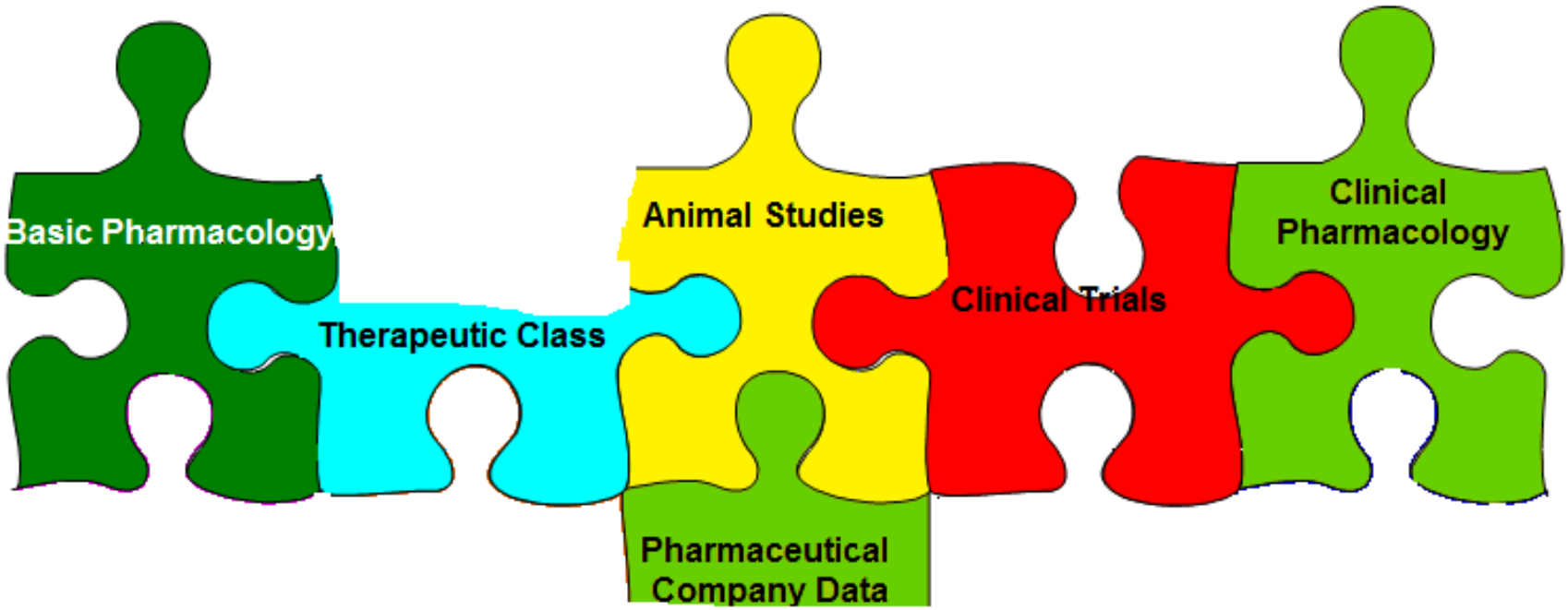
- Many types of data that can be used to monitor potential safety signals.

- The largest and most important is that gathered from spontaneous reporting

- Others include:

PILs SPC Clinical Trials Literature Internet searches

IN REALITY!


Basic Pharmacology
Therapeutic Class
Animal Studies
Pharmaceutical Company Data
Clinical Trials
Clinical Pharmacology

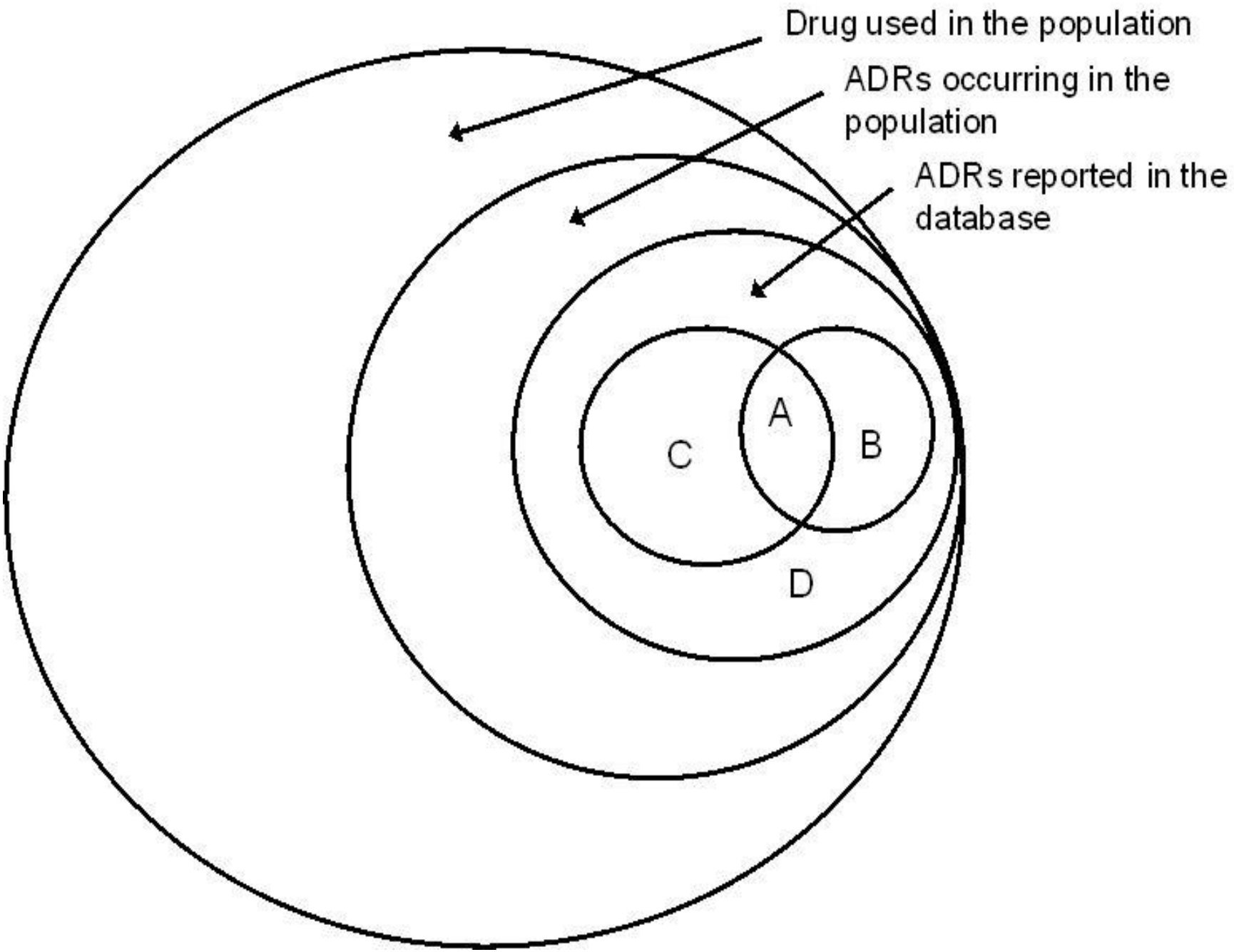
USE OF STATISTICS IN PV

Disproportionality; comparing the *observed* number of reports to the *expected* number of reports in the background data

PRR – Proportional Reporting Ratio calculation =

$$\frac{A/(A+B)}{C/(C+D)}$$

Where….


Drug used in the population
ADRs occurring in the population
ADRs reported in the database
A
B
C
D

STATISTICAL WEIGHTING

- **Important associations were given a higher numerical value**
- **Augmented disproportionality**
- **Potential signals detected earlier ?**

Rationale behind chosen medical concepts to weight

At the centre of this research was the ability to **identify** the important risk factors to monitor during initiation of a medicinal product to the market from information available **prior** to widespread marketing authorisation.

The rationale came from SPCs and PILs submitted to the EMA when applying for marketing authorisation.

The main issues with current treatments for diabetic patients were concerns about adding to the *cardiovascular risk, weight gain, oedema,* potential association with *pancreatitis,* concerns about *renal function,* and unknown long-term safety.

SMQS
(STANDARDISED MEDDRA QUERIES)

SMQs group terms from various SOCs together to aid identification of a medical concept.

The SMQ *Cardiac Failure* has terms from

- Cardiac disorders
- Vascular disorders
- Investigations
- Respiratory, thoracic and mediastinal disorders
- Pregnancy, puerperium and perinatal conditions

TERMS TO MODEL WEIGHTING AND THE AVERAGES OBTAINED FROM THE PHYSICIAN RATINGS

Preferred Term	Average rating
Left ventricular failure	2.82
Oedema	1.55
Oedema peripheral	1.70
Cardiac failure	2.91
Cardiac failure congestive	3
Pulmonary oedema	2.18

Terms and weightings applied

Preferred Term	Weight 1	Weight 2	Weight 3
Left ventricular failure	2.82	1.69	1.97
Oedema	1.55	0.93	1.08
Oedema peripheral	1.7	1.02	1.19
Cardiac failure	2.91	1.75	2.04
Cardiac failure congestive	3	1.8	2.1
Pulmonary oedema	2.18	1.31	1.53

Where: Weight 1 = mean rating

Weight 2 = Mean*0.6

Weight 3 = Mean*0.7

PHASE 2 – APPLYING WEIGHTING

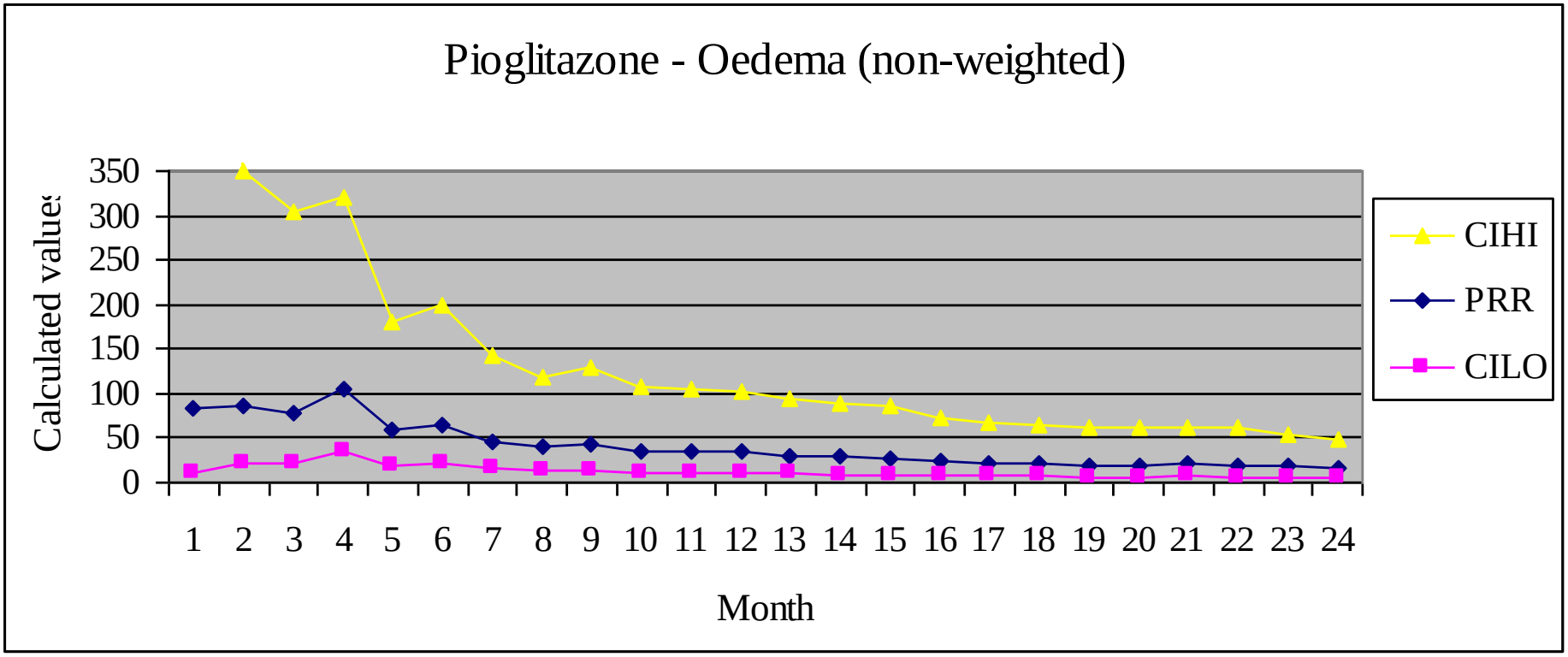
First data set

- 2 years (2005-2007)
- PRRs, Confidence Intervals lower and higher, and chi-squared calculated every month
- Dynamic PRR reports produced

Second data set

- 10 years (2000-2010)
- PRRs, Confidence Intervals lower and higher, and chi-squared calculated at the end of the 10 years
- Static PRR reports produced

An example of a dynamic PRR report



PRR

The null value for PRR is 1.

If PRR = 1 then the number of drug/event reports for that drug is proportionate to the number of drug/event reports in the whole database.

PRR > 1 means the drug/event combination is disproportionate to the background data and requires further investigation.

Summary table for pioglitazone- *oedema*					
Month_signal	**Weighting factor**	**PRR**	**CILO**	**CHI2**	**No. of cases**
4	none	104.82	34.26	247.59	3
4	1.55 (mean)	107.84	36.06	468.48	3
4	0.93 (mean*0.6)	71.02	9.32	109.09	3
4	1.08 (mean*0.7)	84.09	22.98	280.43	3

The disproportionality was so far above the thresholds that once the minimum 3 reports were received it was a potential signal for further review.

Oedema Peripheral - Pioglitazone

	Month became potential signal			
PT	Non-weighted	Weight 1 (mean)	Weight 2 (mean*0.6)	Weight 3 (mean*0.7)
LVF	24	24	24	24
Oedema	4	4	4	4
Oedema peripheral	**10**	**9**	**17**	**9**
CF	-	-	-	-
CF congestive	-	-	-	-
Pulmonary oedema	-	-	-	-
Nausea	-	-	-	-

- PT did not become a potential signal for pioglitazone with that weighting factor applied

Oedema Peripheral - Rosiglitazone

	Month became potential signal			
PT	**Non-weighted**	**WF 1 (mean)**	**WF 2 (mean*0.6)**	**WF 3 (mean*0.7)**
LVF	-	-	-	-
Oedema	19	19	19	19
Oedema peripheral	**19**	**17**	**23**	**18**
CF	3	3	3	3
CF congestive	15	15	15	15
Pulmonary oedema	15	15	15	15
Nausea	-	-	-	-
- PT did not become a potential signal for pioglitazone with that weighting factor applied				

10 YEAR DATA SET
OEDEMA PERIPHERAL - PIOGLITAZONE

Weight	PRR	CILO	CIHI	CHI^2
None	1.84	1.22	2.76	8.55
1.70	**3.12**	**2.29**	4.25	**51.40**
1.02	1.87	1.25	2.81	9.28
1.19	**2.18**	**1.50**	3.17	**16.74**

Oedema peripheral

- Considered a “true” signal for pioglitazone and rosiglitazone in the original non-weighted 2 year data.
- Not a “true” signal in the 10 year data set.
- Now know from literature that *oedema peripheral* is associated with pioglitazone(1) and rosiglitazone(2) use(3;4).
- Based on clinical studies, *fluid retention* and *oedema peripheral* are reported in up to 7% of patients using glitazones, and up to 15% of patients using pioglitazone with insulin(5).

THIS RESEARCH AIMED TO INVESTIGATE THE ROLE OF THE ADDITIONAL DATA SOURCES IN *EARLIER* SIGNAL DETECTION.

- Fair to moderate agreement for the terms rated as very important (3)
- Applying the mean rating had the biggest affect on disproportionality
- All true positive drug/event term pairs were identified will all weighting factors

IN CONCLUSION

The enhanced detection process may allow more accurate and earlier prioritisation of ADR reports for further investigation, thus leading to *improved, proactive* signal detection.

FURTHER RESEARCH

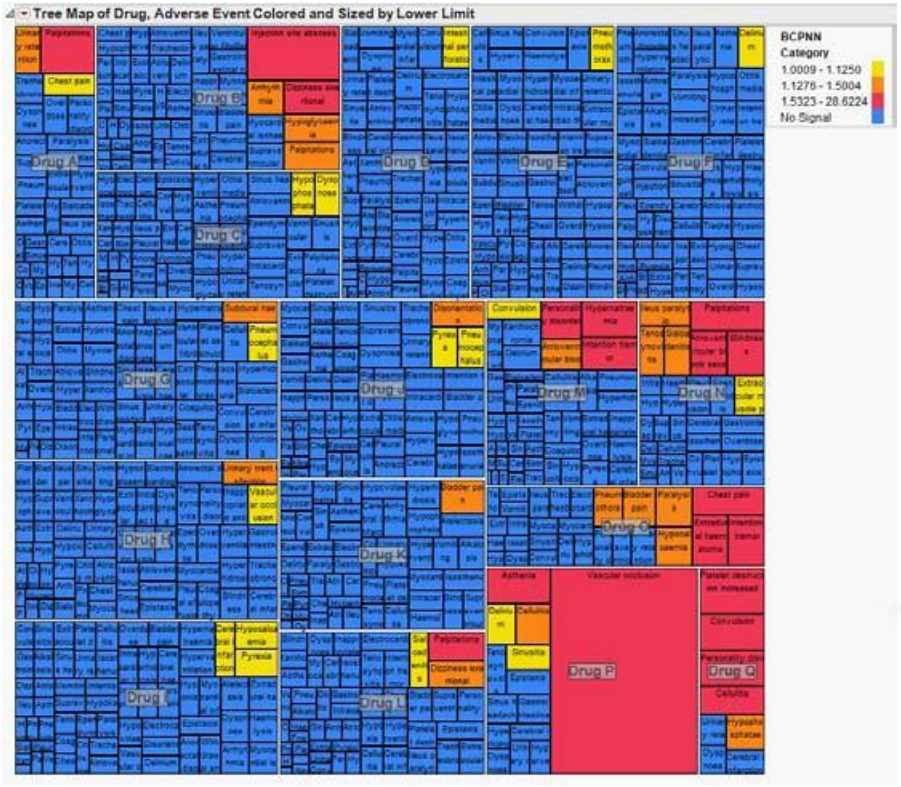
- Rating of terms for more medical concepts by a refined group of experts for each medical area.

- Application of weighting factors to more terms for more drugs in a large spontaneous reporting database.

- Incorporate visual evaluation tools to aid the signal review phase of PV.

VISUAL EVALUATION TOOLS

Examples that exist already include Oracle and JMP clinical tree map of ADRs shown below.

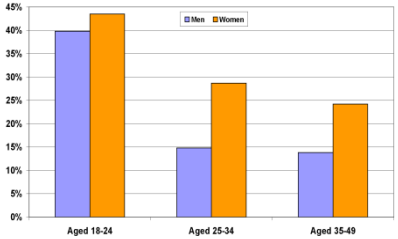



Temporality
Plausibility
Consistency
Strength
Dose-response relationship
Specificity
Reversibility
Coherance
Analogy
Bradford Hill Criteria

VISUAL TOOLS

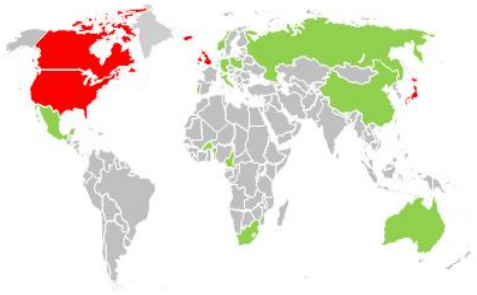
Drug-Active ingredient

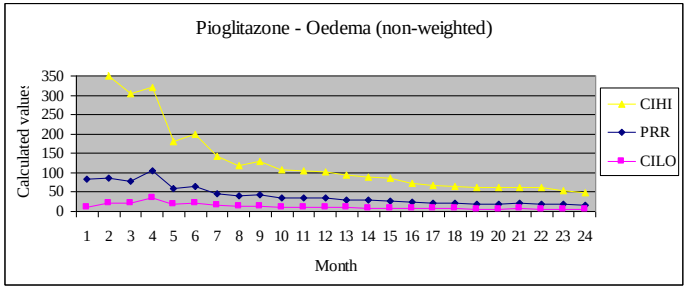
Event-Preferred Term

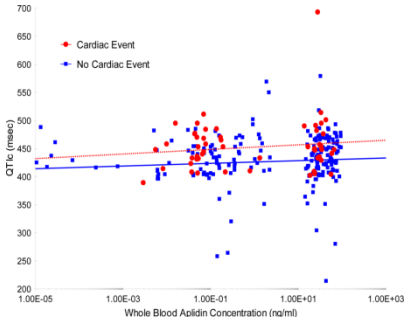


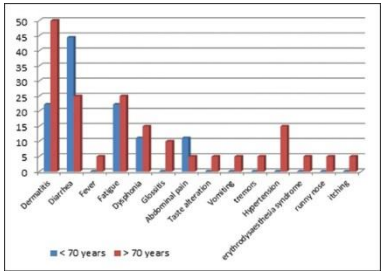
WHO-UMC causality criteria	Number of ADRs (%)	Naranjo algorithm	Number of ADRs (%)
Certain	0 (0)	Definite	0 (0)
Probable	10 (1)	Probable	2 (0.2)
Possible	857 (93.9)	Possible	906 (99.2)
Unlikely	35 (3.8)	Doubtful	5 (0.6)
Unclassified	5 (0.6)		
Unclassifiable	6 (0.7)		

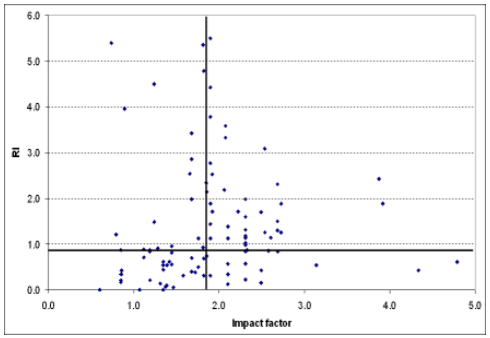
WHO-UMC = World health organization-uppsala monitoring center











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