ISPE Whitepaper - Evaluating the Effectiveness of Additional Risk Minimisation
Measures via Surveys in Europe: Challenges and Recommendations

Disclaimers

- Terri Madison, PhD, MPH is an employee of Mapi

- Rachel Sobel, DrPH, FISPE is an employee of Pfizer

This paper was developed by members of ISPE who are part of the Benefit Risk Assessment, Communication, and Evaluation (BRACE) Special Interest Group (SIG), and was also consulted with the full BRACE SIG.

Any views expressed in this presentation are the personal views of the authors or represent and perspective of the ISPE BRACE SIG whitepaper authors.
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Background

- New PVG legislation, effective in 2012, added an explicit requirement to evaluate the effectiveness of RMM, and that "studies to measure the effectiveness of a risk minimisation activity" should be classified as PASS

- GVP Module XVI, published in 2014, noted that RMM effectiveness indicator evaluations should include both "process" and "outcome" indicators
  - Process indicators measure implementation and/or delivery of the plan, and may include measures of distribution, assessment of knowledge, and assessments of clinical actions
  - Outcome indicators are defined as safety outcomes

- Studies to evaluate the effectiveness of process indicators in the EU are relatively new
  - Surveys are a well-established standard to measure process indicators
  - Surveys fall lower in the evidence hierarchy, mainly due to potential for substantial selection bias
  - For RMM effectiveness surveys, it's important that the methodology promotes unbiased and statistically stable results that are interpretable and actionable.

Overview of Survey Studies to Evaluate the Effectiveness of RMM

- Strengths
  - Most rigorous method by which to determine what a stakeholder knows or believes
  - If well-designed and well-executed, are reliable, cost effective, and versatile instruments to systematically study a large group of individuals
- Disadvantages
  - Concerns with generalisability and bias (mainly selection and reporting bias)
- Measuring success
  - Process indicator metrics (e.g. knowledge rates)
  - Current guidance documents do not stipulate a threshold that would indicate success
  - If the threshold for success is not met, need to analyse reasons for failure

Challenges in Implementing Surveys in the EU to Evaluate RMM Process Indicators

Classification as PASS

- Survey studies fall in "the grey zone" (GVP Module XVI, section B.4 "…if a study is conducted to assess behavioural or safety outcome indicators the detailed guidance for conducting a PASS… should be followed. Such guidance does not apply to the measurement defines process indicators")
- In practice, several national CAs, HCPs, and institutions will automatically classify these as PASS, especially if stated as such in the protocol and registered on the EU-PAS register
- Country-specific regulations for PASS, and interpretation if these surveys are PASS, vary widely

Example – UK

- Study 1: Knowledge and behaviour survey to evaluate effectiveness of additional HCP-directed educational materials
  - Notification to MHRA
  - November 2015 - Submission to Health Research Authority, 5 weeks from submission to approval
- Study 2: Knowledge and behaviour survey to evaluate effectiveness of DHPC and additional HCP-directed educational materials
  - May 2016 MHRA response to "should this study be classified as a PASS?": *Evaluation of prescribing behaviour is considered a process indicator, as described in GVP XVI. However, this simple survey would not be considered adequate to provide robust data on the effectiveness of the risk minimisation measures in changing clinical behaviour. Therefore, this would not be considered a PASS study…"*

Challenges in Implementing Surveys in the EU to Evaluate RMM Process Indicators (cont'd)

Recruitment challenges

- PASS designation may jeopardise selection of a representative sample due to feasibility concerns
  - Theoretically, the sampling frame should support recruitment of a representative sample of HCPs targeted for the RMM; however, feasibility constraints may result in limiting the sampling frame
  - Challenges with incentivising participation under PASS categorisation may further contribute to potential for selection bias
    - Fair Market Value to "complete a survey" is inconsistent with level of requirements to approve a PASS study in some countries, causing either lack of interest or prohibitively high fees; this is a substantial deterrent to the feasibility of recruiting a generalisable sample
- Due to privacy/restricted access to contact information for several EU countries, it may not be possible to use lists developed for implementation of aRMM to subsequently contact the same HCPs to participate in the survey

Example: Required Approvals for PASS – Spain

Studies should follow the "orden SAS/3470/2009" (issued by the Spanish health authority, AEMPS) that regulates post-authorisation studies in Spain. There are different types of post-authorisation studies and each must follow a different regulatory flow

CUADRO I: Rutas administrativas de los Estudios Posautorización
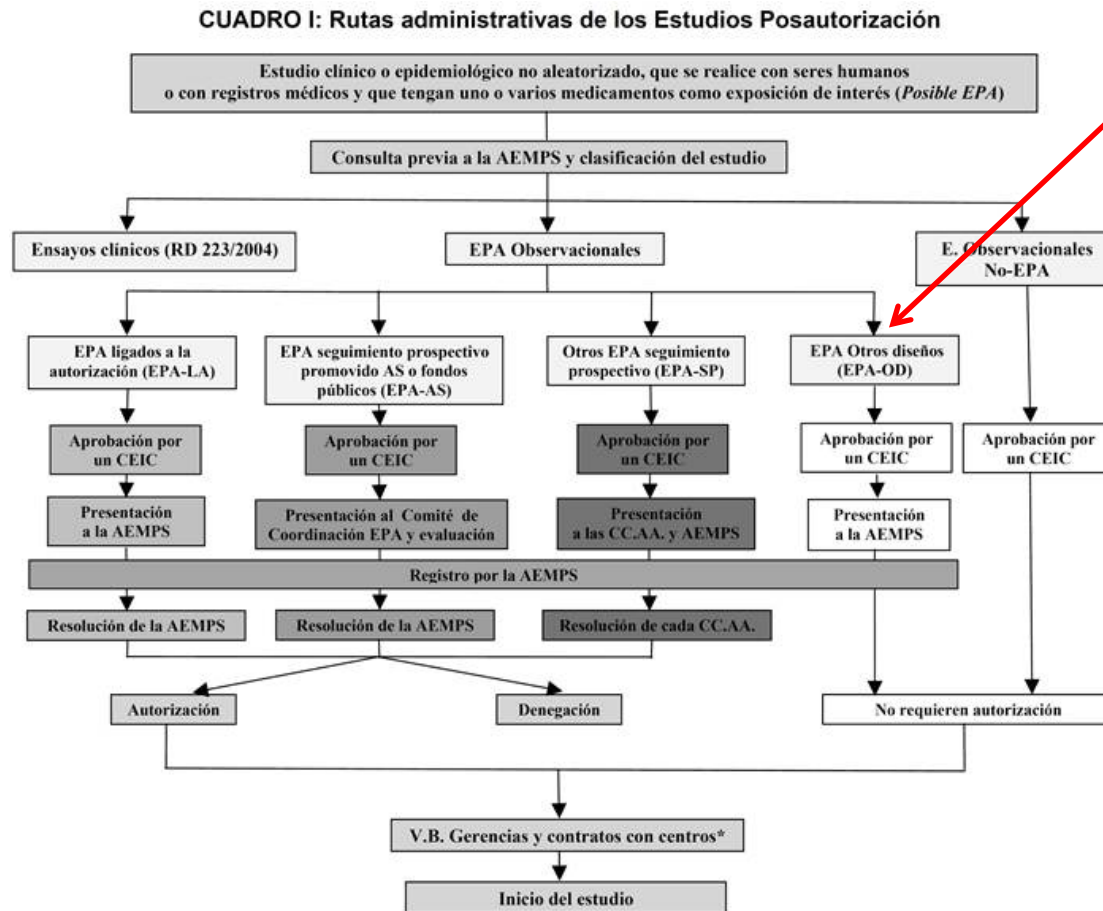
Evaluation includes a medicinal product, so may fall under "other designs" (survey), requiring ethics to present a favourable opinion, AEMPS to authorise, the execution of contract to meet regional/institutional requirements. This entire process takes usually a minimum of 6 months.

http://www.pharmacoepi.org/

Implications

- Lack of overall feasibility to conduct pan-European survey studies in a timely, efficient, and effective manner
  - Partially due to the omnibus classification of all studies to evaluate the effectiveness of aRMM as PASS
- Potential for severe selection bias and therefore lack of generalisability of results, given the lack of overall feasibility
- Potential for information bias
  - Variation in RMM between countries
  - Different country-specific requirements for regulatory and ethics submissions
- The applicability of pre-set thresholds to measure success, given the operational challenges

ISPE Recommendations

Endorsed by ISPE Board of Directors

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Recommendation 1 (Aspirational)

Update GVP Modules V, VIII, and XVI (as applicable) to clarify that survey studies of knowledge of risks and risk minimization behaviors to evaluate *process indicators* of the effectiveness of aRMM are **not PASS**.

Align GVP Mod XVI with CIOMS IX in classification of behavioral endpoints

[Mod XVI = process indicator]
[CIOMS IX = outcome indicator]

Add recommendations to Mod XVI for robust survey methodology, pre-testing, and analytic approaches to improve consistency, scientific rigor and avoid "market research" categorization

Recommendation 2

Promote consistent and/or centralised processes to enable survey studies to be conducted in multiple EU countries *without* requiring individual country-specific approvals
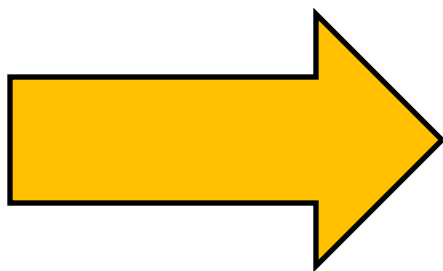
Diminishes operational challenges and scientific impacts

Austrian process desirable model: if Competent Authority notified and posted on ENCePP, no separate EC submissions/ approvals required

Other Recommendations for EU GVP Module XVI

Process Indicators are Category 3:
specifically state that survey studies to evaluate process indicators of the effectiveness of aRMM are almost always category 3 (see Module V)

Clarify when *routine* RMM effectiveness is required:
clarify under what conditions routine RMM require effectiveness assessments

Evaluation Frameworks:
specify that plans for evaluating the effectiveness of aRMMs should be guided by social science evaluation frameworks

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- Session 3.3: Measuring impact: a review of survey studies to evaluate the effectiveness of additional risk minimisation measures in Europe
  - Nawab Qizilbash

Clarification Questions