EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Overview of methodologies and studies evaluating risk minimisation measures

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EMA – 16 September 2015

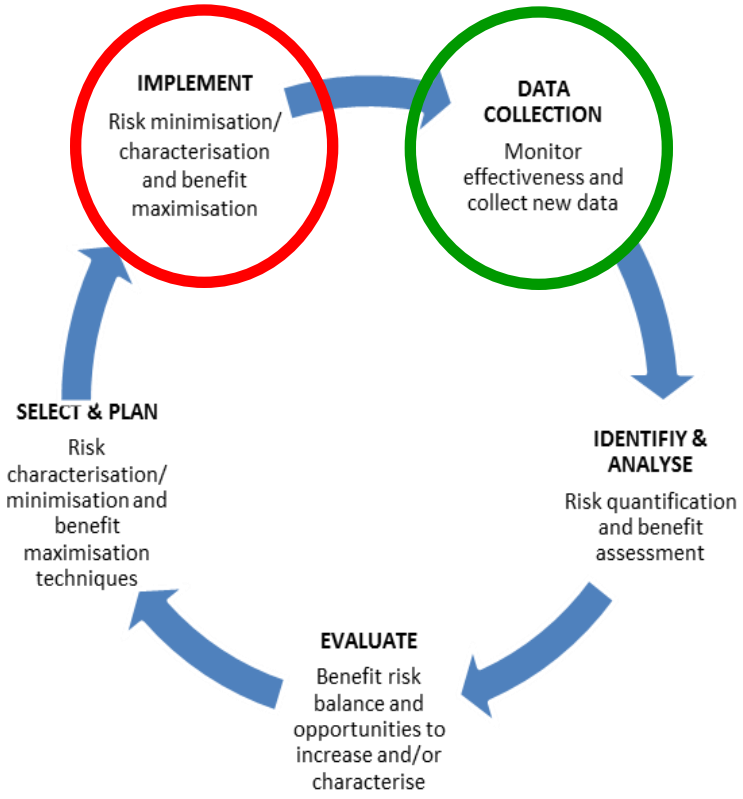
Outline

- To highlight the role of the studies evaluating the effectiveness of RMMs in life-cycle approach of risk management planning
- To describe the models and methods for evaluation
- To provide a real-life overview of these studies

The life-cycle approach of the risk management

Risk management has three stages which are interrelated and reiterative:

1. Identification of the safety profile of the medicinal product
2. Planning of pharmacovigilance activities to characterize and/or identify risks
3. Planning and implementation of risk minimization or mitigation and **assessment of the effectiveness of these activities**



Studies measuring the effectiveness of RMMs

Routine RMM

(Product information [SmPC, PIL])

Can be requested (or proposed) during the MA procedure or in the post-marketing phase

aRMM

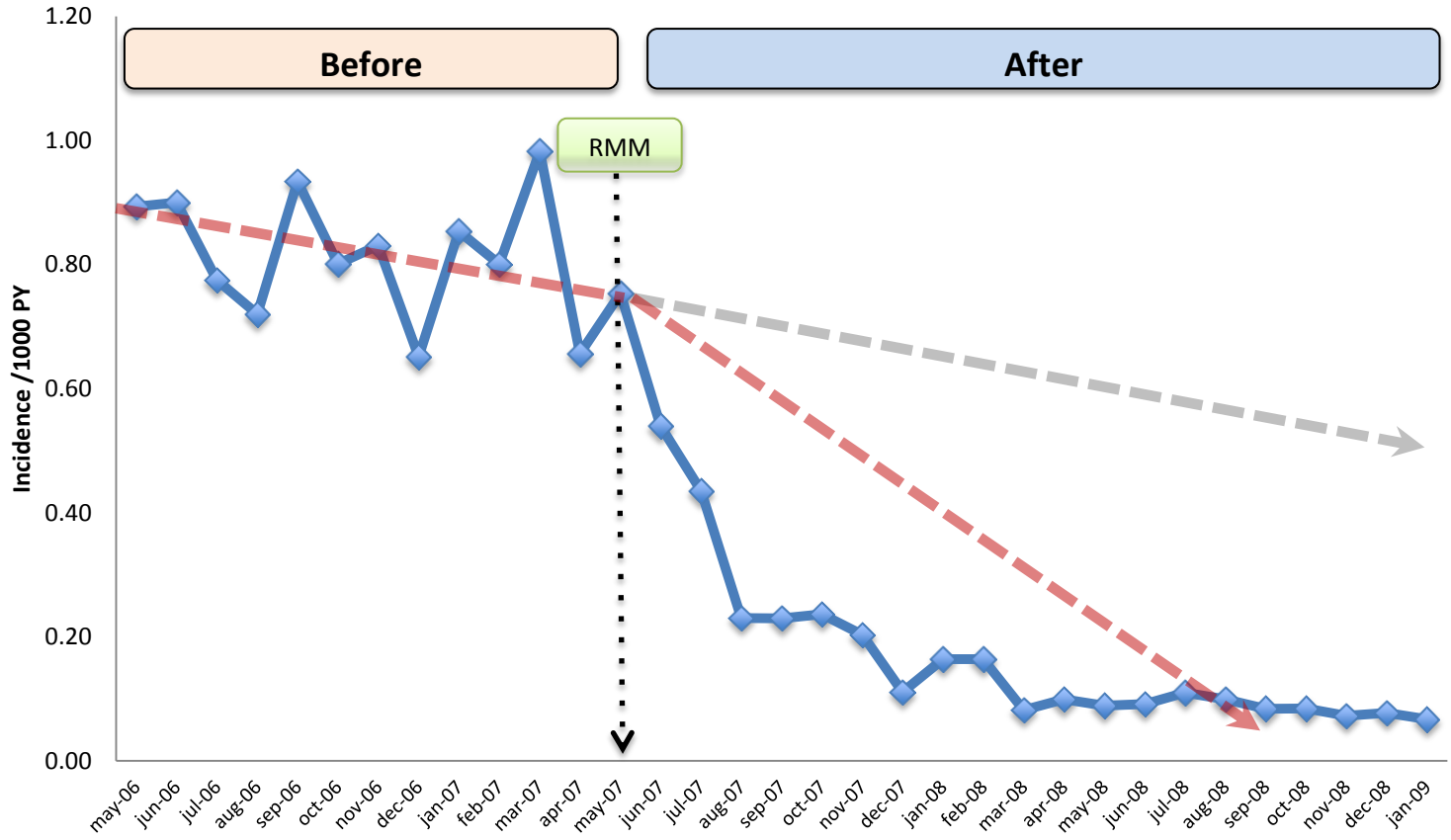
(Healthcare professionals [HCPs]/patients guide; PAC, controlled access)

Mandatory requirement

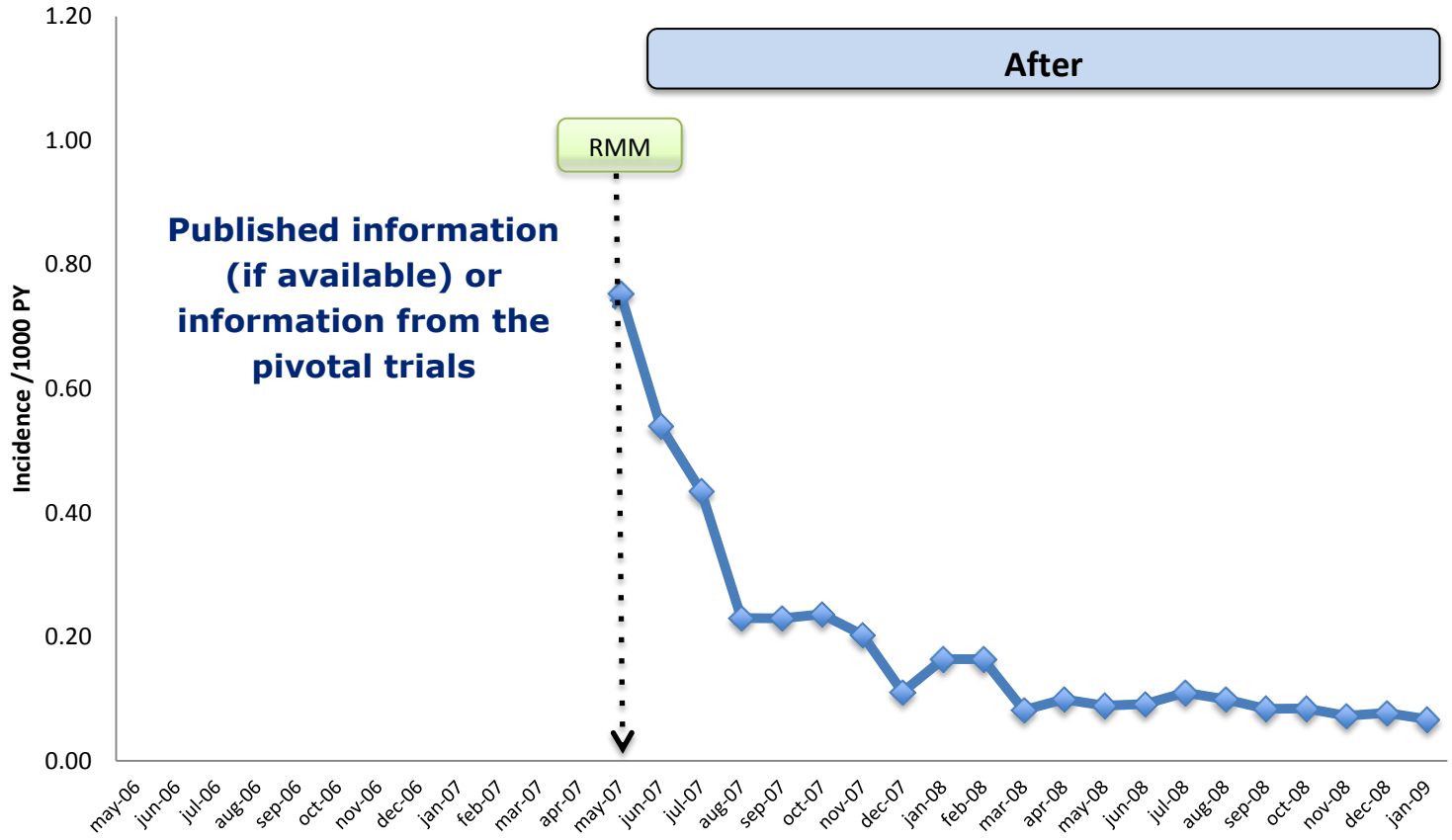
Definition

Studies aimed to establish whether an intervention requested to minimise the risk of a medicinal product has been effective or not, and if not why not and which corrective actions are necessary

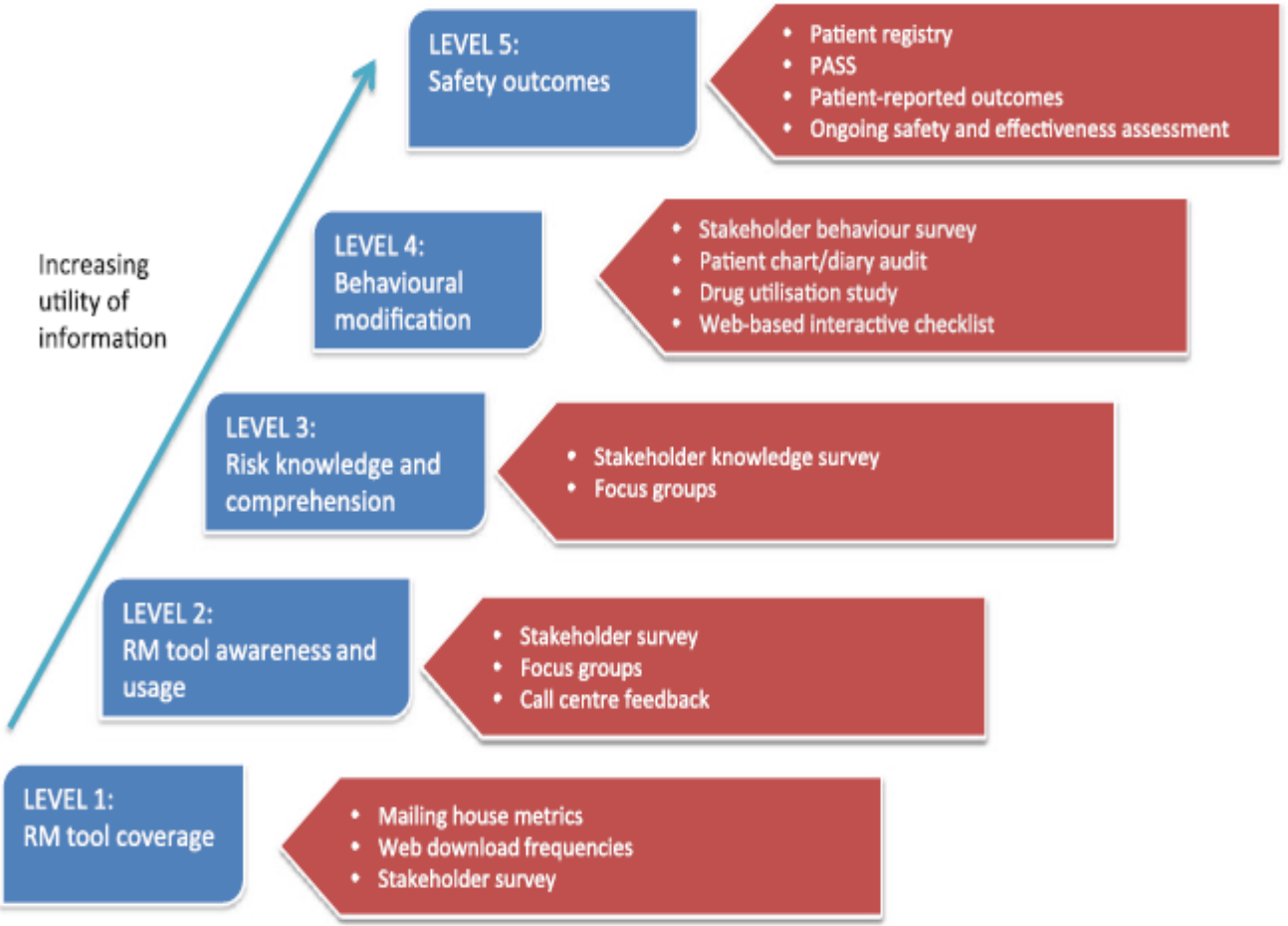
Measuring the impact of RMMs using a pre- post-comparison design



Measuring the impact of RMMs only with post-implementation information



What to measure?

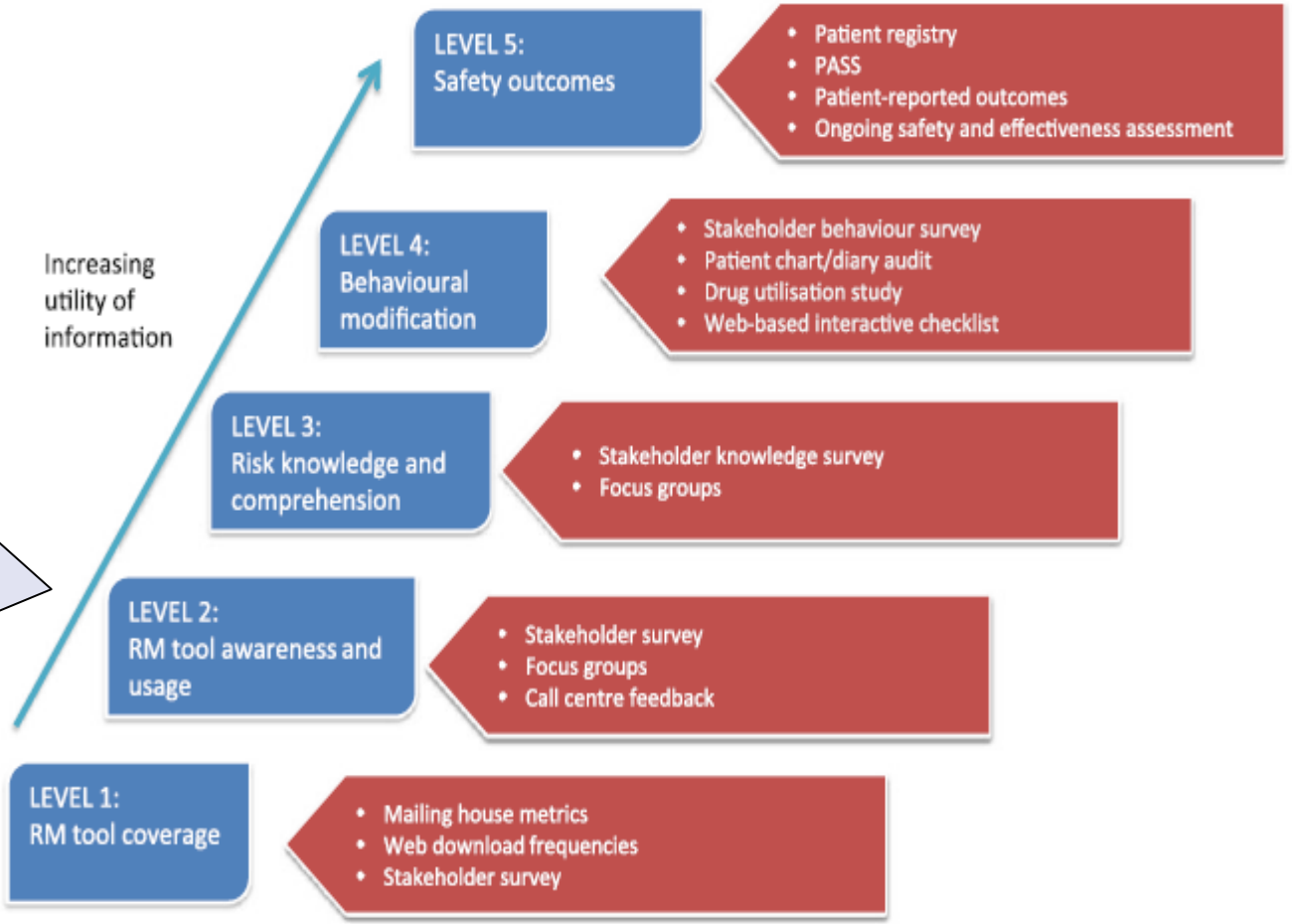


Smith et al. Therapeutic risk management of medicines. 1st ed. Cambridge: Woodhead Publishing; 2013.

Evaluation strategy

- All models emphasise the common principle that the ideal approach would require a stepwise assessment with increasing utility of information (but with increasing study complexity)
- Safety outcomes remain the essential objective of the evaluation
- In real life the criteria for judging the best approach for evaluation are based upon:
  - Time (need for timely results)
  - Data sources (data available on behavioural modification and safety outcomes, feasibility, reliability, etc.)
  - Safety concern (severity/seriousness of the risk addressed by the RMM)

What to measure:
coverage/awareness/knowledge



Are HCPs aware of the new recommendations?

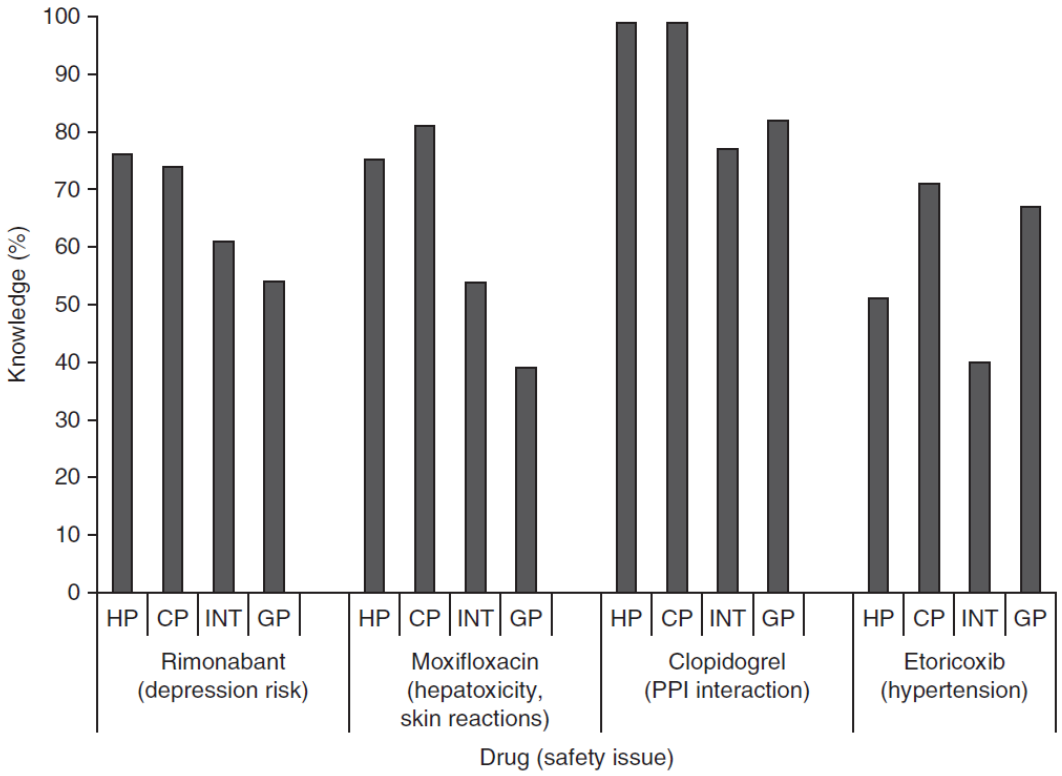
Did the DHPC/PI/EM arrived?

Did the HCPs read it?

Did the HCPs understand it?

Healthcare Professionals' Self-Reported Experiences and Preferences Related to Direct Healthcare Professional Communications

- 16% of HCPs (ranging from 5% of the hospital pharmacists to 28% of the GPs) were not familiar with DHPCs.
- The majority (58%) of the HCPs indicated that they read only the DHPCs that contained information that was relevant to them
- 30% of the community pharmacists read all letters they received from the pharmaceutical industry

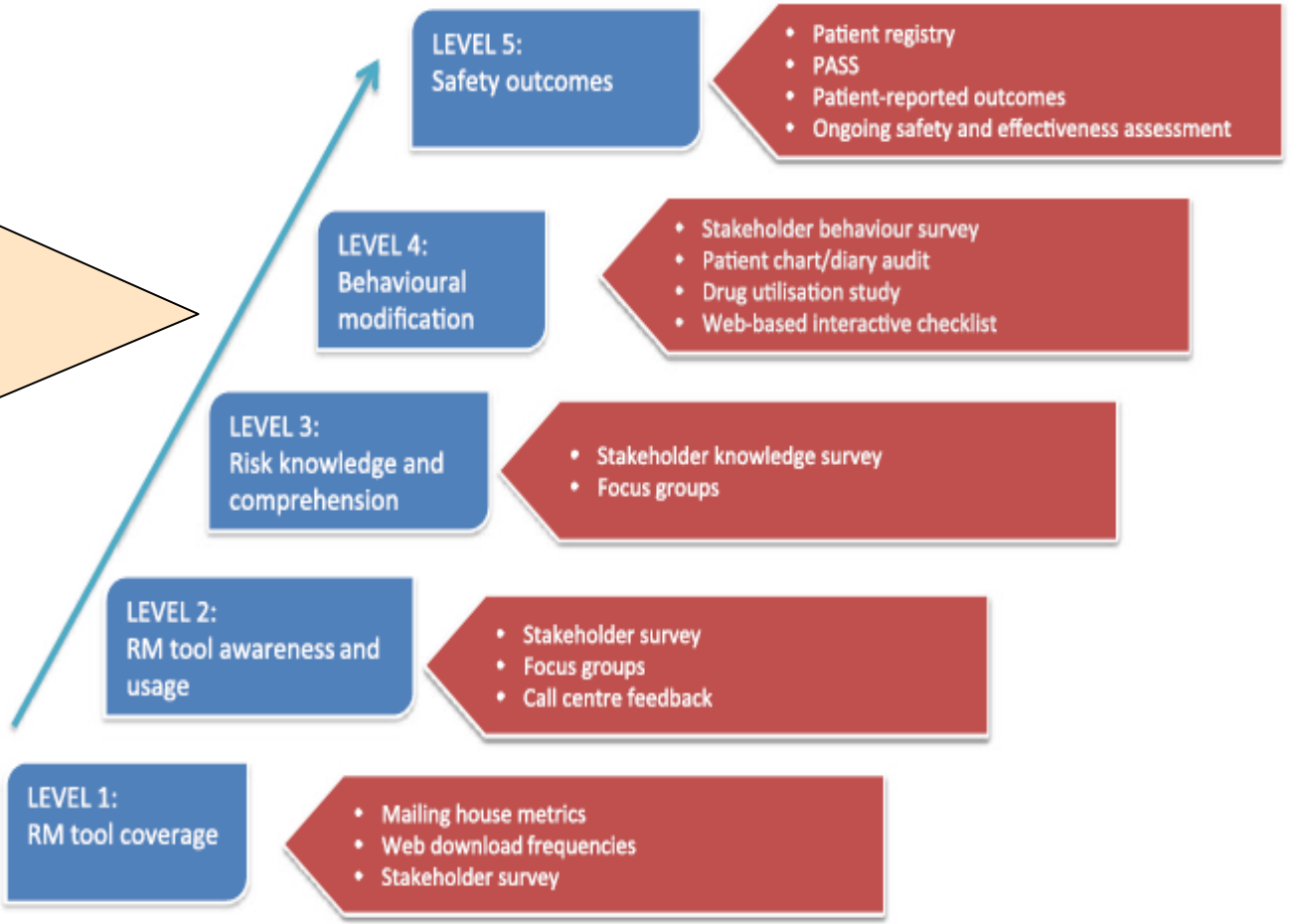


Drug Saf 2012; 35 (11): 1061-1072

What to measure: clinical actions/behaviour

Have HCPs changed their prescribing behaviour?

1. Did the HCPs treat only patients within the approved indication?
2. Did the HCPs stopped treatment among patients with new contraindications?
3. Did the HCPs initiate treatment among patients new contraindications?
4. Did the HCPs regularly assess the baseline risk in patients exposed with the drug?



May 2007

FDA Issues Safety Alert on Avandia

The U.S. Food and Drug Administration (FDA) is aware of a potential safety issue related to Avandia (rosiglitazone), a drug approved to treat type 2 diabetes. Safety data from controlled clinical trials have shown that there is a potentially significant increase in the risk of heart attack and heart-related deaths in patients taking Avandia. However, other published and unpublished data from long-term clinical trials of Avandia, including an interim analysis of data from the RECORD trial (a large, ongoing, randomized open label trial) and unpublished reanalyses of data from DREAM (a previously conducted placebo-controlled, randomized trial) provide contradictory evidence about the risks in patients treated with Avandia.

Patients who are taking Avandia, especially those who are known to have underlying heart disease or who are at high risk of heart attack should talk to their doctor about this new information as they evaluate the available treatment options for their type 2 diabetes.

European Medicines Agency
Press office

London, 23 May 2007
Doc. Ref. EMEA/230057/2007

PRESS RELEASE
EMEA statement on recent publication on cardiac safety of rosiglitazone (Avandia, Avandamet, Avaglim)

An article published in the New England Journal of Medicine (NEJM) has raised concern about a small increased risk of myocardial infarction and cardiovascular death in patients with type 2 diabetes treated with rosiglitazone. The article, based on an analysis of data retrieved from 42 clinical studies, showed a small increased risk for myocardial infarction and cardiovascular death among approximately 15,500 patients treated with rosiglitazone. However, death from all causes was not significantly increased.

January 2008

European Medicines Agency
Press office

London, 24 January 2008
Doc. Ref. EMEA/42232/2008

PRESS RELEASE
EMEA recommends new warnings and contraindications for rosiglitazone

The European Medicines Agency (EMEA) has recommended updating the product information for rosiglitazone-containing antidiabetic medicines. Rosiglitazone is available in the European Union as Avandia (rosiglitazone maleate), Avandamet (rosiglitazone maleate/metformin) and Avaglim (rosiglitazone maleate/glimepiride).

During its January 2008 meeting, the Agency's Committee for Medicinal Products for Human Use (CHMP) adopted a scientific opinion recommending the inclusion of a new warning stating that the use of rosiglitazone in patients with ischemic heart disease and/or peripheral arterial disease is not recommended.

The CHMP also adopted an opinion recommending the addition of a new contraindication stating that rosiglitazone must not be used in patients with an acute coronary syndrome, such as angina or some types of myocardial infarction, because the medicine has not been studied in controlled trials in this specific patient group.

Prescribing pattern of glitazones in the UK in the years 2006-2009: a focus on the effects of safety warnings about rosiglitazone

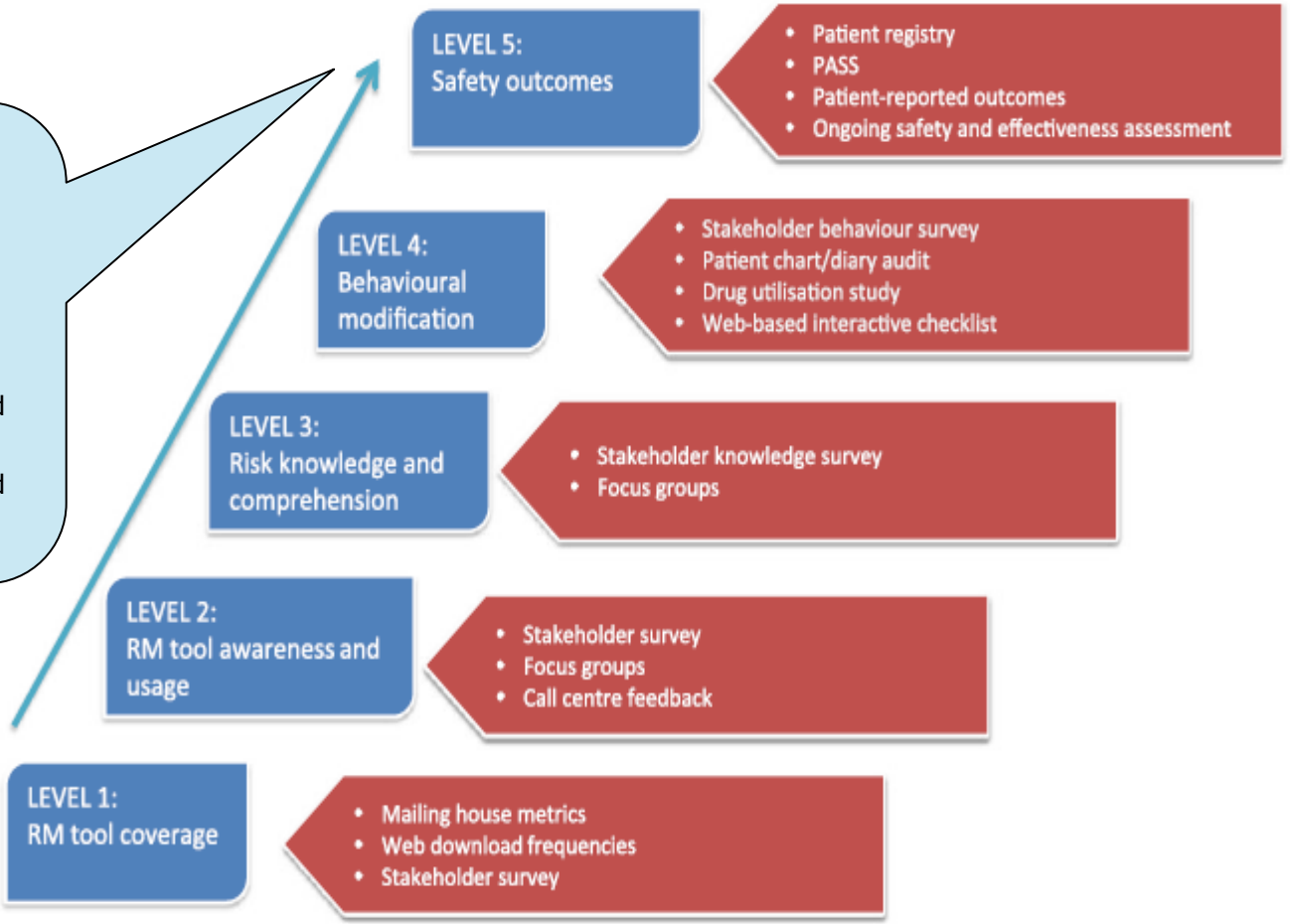
	Rosiglitazone Period 1	Period 2	Period 3	P_{trend}
Number of new users	1972	923	269	–
TZD as first GLD drug ever (%)	44 (2.23)	18 (1.95)	4 (1.49)	–
Age (SD) (years)	61.70 (12.38)	61.40 (12.39)	61.18 (13.23)	0.523
Male (%)	1135 (57.56)	516 (55.90)	150 (55.76)	0.390
Users with concomitant use of insulin (%)	18 (0.91)	15 (1.63)	7 (2.60)	0.011
Angina (%)	222 (11.26)	82 (8.88)	15 (5.58)	0.001
History of myocardial infarction (%)	182 (9.23)	75 (8.13)	14 (5.20)	0.031
History of coronary heart disease*	314 (15.92)	122 (13.22)	23 (8.55)	<0.001
History of congestive heart failure (%)	45 (2.28)	14 (1.52)	5 (1.86)	0.286
History of hypertension (%)	1011 (51.27)	473 (51.25)	139 (51.67)	0.934
Obesity (%)	419 (21.25)	214 (23.19)	70 (26.02)	0.055
Lipid metabolism disorders (%)	551 (27.94)	249 (26.98)	81 (30.11)	0.806
History of cerebrovascular disease (%)	77 (3.90)	23 (2.49)	8 (2.97)	0.112

Br J Clin Pharmacol. 2013;75:3 861–868

What to measure: safety outcomes

Is the incidence of the AE decreased following the implementation of the RMM?

Assess the incidence among exposed patients pre- post-implementation?
Assess the incidence among exposed patients in and off-label?



Article

Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents

FIGURE 1. SSRI Prescription Rates in the United States, 2002–2005, Stratified by Age Group and Expressed as a Percentage of the 2003 Rate

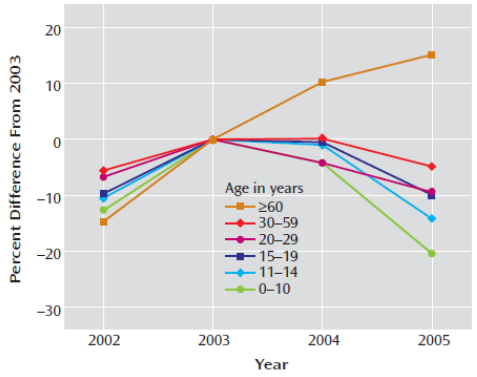
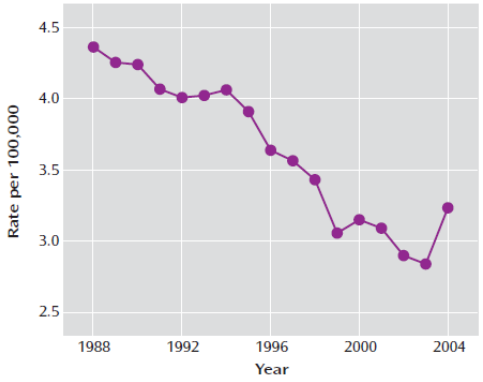


FIGURE 2. Suicide Rate in Children and Adolescents (Ages 5–19 Years) in the United States, 1988–2004



Objective: In 2003 and 2004, U.S. and European regulators issued public health warnings about a possible association between antidepressants and suicidal thinking and behavior. The authors assessed whether these warnings discouraged use of antidepressants in children and adolescents and whether they led to increases in suicide rates as a result of untreated depression.

Method: The authors examined U.S. and Dutch data on prescription rates for selective serotonin reuptake inhibitors (SSRIs) from 2003 to 2005 in children and adolescents (patients up to age 19), as well as suicide rates for children and adolescents, using available data (through 2004 in the United States and through 2005 in the Netherlands). They used Poisson regression analyses to determine the overall association between antidepressant prescription rates and suicide rates, adjusted for sex and age, during the periods preceding and immediately following the public health warnings.

Results: SSRI prescriptions for youths decreased by approximately 22% in both the United States and the Netherlands after the warnings were issued. In the Netherlands, the youth suicide rate increased by 49% between 2003 and 2005 and shows a significant inverse association with SSRI prescriptions. In the United States, youth suicide rates increased by 14% between 2003 and 2004, which is the largest year-to-year change in suicide rates in this population since the Centers for Disease Control and Prevention began systematically collecting suicide data in 1979.

Conclusions: In both the United States and the Netherlands, SSRI prescriptions for children and adolescents decreased after U.S. and European regulatory agencies issued warnings about a possible suicide risk with antidepressant use in pediatric patients, and these decreases were associated with increases in suicide rates in children and adolescents.

(Am J Psychiatry 2007; 164:1356–1363)

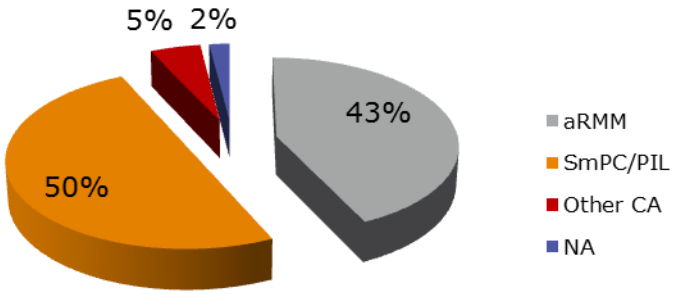
Critical shortcomings in the evaluation system

1. Appropriate data collection from HCP' surveys (i.e. unrepresentative sample size, lack of objective standards to measure knowledge)
2. Appropriate data collection from electronic healthcare databases (i.e. unrepresentative country, lack of relevant data routinely captured, incorrect definitions of outcomes/covariates)
3. Lack of meaningful outcomes (i.e. inability to translate in measurable indicators the proposed RMM)
4. Lack of benchmark (i.e. difficulties in defining what acceptable levels of distribution, tool uptake and impact on knowledge, behaviours and outcomes, constitute success)

Drug Safety, 2014; 37:33–42

Studies measuring the impact of RMMs: overview

- 176 out of 248 **(70.9%)** RMPs on active CAPs approved with cardiovascular, endocrinology and metabolic indications
- Data Lock Point: February 2015
- 52 CAPs out of 176 with RMP **(29.5%)** have studies in the PhV plan assessing (ongoing) or having assessed (final) the effectiveness of RMMs or the adherence to recommendations
- A total of **58 studies** (20 finalised, 37 ongoing, 1 NA) were considered



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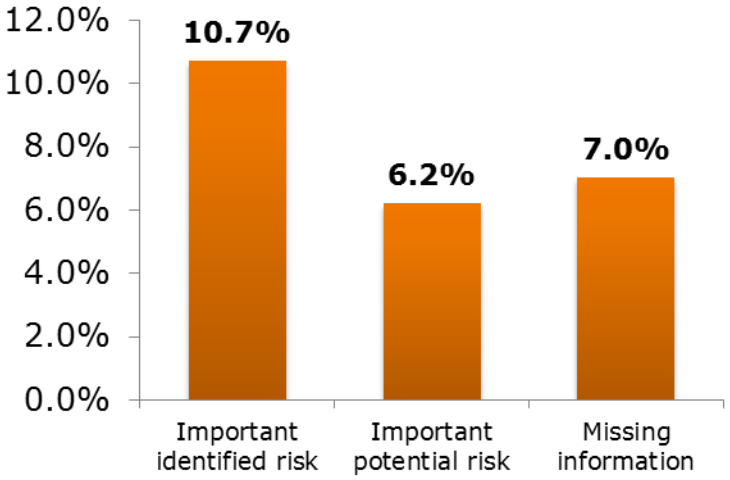
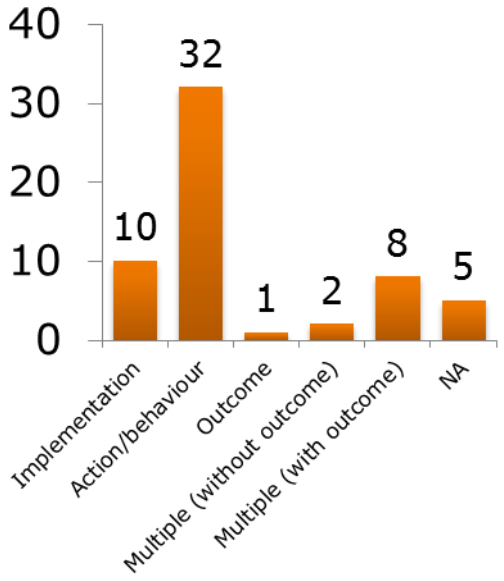
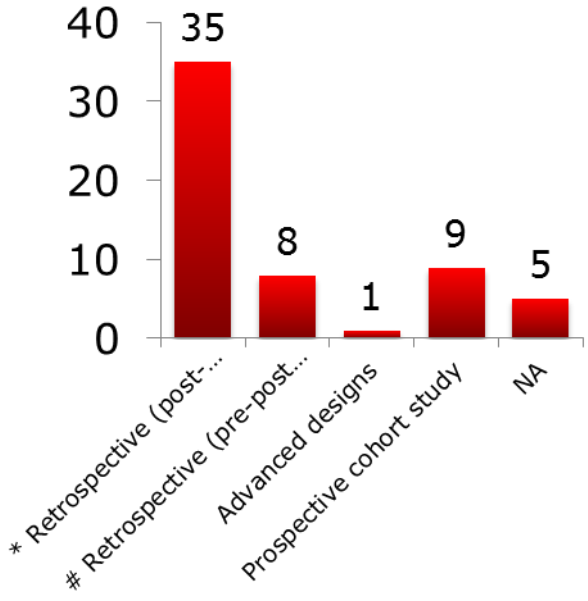


Study protocols

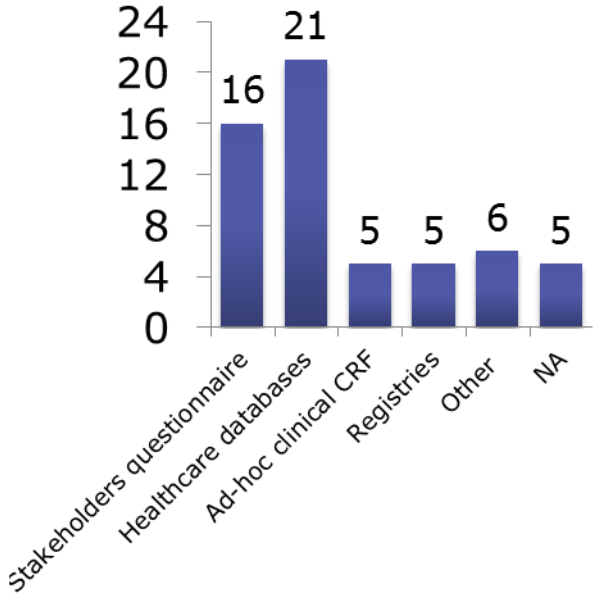
Indicators



Study design



Data source



* frequency analysis only with post-implementation time unit(s) (either cross-sectional or retrospective cohort)

\# pre-post comparison (either cross-sectional or retrospective cohort)

Take-Home Messages

1. The role of the studies to monitor the effectiveness of RMMs is clearly embedded in the life-cycle approach to the risk management
2. Measuring the effectiveness is a complex task and it should ideally consider different levels of evaluation; however, the assessment of safety outcomes remains the main objective of such evaluation
3. The evaluation of safety outcomes is difficult and regulators sometimes rely on other evaluation measures (i.e. Clinical behaviour)
4. It is difficult to define what acceptable level of distribution, tool uptake and impact on knowledge, behaviours and outcomes, constitute success as it is might vary on a case-by-case basis