Effectiveness Evaluation of Risk Minimisation Measures

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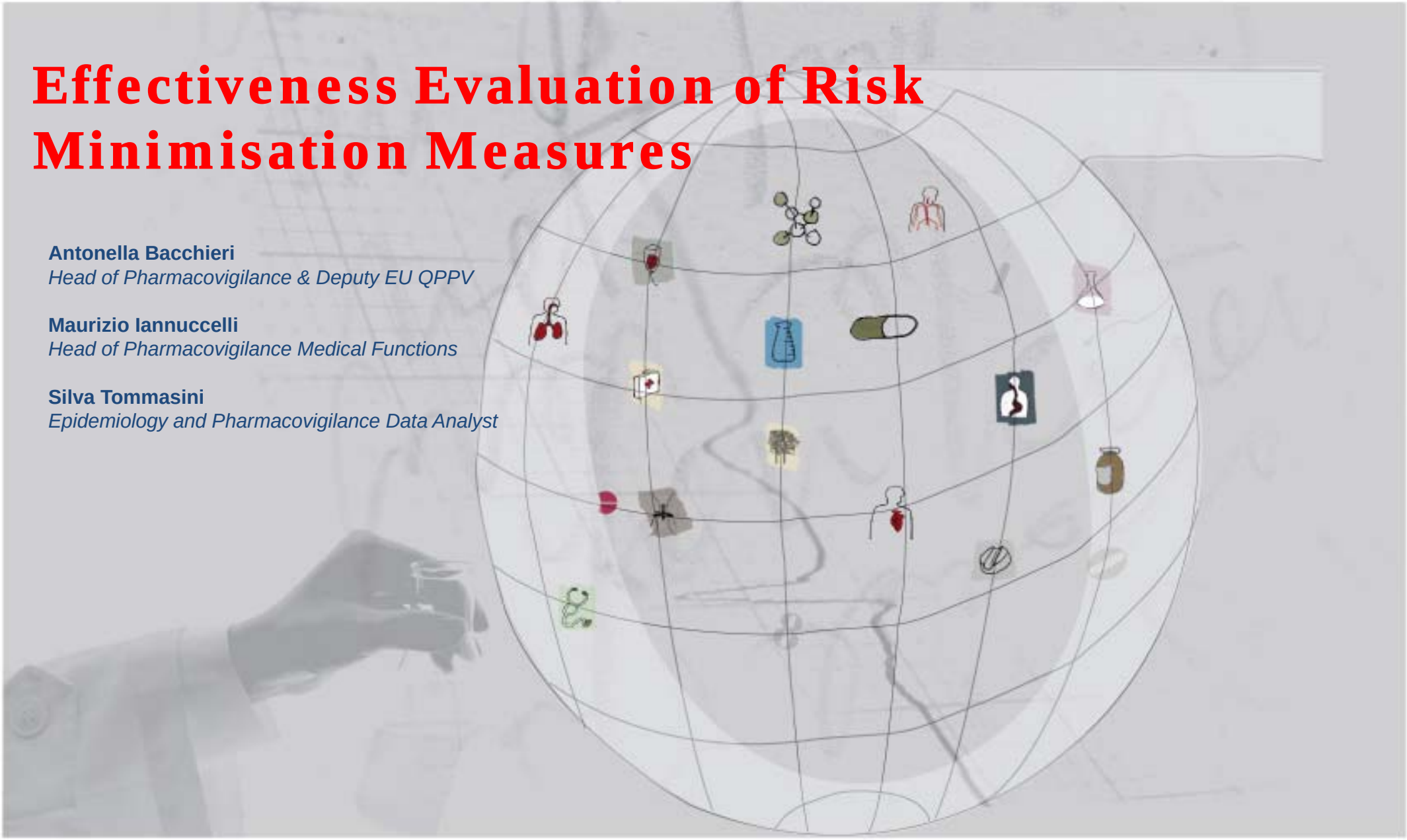

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«*Facere de necessitate virtutem*»

S. Girolamo

Road Map

General overview on implementing risk minimisation measures and assessing their effectiveness

Sigma-Tau experience with a centrally registered product at EMA

Challenges in measuring effectiveness of risk minimisation measures

What are the Risk Minimisation Measures

Risk minimization measures are «*interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur.*»

...

They should guide to "*the provision of the right medicine, at the right dose, at the right time, to the right patient and with the right information and monitoring.*»

(GVP Module XVI)

Risk minimisation measures may consist of routine risk minimisation or additional risk minimisation measures.

Additional Risk Minimisation Measures

Based on:

- Educational programmes, targeted at HCPs or patients or both, using a combination of tools and media.
- Controlled access programmes.
- Controlled distribution systems.
- Pregnancy prevention programmes.
- Direct healthcare professional communications (DHPC).

Routine vs Additional Risk Minimisation

Safety concerns should be prioritized in terms of:

frequency / seriousness / severity / impact on public health / preventability

in order to determine if additional risk minimisation activities are needed.

Additional risk minimisation measures should focus on the most important, preventable risks and the burden of imposing additional risk minimisation should be balanced with the benefit for patients.

Legal Basis for Effectiveness Measurements

In general, measurement of effectiveness is required only for the additional risk minimisation measures.

Directive 2001/83/EC indicates that the Marketing Authorisation Holder shall "*monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a*" (DIR Art 104 (2) (d)).

Legislation

"*The legislation defines "Any study ….measuring the effectiveness of risk management measures" as a* ***post-authorisation safety study*** *[DIR Art 1 (15)].*

Therefore, … the detailed guidance for conducting a post-authorisation safety study, which is provided in Module VIII, should be followed."

(GVP – Module XVI)

Effectiveness of Risk Minimisation Measures

Why

- Necessary to establish whether an intervention has been effective or not, and if not why not and which corrective actions are needed.
- Evaluation should be performed for the additional risk minimisation tools individually and for the risk minimisation programme as a whole.

Timing

- Effectiveness evaluation should be conducted at a pre-defined time.
- Periodic review of the effectiveness should be planned.

Effectiveness Evaluation: Which Aspects

Effectiveness evaluation should address different aspects of the risk minimization measure(s):

- **Process**

  To what extent the programme has been implemented as planned.

  Is the measure(s) improving knowledge in the target audience?

  Is the measure(s) producing behavioral change in the target audience?

- **Outcome**

  To what extent the predefined primary objectives of risk minimisation were met, in the short and long term.

  For example, where the objective of an intervention is to reduce the frequency and/or severity of an adverse reaction, the ultimate measure of success will be measurment of adverse event frequency/severity.

(GVP – Module XVI)

Effectiveness Evaluation: Process Indicators

Reaching the target population

These indicators should focus on assessing whether the materials were delivered to the target audience and whether they were actually received by the target population. Proofs of delivery and receipt should always be generated.

Assessing clinical knowledge

Rigorous survey methods should be applied. Protocols are necessary where the following is described: research objectives, study design, sample size and representativeness, operational definition of dependent and independent variables, statistical analysis, and data collection instruments (e.g. questionnaires).

Assessing clinical actions

Clinical actions stemming from the risk minimization programme (i.e. prescribing behavior) should be measured, for example with drug utilisation studies, systematic analysis of prescription records, analysis of cohorts of medicine users.

Effectiveness Evaluation: Outcome Indicators

Safety outcomes, for example frequency and/or severity of adverse reactions in relation to patients' exposure to the medicine (generally estimated in *ad hoc* PASS).

- Spontaneous reporting should be considered with caution and is acceptable only in specific circumstances.
- The selection of the reference group for comparison is important and should be justified.
  - Comparison of frequency before and after the implementation of the risk minimisation measures (pre-post).
  - Comparison of an outcome frequency indicator obtained post-intervention against a predefined reference value obtained from literature review, historical data, expected frequency in general population.

Generally both process and outcome indicators are to be measured.

"*In rare circumstances, when it is fully justified that the assessment of outcomes indicators is unfeasible (e.g. inadequate number of exposed patients, very rare adverse events), the effectiveness evaluation may be based exclusively on the careful interpretation of data on process indicators*".

(GVP-Module XVI)

Effectiveness Evaluation: Possible Conclusions

The conclusions of the effectiveness evaluation may be that the risk minimization measures should:

- Remain unchanged.
- Be modified:
  - ✓ Be strengthened (they were proved to be insufficient).
  - ✓ Be reduced or simplified (they were disproportionate or lacking a clear focus).
- Be removed (they generated unintended consequences, for example undue burden on the healthcare system, or discontinuation of a product even if its risk-benefit balance remains positive).

Results must always be included in the RMP

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Eurartesim

Combination of dihydroartemisinin (DHA) and piperaquine (PQP), co-formulated in a single tablet, indicated for the treatment of uncomplicated *P. falciparum* malaria.

DHA is the active metabolite of artesunate and arthemeter, which are both artemisinin-derived anti-malarial drugs.

PQP is a bisquinoline. The exact mechanism of action of piperaquine is unknown, but it likely mirrors that of chloroquine, a close structural analogue.

One known side effect of Eurartesim is QTc prolongation. This risk was confirmed in a formal QTc study, where it was found to be correlated to PQP plasma concentration, which is dependant on food intake.

Other potential risks are teratogenic effects, neurotoxicity and phototoxicity. All these risks are included in the RMP.

Effectiveness Study on Eurartesim

- Eurartesim has been centrally authorized in late 2011.
- The RMP required dissemination of educational material (EM) to all physicians who are expected to prescribe or use Eurartesim immediately after product launch (one-off distribution).
- EM for Eurartesim is comprised of a HCP Guide and a Checklist, both focused on QTc prolongation and pregnancy.
- Eurartesim fits the situation where it is acceptable to measure process indicators only. An effectiveness study to assess physician understanding of the EM and knowledge of Eurartesim was to be made.
- The survey was to be performed 12 and 24 months after distribution of EM.

Eurartesim Effectiness Study: Protocol (1)

Study design
European multi-centre survey (cross-sectional), conducted in three EU countries.

Primary Objective
To ascertain the physician understanding of the EM and the knowledge about Eurartesim, in terms of drug indication, prescription and administration modalities, high-risk patients, and potential side effects.

Secondary Objective
To ascertain physician awareness of available sources of information regarding the medication.

Sample Size

60 Physicians per country were expected to participate.

Physicians were recruited among a list of 300 names per country, randomly selected from the initial lists of EM dissemination (so expected response rate = 20%).
Sample size computation was based on precision, i.e. confidence interval width.

Eurartesim Effectiveness Study: Protocol (2)

Recruitment process

- A recruitment mail containing the study summary and a participation form was sent to all Physicians of the lists with the request to send back the completed participation form.
- Characteristics of physicians, and if applicable, reason(s) for non-participation were included in the participation form.
- Non-responders were contacted by telephone (at least 3 attempts) by the monitors to know if they agreed to participate in the survey.
- The survey questionnaire was administered by phone to the Physicians selected for the survey and willing to participate.

Eurartesim Effectiveness Study: Results (1)

Survey at 12 months
Countries: France, Spain, UK

Actual sample size:
56 physicians in total

Survey at 24 months
Countries: France, Germany, Italy

Actual sample size:
77 physicians in total

Reaching the target population

Almost half of participating physicians declared they did not receive the EM or that they did not remember.

Reference group for comparison

Physicians declaring to have received the EM vs other Physicians.

Eurartesim Effectiveness Study: Results (2)

Assessing clinical knowledge

Both surveys showed that:

The main information about Eurartesim indication, prescription and administration modalities, and potential side effects was well-known by most physicians.

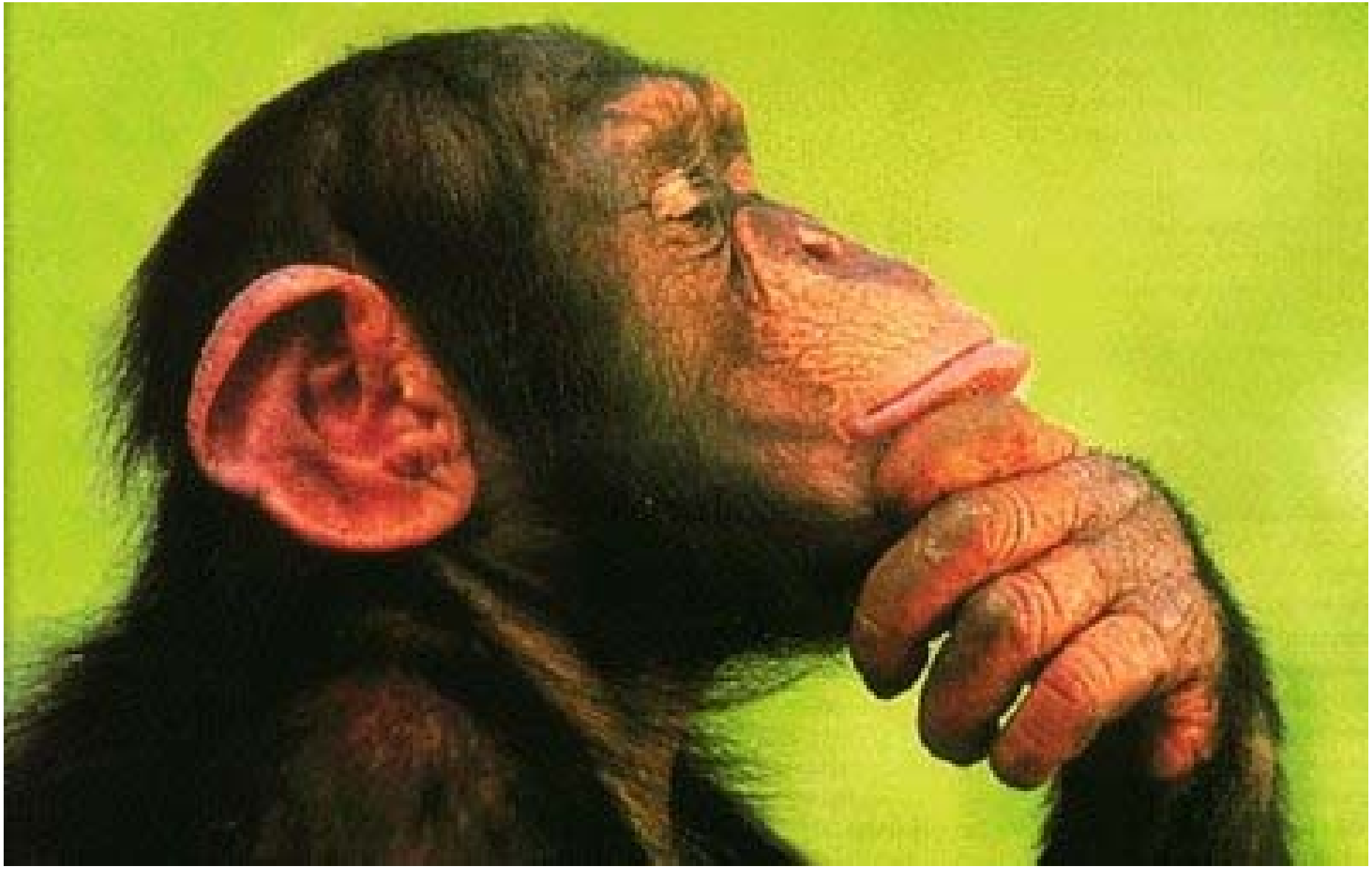
For the more in-depth information, such as impact of food intake on QTc interval prolongation, and medication use in pregnant women:

HCPs declaring to have received the EM ⟺ HCPs declaring the opposite

percentage of correct answers was lower

and

difference in the rate of correct answers was ~ 20% in favor of the first group



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Eurartesim Effectiveness Study: Conclusions

The results showed that the implemented risk minimisation measure has been partially successful.

… The proposal made to EMA (approved) was to re-distribute revised EM and re-do the survey using a partially modified questionnaire …

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Challenges (1)

The physician response rate is low (less than 10% of the group initially contacted) *

Many efforts must be made in order to obtain samples of reasonable size:

- involve many countries/sites/physicians;
- use different media, e.g. paper/mail/web/phone;
- be prepared to make many conctact attempts;
- consider use of incentives, e.g. **feed** back results from survey.

Several kinds of bias can be present in such conditions and, therefore, representativity of the sample is uncertain.

Ethical and privacy requirments at country level may be a significant «complicating» factor.

** Risk Evaluation and Mitigation Strategy Assessments: Social Science Methodologies to Assess Goals Related to Knowledge, Issue Paper, June 7, 2012, FDA*

Challenges (2)

Questionnaires are often used in the “real-world studies” as method of active Pharmacovigilance surveillance (surveys, registries,…). Questionnaires are widely used to assess whether the information to HCPs is being effectively communicated.

Some hints for designing effective questionnaires

Questionnaires must be short and clear:

- Define the initial list of questions using simple language.
- Order the answer categories always in the same way.
- Offer both positive and negative questions.
- Avoid the open-ended questions and the response “other”.
- Ask a feedback to a representative sample of responders (User-testing).

Challenges (3)

The studies for measuring the effectiveness of risk minimisation measures are expensive and time consuming.

Defining the right reference group for establishing meaningful comparisons is difficult.

Our comparison was established *a posteriori*

The situation for drugs with small markets provides additional challenges.

Almost half of physicians declared they did not prescribe Eurartesim over the previous 12 months.
Median # of Eurartesim treated patients = 3!

Take home messages

… «*Facere de necessitate virtutem*»…

Be very conservative in setting expectations for response rates.

Take into account:

- Use of different tools for reaching the physicians.
- Incentives to improve response rate.
- Ethical and data privacy heterogeneity among countries.

Methods for surveys (for example questionnaires) must be clear and to the point.


Thanks for your attention
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