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IMPROVING CLINICAL DEVELOPMENT TOGETHER!

The European Annual Safety Report: A case study in best practice for outsourcing pharmacovigilance writing to a global CRO

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Agenda

- Case study: the European Annual Safety Report (ASR)
 - Overview of the ASR
 - Lessons learned and best practice for the medical writer in a CRO
- Pharmacovigilance audits and the medical writer



Annual safety reports



Pre-approval periodic safety reports

- EU Annual Safety Report (ASR):
 - Directive 2001/20/EC and ENTR/CT3 Sec. 5.2
 - implemented in May 2004
- US IND Annual Report:
 - 21 CFR 312.33
- Japan: periodic report from 1 April 2009



Developmental Safety Update Report

- ICH E2F: Developmental Safety Update Report (DSUR) would replace regional reports
 - Step 4: Autumn 2009
- Similar to PSURs and ASRs
 - DSUR for marketed product overlaps with PSUR
 - Experience with PSURs/ASRs helpful



Why are ASRs outsourced?

- Lack of capacity
 - Not enough writers, no writing function
 - Part of full service package
 - Buy in expertise:
 - Guidance on a specific document type
 - Independent view of the data
- ⇒ As a medical writer in a CRO, you need to understand why outsourcing has occurred



ASRs

- Assessment of safety conditions of subjects in the trial
- Provides benefit-risk assessment of investigational medicinal product
- Target audience
 - Competent Authorities, Ethics Committees
 - Sponsor
- Must be standalone document



ASR guidance

- Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, April 2006
 - Not detailed instructions
 - Use common sense to present the data in the best way



ASR timing and scope

- Data lock: 1 year after first authorisation in any Member State [DSUR: in any country]
- Submission 60 days after data lock [DSUR√]
- Single report per product [DSUR √]
- Required if at least one EU centre
 - Include sponsor's other trials with product even if no EU centres in those trials



ASR listings

- Line listing of all suspected serious adverse reactions (SARs) [DSUR ✓]
 - Reported during the period
 - Include all SARs reported outside the EU
 - Indicate suspected unexpected SARs (SUSARs)
- ⇒ Develop a template!



Example ASR listing

Product XXX (period: dd mmm yyyy to dd mmm yyyy)

Case Number	Trial Number	Country	Center ID*	Patient ID	Age	Sex	Serious ADR term as reported (verbatim term)	MedDRA lower level term	Treatment	Daily dose	Date of onset of reaction	Dates of treatment (duration)	Outcome	Listed Y/N	Comments **
1234_5678	A123	Outer Mongolia	012	234	45	M				Xx mg Tablets, orally	Dd mmm yyyy	Dd mmm yyyy to dd mmm yyyy (x months)	Resolved	y	
etc															

*optional – column may be removed if patient ID is unique for the trial

**if this field cannot be automatically populated for example because there is no defined field in the safety database then it can be left blank

Example DSUR listing

INTERVAL LINE LISTINGS OF SERIOUS ADVERSE REACTIONS (SARS)

Study ID EudraCT number	Case ID Subject number	Country Gender Age	Serious ADR(s)	Outcome	Date of onset Time to onset	Suspect drug	Daily dose Route Formulation	Dates of treatment Treatment duration	Comments
Gastrointestinal disorders									
12345 2008-000603-21	MO_5678 9999	Outer Mongolia 45 M	Abdominal pain	Resolved	Dd mmm yyyy	Y	Xx mg Tablets, orally	Dd mmm yyyy to dd mmm yyyy (x months)	
etc									



ASR summary tabulation

- Summary table of suspected SARs
 - Unexpected events (SUSARs) clearly indicated
 - By system organ class (SOC) and treatment arm
- DSUR is different: cumulative summary of SAEs
 - By SOC and treatment arm
 - EU appendix with equivalent ASR table



Analysis of subject safety

ASR guidance requires analysis of subject safety in the concerned clinical trial(s)

- Need clear listings and tabulations!
 - Data from a safety database may be lacking in detail or currently being queried
 - Safety database should support specific query requests



Analysis of subject safety (cont'd)

- Literature search:
 - Evidence pertinent to benefit-risk of product.
- Other sources
 - Other clinical trials
 - non-clinical data
 - Spontaneous reports for products with Marketing Authorisation.

DSUR ✓



Lessons learned for ASRs



Lessons learned: two main themes

- Timeline and process management
- Communication

⇒ Not “new news” for medical writers!



Keeping to timelines

- Know when the ASR is due
 - CRO responsibility for full service trial
- Have a well defined process
- Clear template: guidance on content
 - Helps CRO medical writer (MW) to respond to short notice requests
- Plan and agree timelines in advance
 - Take into account CRO review process
 - Any Sponsor review cycle



Communication

- Document key contact information
 - Obtain Sponsor contact names at kickoff
 - CRO MW should consider using safety reporting form, e.g.
 - Key contacts at Sponsor and CRO
 - Review team and process
 - Literature databases to be searched
 - Who will submit report
- Sponsor or CRO template and SOPs?



Communication (cont'd)

- Agree listing/summary format upfront
 - Confirm who (Sponsor/CRO) provides listings/summary tables
 - If Sponsor, CRO MW should request template in advance
 - If CRO to Sponsor format, plan time to validate the format
 - How to present blinded vs unblinded data
 - Confirm how the data will be queried



Obtain complete data

- Are all relevant studies, current protocols and amendments included?
 - Especially if CRO not running all trials
 - Data Monitoring Committee?
 - PSUR or RMP for product?
 - CRO MW should consider using Sponsor ASR checklist
- ⇒ Even more important for DSURs



Data quality

- Good data entry/data quality is key
 - Garbage in, garbage out!
 - CRO MW is the Sponsor's point of contact on data issues
- QC process for listing/summary generation
 - Changes go back to source
 - MW should not edit listing/summary



Unblinded data

- ASR may include unblinded data
 - SUSARs are unblinded
 - Other SARs may have been unblinded
- Who must remain blinded?
 - Decide how to handle unblinded data within internal team
 - Check which (if any) Sponsor staff may see the ASR
- Refer to any Data Monitoring Committee



Overall safety evaluation

- MW prepares draft text
- Final conclusions, including any change to risk-benefit evaluation, requires input from physician who is
 - Aware of drug safety profile
 - Monitoring it on an ongoing basis
- Will this input come from CRO or Sponsor physician?
- Ensure adequate time for preparation and review of this section



Pharmacovigilance audits



Pharmacovigilance audits and MW

- MWs are called to participate in:
 - Sponsor pharmacovigilance audit of service provider
 - CRO support during pharmacovigilance inspection of Sponsor
 - Regulatory inspection of CRO
- Be prepared!
 - Establish and test your process for preparation of pharmacovigilance documents



Example audit findings

ASRs

- Inadequate discussion of risk-benefit evaluation
- No cross-referencing between ASR and PSUR

PSURs

- No SOP for PSUR preparation
- Inadequate literature search strategy
- Cases missing from line listings
- Line listing and executive summary did not agree
- Study results not adequately discussed
- PSUR not in required format, incomplete, late

Good Pharmacovigilance Practice Guide, Common Inspection Findings at www.mhra.gov.uk



Conclusions

- Pharmacovigilance documents have not traditionally been written by MWs
 - The MW skillset helps to ensure high quality, compliant documentation
- When working on these documents, many considerations for the MW are similar whether working for a CRO or pharma
- In addition, the CRO MW can ensure efficient interaction and successful outcomes for the Sponsor and CRO team



Questions?

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European ASR

- Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, April 2006 (ENTR/CT3 Sec. 5.2) (<http://ec.europa.eu/enterprise/pharmaceuticals/eudralex>)
- Good Pharmacovigilance Practice Guide, pp 142-143. MHRA. Pharmaceutical Press 2009. ISBN 978 0 85369 834 0
- EU Directive 2001/20/EC

US IND Annual Report

- 21 CFR 312.33

DSUR

- ICH E2F Note for Guidance on Development Safety Update Report (EMA/CHMP/ICH/309348/2008) (www.emea.europa.eu/pdfs/human/ich/30934808en.pdf)

