QUANTITATIVE REVIEW OF EFFECTIVENESS OF RISK MINIMISATION MEASURES IN SURVEYS & OUTCOME STUDIES IN EUROPE

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CONFLICTS OF INTEREST

OXON Epidemiology: Conducts field & database observational studies for industry

- Esther Artime, MSc, Manager, Pharmacoepidemiology & Risk Management Centre for Real World Field Studies, Madrid
- Kirsten Rennie, MA(Cantab) MSc PhD, Director of Epidemiology Centre for Real World Database Studies, London

Stuart Pocock, Professor of Medical Statistics, London School of Hygiene & Tropical Medicine

Bayer AG, Epidemiology:
- Montse Soriano Gabarro, MD, MSc, Head of Epidemiology
- Alex Asiimwe, MSc, PhD, Director Epidemiology
- Pareen Vora, MSc, Epidemiologist

EMA: Thomas Goedecke
ENCePP S.I.G on Measuring Impact of PV Activities
AGENDA

1. SURVEY STUDIES
2. OBJECTIVES
3. METHODS
4. RESULTS
5. LIMITATIONS
6. CONCLUSIONS & RECOMMENDATIONS
7. OUTCOMES STUDIES
1 SURVEY STUDIES
OBJECTIVES
EU RM SURVEY STUDIES - GUIDANCE

• GVP XVI on Risk Minimisation – Annex 1 on Survey Methodology
• CIOMS Report 2014
• ENCePP Methods Guide – Section 4.1.1 on Surveys
• Standard survey texts

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OBJECTIVES

1. To describe and analyse study characteristics and results of survey studies assessing the effectiveness of risk minimisation measures (RMMs)
   - Participation
   - Receipt
   - Usage
   - Knowledge
   - Behaviour

2. To describe regulatory consequences
DATA SOURCES

- EU PAS Register
- Sponsoring companies
- Freedom of Information request to EMA and National Agencies
- Other: EMA website

Final Study Reports

Assessment Reports of Final Study Reports (consequences)

EPARs, PRAC agendas/ minutes, SmPCs
STUDY INCLUSION CRITERIA

- **Survey** component assessing effectiveness of routine or additional RMMs
- In the **EU PAS Register** until 26 May 2017
- Studies with **reports** (in the EU PAS Register/ from EMA/ from Pharma companies)
- Involvement of ≥ 1 **European country**
3

SURVEY STUDIES

RESULTS:

• Study Selection & Characteristics
• Participation Data
• Receipt
• Use
• Knowledge
• Behaviour
SELECTION PROCESS

Records identified in the EUPAS Register (up to 26 May 2017)

- 1084

Records excluded (not RM studies) (n=990)

- RM studies excluded (n=47)
  - non-European surveys (n=6)
  - without survey component (n=41)

RM studies screened for eligibility

- 94

EU RM Survey studies

- 47

RM studies without report (n=32)
  - 2 'finalised'
  - 17 'ongoing'
  - 12 'planned'

EU RM Survey Studies + Report

- 16

+2 from Companies

EU RM Surveys Included

- Approx. 40%
- 18

EU RM Surveys Excluded

- 29

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## STUDY CHARACTERISTICS (I)

### Population
- HCP: 14/18
- Patients: 1/18
- HCP and Patients: 3/18

### DRUGS: ATC
- N-nervous system: 7/18
- L-antineoplastic and immunomodulating: 3/18
- Others: 8/18

### RMM TYPE
**Additional:** 16/18:
- PACs: 6/16
- DHPCs 5/16
- Brochures for HCPs 13/16
- Brochures for patients/caregivers 4/16

### STUDY DESIGN
- One-wave X-sectional: 15/18
- Multi-wave design: 3/18
STUDY CHARACTERISTICS (II)

**TARGET POPULATION**

**Number of countries:** Median of 7.5; Range 1 - 12

**Type of participants:**
- GPs: 50.0%
- Specialists: 88.9%
- Nurses: 5.6%
- Pharmacists: 16.7%
- Patients or caregivers: 27.8%

**OUTCOMES**

- Outcome evaluations alongside surveys in 5 of 18 (27.8%)
  - Drug utilization: 3
  - Monitoring: 1
  - ADRs: 1
CALCULATED PARTICIPATION DATA

**HCP Surveys**

Completers / eligible: **93.4%** (86.8 - 97.9)

Completers / invited: **5.4%** (3.5 – 7.7)
PARTICIPATION DATA

Reporting scheme

Population

Sample invited

Contacted

Screened

Eligible

Agree

Completers

Target sample size

→ Contact Rate = Contacted / Targeted

→ Response Rate = Completers / Invited

→ Completion Rate = Completers / Eligible

→ Respose Rate = Agreed / Contacted

→ Cooperation Rate = Completers / Agreed

→ Eligibility Rate = Eligible / Screened

→ Completers / Screened
10 studies with **17** educational materials
RECEIPT

HCP Surveys - by Type of Educational Material

HCP CHECKLIST: 19.5% (14.2 – 25.4)

PACs: 48.1% (19.4 - 77.4)

DHPC: 44.2% (40.9 - 47.5)

HCP BROCHURES: 53.4% (36.8 – 69.6)
Receipt by patients of 4 educational materials in 3 studies → 50% - 80%

**RECEIPT OVERALL**

- Study 3B PAC
- Study 13B Patient Information Brochure
- Study 13B PAC
- Study 16 Patient Brochure

**PACs:** 55.6% (52.2 – 59.0)

**BROCHURES:** (61.0 – 82.1)
5 studies with 15 educational materials

80% of educational materials had use levels of 50-70%
Reported use in 2 studies of 4 educational materials: < 30% for 2 items

**Use**

**Patient Surveys - Overall and by Type of Educational Material**

**BROCHURES:** 64.3% (48.3 – 78.8)

**PACs:** 17.9% (2.5 – 43.0%)
13 studies with knowledge of 46 safety concerns

Knowledge of 33 safety concerns:
  - > 80% for half of safety concerns
  - > 50% for 90% of safety concerns
2 Studies with 13 safety concerns

Knowledge < 50% for 60% of safety concerns

Knowledge 50 – 70% for 31% of safety concerns
• Reported in **8/18**

• Data extractable for 25 items in only **4 studies:**
  - All 25 items > 50% correct responses
  - 9/25 items > 80% correct responses
REGULATORY CONSEQUENCES

From PRAC and National Regulatory Reports

8/15

15/18 Studies with Assessment Reports of the FSRs

- No changes to existing RMMs
- Changes to the distribution method
- Further data awaited to assess the need for amendment of the educational materials
- Changes to existing aRMMs
- Removal of aRMMs
- Changes to the SmPC
- aRMMs implemented
- Re-analysis requested by PRAC
- Further discussion planned within the context of the 2017 PSUSA
- Feedback from patients and specialists to determine the goodness and need for updated aRMMs

Not mutually exclusive categories
SURVEY STUDIES
LIMITATIONS
LIMITATIONS

- **Incomplete**: 3 (+4?) studies recently acquired and being evaluated
- **Behaviour** remains to be further analysed
- **Questionnaire validation**: inadequate description 50% not reported

- **Non-systematic**: Limited to FSRs in EU PAS Register (+ some sponsors)
- **Publication bias?**
- **Generalizability?** → biased participant samples?

- **Heterogeneity** of studies by design, characteristics, and results → Case studies may be more relevant
- **Subgroup analyses/meta-regression** hindered by access to detailed data
- **Changes in reporting practices with time?** → More reports for time trends
- **Confounding?**
- **Lack of outcomes** - ~ a third have accompanying outcomes. but process outcomes also needed
SURVEY STUDIES
CONCLUSIONS & RECOMMENDATIONS
SUMMARY & RECOMMENDATIONS

- **Regulatory consequence:** Most frequently no change to RMM
- **Receipt:** moderate and better for HCP/patient brochures
- **Use:** moderate in HCPs and lower in patients
- **Knowledge of AEs:** HCPs > patients

- **Variability in reporting** sampling, participation data, qualitative approaches to testing questionnaires and key endpoints

- **Lessons learned for study conduct (Case studies)**
- **Heterogeneity of results and evaluations** → results interpreted within the context of each evaluation

- **Need for more specific and detailed guidance**
  - Revise Methods Guide on Surveys
  - Reporting of surveys
STUDIES WITH ‘OUTCOMES’
SELECTION PROCESS

Reports until Aug 2016

872 studies registered in the EU PAS register (30 Aug 2016)

No additional databases were searched

872 records screened for risk minimisation studies

796 records which were not risk minimisation studies were excluded

76 risk minimisation studies assessed against eligibility criteria

57 records were excluded: Studies without study reports or results as planned/ongoing* (n=51)
Non-European (n=6)

19 records with study reports

11 surveys

8 studies using secondary data

*Status for five out of 51 was completed
# STUDY CHARACTERISTICS

**Eight studies**

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RMMs</strong></td>
<td>• All aRMMs + 5/8 also rRMMs e.g. label changes</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td><strong>Retrospective cohort studies</strong>: 7/8 → Drug Utilization Studies</td>
</tr>
<tr>
<td></td>
<td>• 3 with pre-post design (label changes, DHPC)</td>
</tr>
<tr>
<td></td>
<td><strong>Cross-sectional study</strong>: 1/8</td>
</tr>
<tr>
<td><strong>Data Sources</strong></td>
<td>• 2/8 electronic/paper medical records</td>
</tr>
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<td></td>
<td>• 6/8 multiple healthcare databases</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>• Drug utilization</td>
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<td></td>
<td>• Monitoring of laboratory parameters</td>
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<td></td>
<td>• AEs</td>
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RESULTS

As reported

23 indicators in 8 studies:

- ‘success’: 8/23
- inconclusive: 1/23
- 1/23: success in one country but inconclusive in the other country
- Insufficient information: 13/23
Thank you!

Additional information and case studies:
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