Regulatory Expectations on MedDRA Coding Quality

A European perspective

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Topics for today's webinar?

- What are the challenges?
- Background to Data Quality Initiative
- Why is data coding even more important now in 2012 than is 1990's?
- What is the impact on Signal Detection?
- Types of Errors
- Practical Aspects you may want to consider

What are the challenges?

- SUSARs/ICSRs/PMS – coding conventions are variable across regulators and industry
- Standardisation of the collection of data is important
- Need to collect and manage data on the safety of medicines throughout product lifecycle globally
- Systems and processes need to be robust and transparent throughout the organisation
Background to Quality Initiative

- MedDRA is an international terminology which is used in all areas of drug development such as
  - Clinical trials
  - Spontaneous ADRS, Solicited & Post Marketing Studies
  - Regulatory Submissions
  - Product information

- Electronic exchange of information enables submission of cases between regulators and industry across the world and reduces and eliminates the need for manual coding checks of data

- ADR data is made immediately available for qualitative signal detection and evaluation and placed in the public domain

- The E2B standard and use of MedDRA ensures that this information is easily transferred and therefore facilitates uniformity and high quality with regard to the content and format of ICSRs.

Background to Quality Initiative cont

- E2B structure within PV databases was to ensure information on the ADR could be found easily

- However coding inaccuracies are causing
  - An increase of questions for regulators and industry
  - Signal evaluation processes are picking up coding errors (false signals being generated)
  - Case data relating to Adverse Drug Reactions (ADRs) should be placed in structured fields and not in case narrative (missing signals)

- MHRA started looking at these processes and put in place a Quality Audit Process to look at industry data and EMA are also carrying Audits in this area.

- The ultimate aim is to ensure that our inputs for regulatory activities are of high quality so our outputs for signal generation, monitoring RMPs, PSURs, renewals and the ability to monitor benefit risk will be more effective
Why Data Quality is so important for Signal Detection?

- In order to deal with increasing volumes of ADR information- there has been a move to automated signal detection
- This is reliant on ADR information on single cases being coded in relevant structured fields in PV databases
- If data is missing then a signal could be missed – if inaccurate then could generate a false positive
- Data in public domain must be accurate and reflect real time data for any product

High quality data = high quality signals

Therefore in summary

- Electronic ICSR data structure was developed so relevant data on ADRs can be found easily
- Pharmacovigilance databases had good data quality processes built into workflow and data was manually checked
- Now ISCRs data via E2B goes straight intro database ready for signal detection – no manual check and now in public domain
- ICSR data must be placed in structured fields to prevent generation of false signals
- Case narrative to give an account of what happened and must be consistent
- Good data management processes to be put in place to help data quality initiatives
Audits – Sampling exercise

- Impossible to audit all ADR data that you code
- Regulators adopted a sampling size - industry must do the same internally
- Carrying out sampling exercise
- Feedback to individuals within teams
- Initially it is resource intensive until processes established and cross training undertaken
- MHRA developed best practice guide with industry and published in December 2010

The MHRAs Green Guide

- Best Practice on how to code ADRs based on experience of auditing ICSR data and guidance in "Points to consider"
- Important sections
  - Chapters 1, 2, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15
  - Other chapters only relevant to MHRA aspects
  - Requirements for expedited reporting
  - Guidelines on data entry practices and use of the structured data fields
  - Specific information on the coding of drug and reaction information
  - Coding of fatal reports
  - Information which will cause case rejection due to database validation

Common coding Errors

- Missing information from structured fields. Most common are
  - Drug and dose intervals
  - Adverse Drug Reactions
  - Brand names of medicines
  - Medical History
  - Tests

- Drug and Reaction Coding errors
- Accuracy of data – conflicting information
- Administration and database errors that are critical for Duplicate Detection
- Adverse Events Vs Adverse reaction

Missing Information

- Patient age group (if child or elderly)
- Drug dosing information
- History and tests results missing
- ADRs missing

- `<narrativeincludeclinical>` on 12 October, the patient experienced sore throat, fever and developed a rash over body. Two days later it was reported that the patient had developed diarrhoea and mild fever and blood tests showed that his neutrophils were decreased............. `<narrativeincludeclinical>`
Drug Information

- Drug name incorrect or brand name in wrong field or missing brand name (in narrative)
- Missing indication from structured field but present in narrative
- Dates wrong e.g. Drug dates before report sent!
- Only the brand name and active substances should be classified in the `<medicinalproduct>` and `<activesubstance>` tags. Any additional information should be captured in the relevant structured fields and not included as prefixes and suffixes in the drug name tags.
- Frequency for Drug is reported as 'Four times daily' in narrative. Structure this information in:
  - Number of separate dosages (B.4.k.5.3)
  - Interval number (B.4.k.5.4)
  - Definition of Interval number (B.4.k.5.5) fields.

Reaction Information

- Missing reactions and start dates missing from ADR section – but in narrative
- Adverse Event coding along Events
- Outcome incorrect or conflicting in narrative
- Treatments for ADR coded as separate ADRs
- Use of appropriate MedDRA terms- unfamiliarity of terminology
  - Flare up of "a disease" coded as condition aggravated...when specific term is available to code
  - Patient with epilepsy and has ADR of epileptic fit – better term Fit (in known epileptic)
  - Overdose instead of intentional Overdose
Fatal Reports

- What is populated in the reported cause of death fields should reflect what reactions which are coded as fatal. Data must match.

- Reports of disease progression should only be coded as a reaction if the reporter suspects a causal relationship with the suspect drug.

- If the patient experiences a non-fatal ADR, however later dies of an unrelated cause, then the cause of death should be coded in the <patientdeathreport> or <patientdetermineautopsy> fields only.

- If Post-Mortem or Death Certificate details are not available, but information on the report suggests a likely cause(s) of death, this should be entered in the reported cause of death field. Reported cause of death <patientdeathreport>:

- Cause(s) of death identified in autopsy entered in <patientdetermineautopsy>:. For each MedDRA term provided the corresponding MedDRA version must also be populated.

Test results

- Test results should be in structured fields (B.3.1) not narrative.

  - Tests are in narrative including tests like X-ray, CT scan, ECG.

  - When the character limit in the structured field is not enough – the free text test field should be used (B.3.2resultstestprocedures)
Test results

| No | <resulttestsprocedures>on 12-Oct-12 blood sodium levels were 125</resulttestsprocedures> |
| Yes | <test><testdateformat>102</testdateformat><testdate>20121012</testdate><testname>blood sodium level</testname><testresult>125</testresult><testunit>UNK</testunit><lowtestrange></lowtestrange><hightestrange></hightestrange><moreinformation></moreinformation></test> |

Case narrative

Contradictory information.

- If reporting physician assessed the event as possibly related to Drug but commented that the causal relationship between Drug and the ADR was "unknown." AND it is coded as 'Unlikely' in Drug Reaction Relatedness (B.4.k.18.4). Information does not match.

- The case narrative lists recovering and resolving for ADRs reported however data in structured E2B outcome fields says Not Recovered

- Many examples as every case is unique

- Structure all data from case narrative
Incorrect data & Administration Errors

- ADR recovered after X years after stopping drug when calculated recovery is in days
- Patient Age 153 years
- Coded as spontaneous when Study/other study
- Check you are sending to right Database Human, Clinical trial, Vet etc
- Cases reported when Patient has no ADR
- Concomitant drugs often captured in past drug history instead of concomitant drugs field

Incorrect Reports Expedited

- Check Expedited rules against EU
- Do not need to expedite reports in EU with no ADR such as
  - Overdose
  - Medication Error
  - Invalid reports with no patient identifiers
- But collect this data in your database
- Updates needed now for new PV legislation
Data Confidentiality

- Data Protection Laws – Patient and Reporter
- Remove any identifiers from narrative
- Patient names and dates of birth and reporter names and addresses, Hospital admission details etc

Other Regulatory Information

- Guidance in EU states MedDRA should be used
  - Summary of Product Characteristics (in particular for the Contraindications, Special warnings and precautions, and Undesirable effects sections)
  - EU Risk Management Plans (EU-RMP) requires that data are coded in MedDRA terms where appropriate. To allow the identified and potential risks to be monitored in the context of suspected adverse reactions reported to EudraVigilance
Other Regulatory Information

- Allows consistency between risk management plans (identified and potential risks) so you can map terms into Signal detection processes
- Terms used in regulatory information are not always consistent with clinical practice
- To optimise the advantages above we need to agree best practice in coding! Company first then agreement across regions with Regulators.
- Need more published case studies

Considerations

- Set up Internal Audit so coding errors related to Signal detection activities (missing ADR data related to Patient, Drug, Reaction) can be assessed.
- What impact does missing data have on the benefit risk profile of your product?
- Issues must be investigated and root causes found and corrected
- You may need to seek clarifications from regulators to understand the finding
- Corrective actions documented (Training, SOP updates, additional QC checks added)
- Opportunity to carry out Compliance System Review and update processes
Database Considerations

- Standardise coding practices
- Database validations - business rules. Reconfigure database QC validations
  - common sense quality checks e.g. patient age < 120, patient weight < 500kg, drug start date not later than report date etc
- Acknowledgements, Follow-ups and Duplicate Detection algorithm
- Common Medical Dictionary - mappings to alternative medical terminology. Seriousness & Alert terms (product based)
- Drugs Dictionary – aggregate information
- Check database front end fields are populated into correct XML tags in E2B file.

Recommendations

- Review "Points to consider" and "MHRA best practice guide" and "company coding conventions" and incorporate into SOPs for staff conducting coding of any ADR data
- Review your conventions and put in place Quality Assurance Process
- Put in place a quality audit of your data (twice yearly-risk based approach depending on error rate)
- Standardise coding practice across departments so there is agreement on how ADRs should be classified e.g. Fatal outcomes. When disagreement set up a process to discuss?
Conclusions

- We need to standardise data quality initiatives globally across regions so there is agreement on what is acceptable.

- New PV legislation adopted in July 2012 will have impact with regards to widening ADR definition, expedited reporting requirements.

- Need to build in long term solutions with regular review within industry.

- Good data quality enhances signal detection capability and maximises the quality of the information being used to monitor the benefit risk profile of a product.

Glossary

- **EMA** – European Medicines Agency
- **EU** – European Union
- **ICSR** - Individual Case Safety Reports
- **MA** – Marketing Authorisation
- **MAH** – Marketing Authorisation Holder
- **MedDRA** – Medical Dictionary for Regulatory Activities
- **MS** – Member State
- **PMS** – Post Marketing Surveillance
- **PSUR** – Periodic Safety Update Report
- **PV** - Pharmacovigilance
Questions?

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