MHRA

Overview of Signal Detection and Disproportionality

Medicines & Healthcare products Regulatory Agency

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The Yellow Card Scheme

- UK spontaneous reporting scheme collecting suspected Adverse Drug Reactions, established in 1964 following thalidomide disaster.

- Vital public health mechanism to:
  - Identify previously unrecognised adverse drug reactions
  - Gain further information about the occurrence of adverse drug reactions in ordinary practice.

- Essential component in MHRA's pharmacovigilance work

- Reports submitted in confidence and voluntarily by:
  - Any health professional
  - Patients and their representatives

- Reports from pharmaceutical companies – legal obligations

Spontaneous reports

Positives

- High volume
- Rapid receipt
- Suspicion (establishment of causality not necessary to detect safety issues)
- Low cost

Challenges

- Low level of completeness
- Limited impact of individual case follow up
- Not from a controlled environment
- Assessment of confounding factors challenging

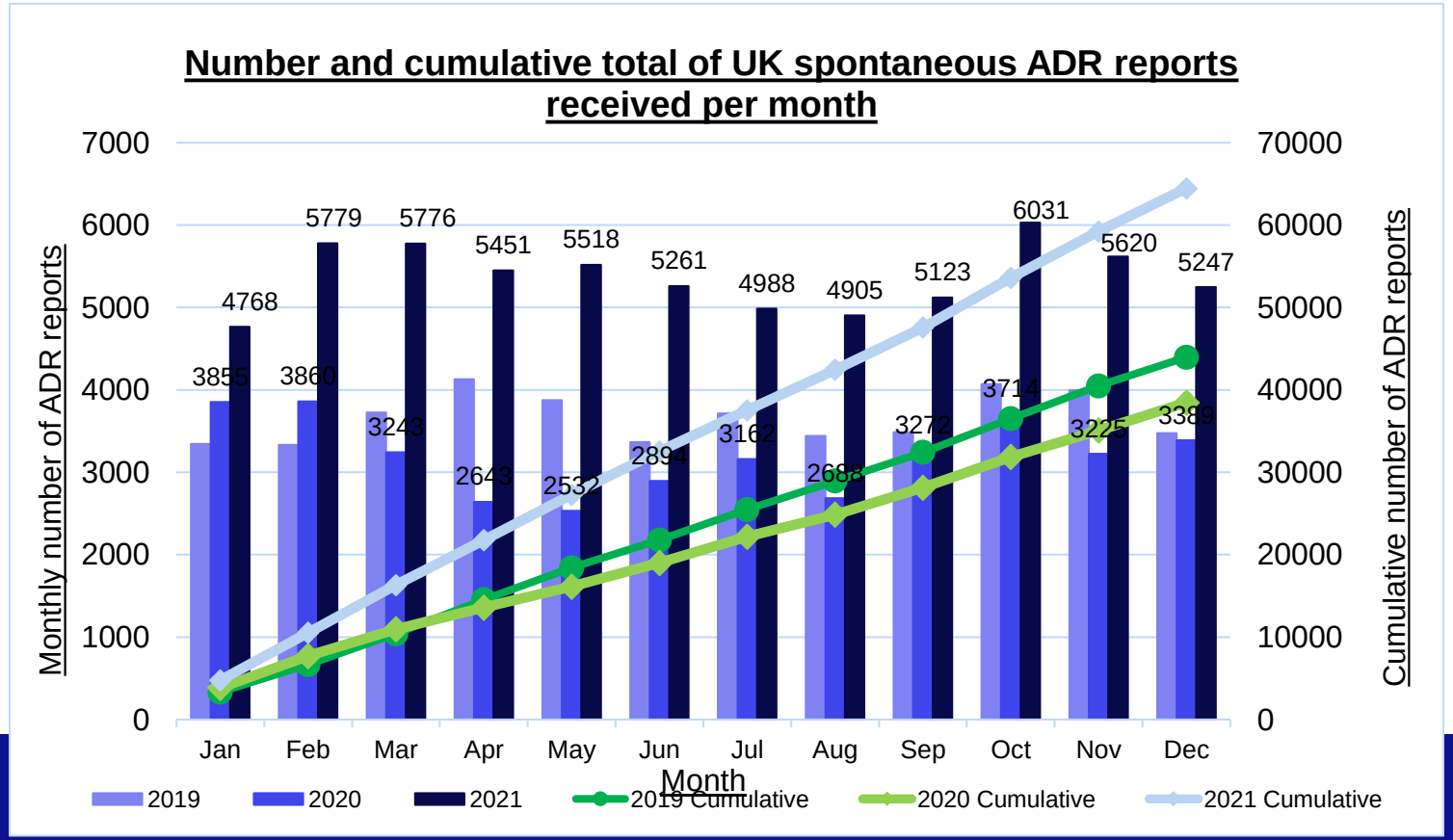
Opportunities

- Use of international datasets can supplement national data to increase sensitivity
- Signals can be detected faster by pooling data from across the globe rapidly increasing knowledge of the safety profile of a product

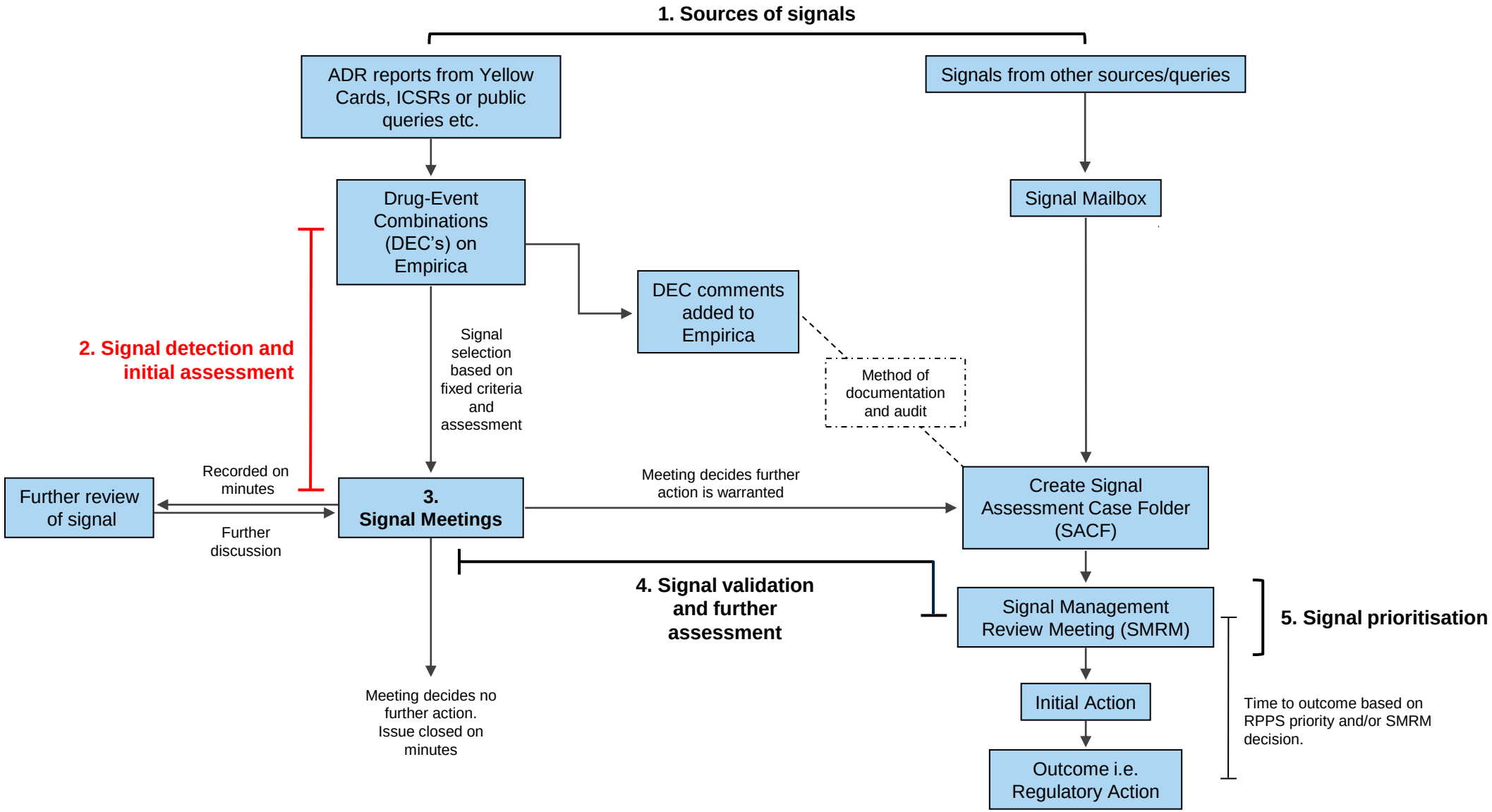
ADR Reporting 2019-2021

- Prior to the pandemic, around 40,000 reports were received annually on average.
- We have received around 64,000 reports in 2021 alone due to the introduction of the COVID-19 vaccines, an additional 425,000 reports in 2021 for the COVID-19 vaccines
- More than 1,000,000 UK reports received to date.

Due to the increased awareness of the Yellow Card Scheme since the start of the COVID-19 pandemic, the Agency has seen an increase in reporting rates for non-COVID-19 vaccine substances too.



Signal Management Process Overview



Signal Detection Processes at the MHRA

- Each new report might be a potential signal – consider if a report represents or contributes to a new signal
- Weekly review of fatal/serious reports received the previous week
- Use statistical tools to facilitate decision making:
  - Empirica programme provides automated statistic calculations of the EBGM to indicate disproportionate rates of reporting
- Signals of potential interest are flagged for assessment based on pre-determined criteria

Signal Detection Processes at the MHRA

- Routine signal detection data are sub-grouped within established medicines and black triangle/additional monitoring medicines by:
    - Vaccine / Non-Vaccine reports
    - UK / Non-UK reports

- Different thresholds for between these data groups:
    – Statistical filtering (~ 85% drug-event pairs filtered out)
    – Rule based approaches (Fatal, paediatric, parent-child, alert terms)

- Multi-disciplinary approach

Why do the MHRA use automated signal detection?

- Traditional method of reviewing every new report
  - Large database at MHRA, over 1000 reports received a week
    (This number may fluctuate with introduction of new medicines, media attention, national vaccination programmes)
- Statistical methods used to automate signal detection:
  - Identify drug-ADR combinations that are disproportionately present in database
  - Systematic and practical means of screening large datasets
  - Improved efficiency by focusing pharmacovigilance efforts on key reporting associations
  - Positive contributions to public health by identifying potential safety issues more quickly and/or more accurately than traditional pharmacovigilance methods
  - Better decision support for the pharmaceutical industry and regulators

UK Reports - Signal Criteria for Established Medicines

- Serious (MedDRA and/or CIOMS* definition) drug-event combinations where EBGM ≥2.5, EB05 ≥1.8, n ≥3:
  - ➢ All unlisted drug-event combinations (D) and listed drug-event combinations – where change in frequency detected (proportion of reports received in last quarter ≥ 8%) (R)
- Reactions from fatal reports (F)
- Reactions from reports involving children (≤18 years) (C)
- Reactions from parent/child reports (including spontaneous abortion) (P)
- Reports for ‘Alert’ terms - medical conditions of interest (A)

* The seriousness criteria for ADR reporting were determined by a working group of the Council for International Organizations of Medical Sciences (CIOMS) and are defined as 6 possible categories which are documented on the Yellow Card. Reporters can select one or more of the following criteria by ticking the appropriate box on the Yellow Card. The criteria are: (1) patient died due to reaction (2) life threatening (3) resulted in hospitalisation or prolonged inpatient hospitalisation (4) congenital abnormality and (5) involved persistent or significant disability or incapacity or (6) if the reaction was deemed otherwise medically significant

UK Reports - Signal Criteria for Additional Monitoring

- All new UK reports
  - Fatal
  - Paediatric
  - Parent/Child reports

EBGM calculations used for reference rather than to filter signals.

Non-UK additional monitoring

→ New serious (MedDRA) drug-event combinations only AND no first cases unless there are UK cases or the event is an alert term AND no listed DECs

→ Fatal reports (serious reactions flagged including first cases and listed events)

Signal Detection Methodologies

Disproportionality Analysis

→ Disproportionality analysis - EBGM

- Stratification & subgroup analyses
- Background rates
  - -Smaller datasets or limited drugs can lead to false positive signalling for rarer events
  - -Vaccine analysis occurs separately due to over-representation of some reactions
  - - Masking due to high profile safety issues

Criteria based

→ Seriousness indicators
→ Population groups
→ Reaction terms of interest
→ Number of cases

Individual Case Review

Statistical methods for signal detection

1) Proportional Reporting Ratio (PRR) → *previously used at the MHRA*

2) Reporting Odds Ration (ROR) → *Netherlands Pharmacovigilance Centre and Eudravigilance*

3) Empirical Bayes Geometric Mean (EBGM) – Adjustments made for increased variability associated with small observed and expected report counts → *MHRA and FDA*

4) Bayesian Confidence Propagation Neural Network (BCPNN) → *WHO Uppsala Monitoring Centre*

Disproportionality for Medicines – Relative Reporting Ratio (RRR) and EBGM

- Compare observed vs expected reporting frequency
- EBGM is derived from the RRR score
- Assume independence of cases associated with either a drug or an event
- Drug-event combination of interest is included in the comparator group (unlike PRR)

Total database = 100 cases
Drug - Paracetamol = 20 cases
Event – Rhabdomyolysis = 10 cases

(Probability of the case being related to paracetamol) (Probability of the ADR being rhabdomyolysis)

Expected reporting frequency – (20/100) x (10/100) = 2 reports of paracetamol and rhabdomyolysis

If there were 8 reports in the database, RRR would be 8/2 = 4*

*EBGM would be derived from this value depending on exact shrinkage applied

Disproportionality for Medicines – Proportional Reporting Ratio (PRR)

- Compare observed vs expected reporting frequency
- Assume independence of cases associated with either a drug or an event
- Drug-event combination of interest is **excluded** in the comparator group (unlike RRR/EBGM)

EBGM – Shrinkage

Used by MHRA and FDA

- Shrinks the log of the observed over the expected towards 0.
- Shrinkage important if the expected is small – more extreme results obtained with smaller expected values.

- In large datasets where there is no over-representation of specific products or events, the RRR and PRR are roughly equivalent.
  - When you have over-representation, the RRR and PRR can deviate substantially when a specific product or event dominate a dataset.

Disproportionality for Vaccines

Separate out vaccines for disproportionality analysis

→ Over-representation of vaccine related reactions

→ Healthy population bias = under-representation of other ADRs

COVID-19 Vaccine Reporting
- Disproportionality using expected calculations from entire vaccine database to see a ‘Vaccine Only’ background
- Combined ‘Medicines and Vaccines’ background calculated in parallel
- Observed volumes overtaking expected volumes within the database

Disproportionality for Vaccines

COVID-19 Vaccine Reporting – separate disproportionality assessment for patient cohorts alongside the rollout

- Booster doses

- Heterologous/Homologous schedules

- Paediatric doses

Thank you

Email: SignalManagement@mhra.gov.uk