Regulatory Opportunities and Challenges in Europe:

A proposal from the Italian Experience on Registries

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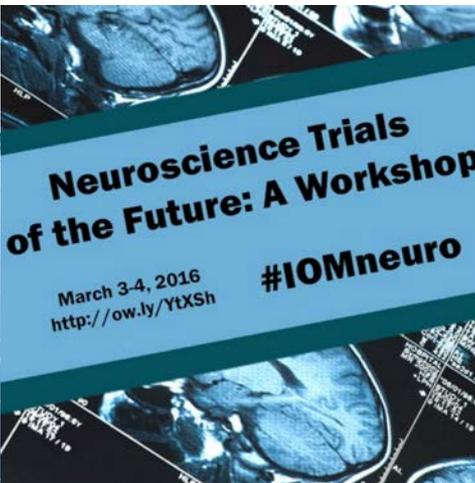CHMP, SAWP Member, European Medicine Agency
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Neuroscience Trials
of the Future: A Workshop

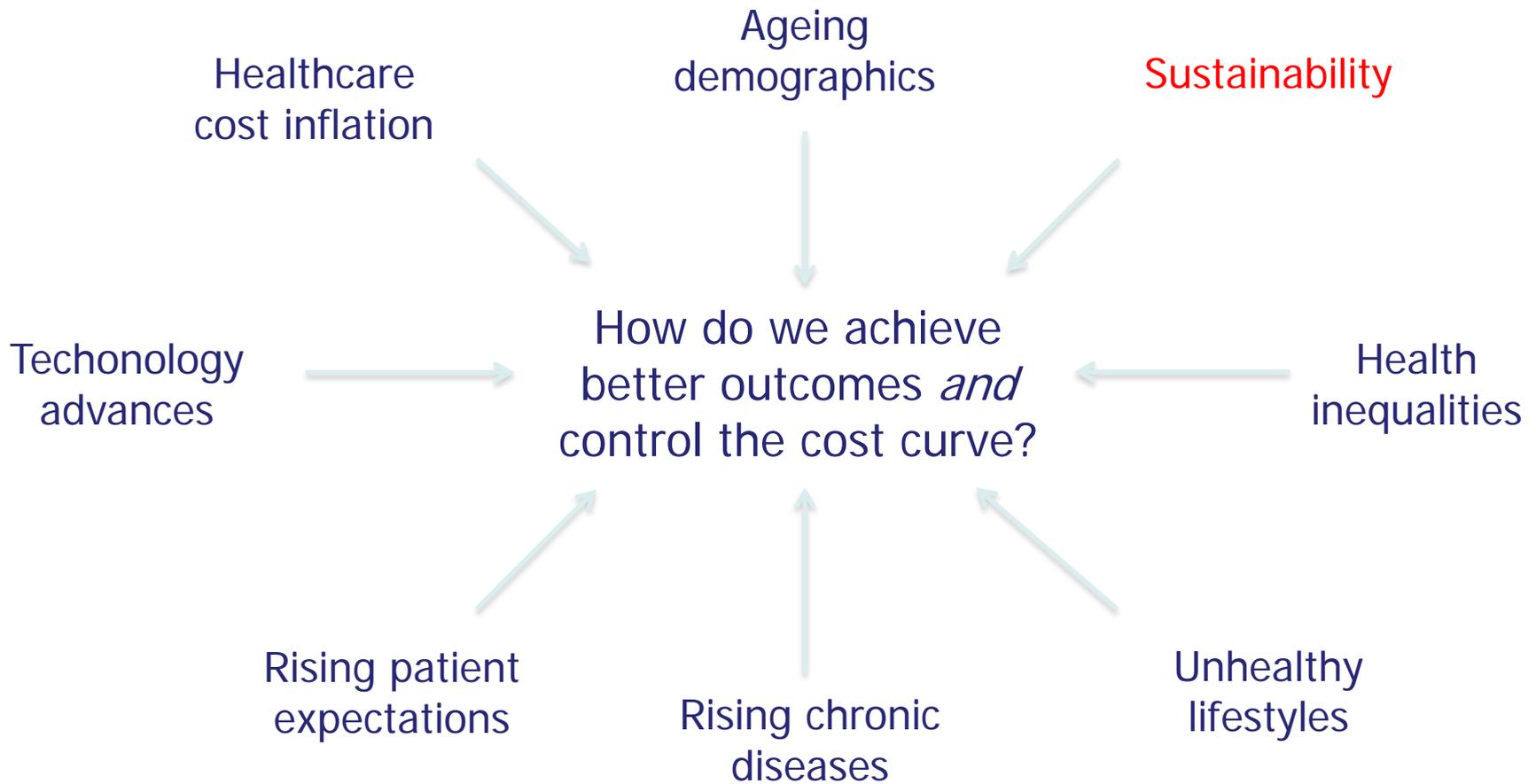March 3-4, 2016
http://ow.ly/YtXSh   #IOMneuro

Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA/EMA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 previous years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

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Most important challenges for Regulators / Payers

Ageing demographics

Healthcare cost inflation

Sustainability

Techonology advances

How do we achieve better outcomes *and* control the cost curve?

Health inequalities

Rising patient expectations

Rising chronic diseases

Unhealthy lifestyles
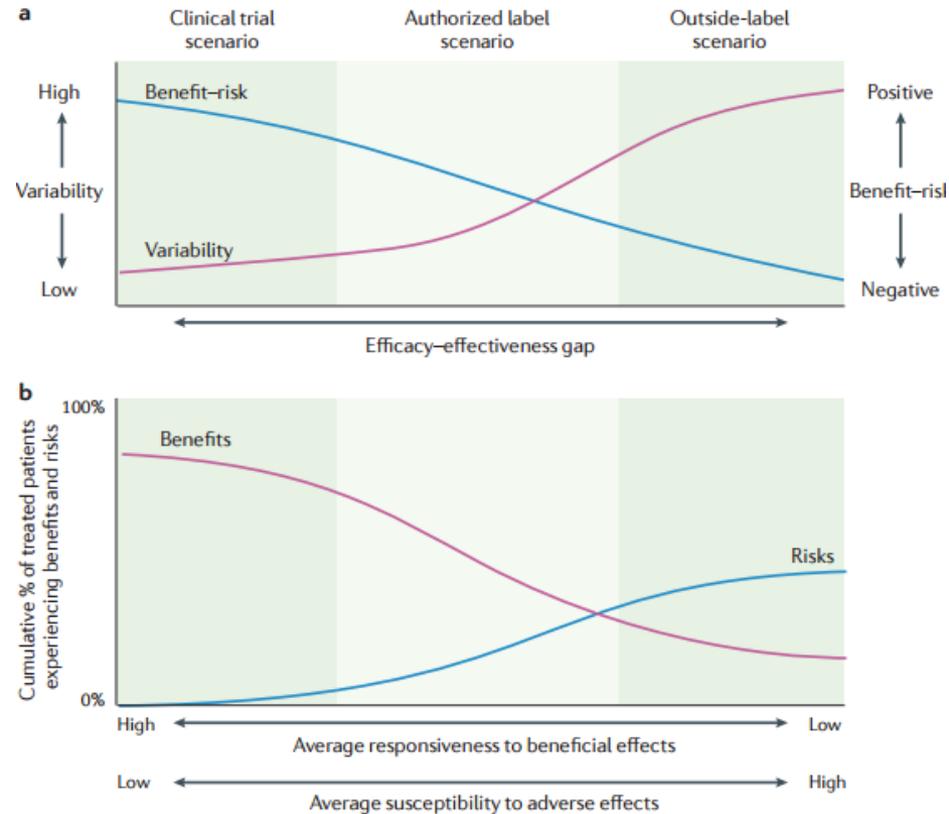
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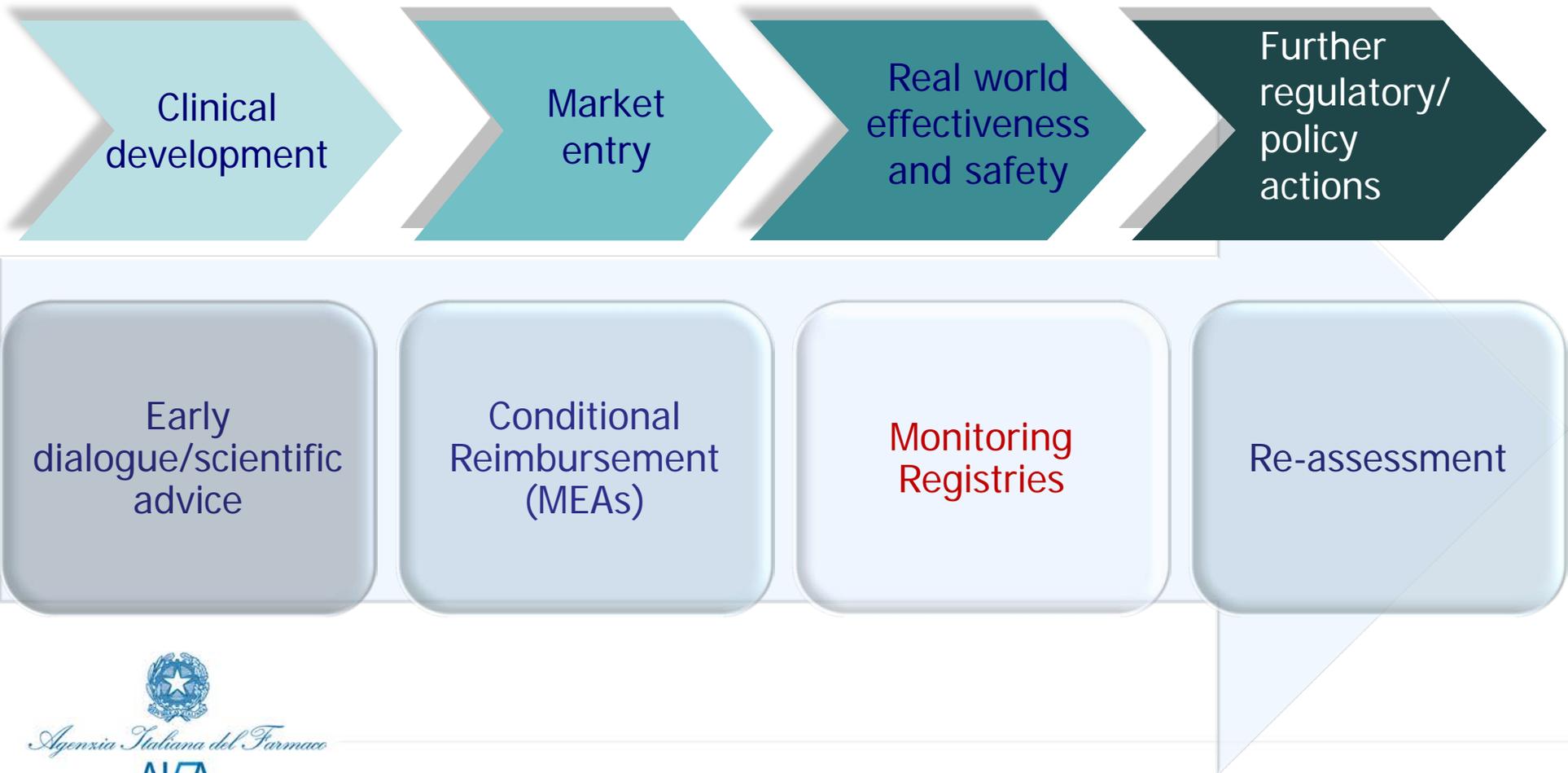
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Bridging the efficacy–effectiveness gap

Patients are not equally responsive to beneficial effects, and not equally susceptible to AEs.

Regulatory decisions are based on population-level information, with an understanding that the B-R will not necessarily be positive for all treated patients.

a

| Clinical trial scenario | Authorized label scenario | Outside-label scenario |

High — Variability — Low

Benefit–risk

Variability

Positive — Benefit–risk — Negative

Efficacy–effectiveness gap

b

Cumulative % of treated patients experiencing benefits and risks

100% — 0%

Benefits

Risks

High — Average responsiveness to beneficial effects — Low

Low — Average susceptibility to adverse effects — High

Bridging the efficacy-effectiveness gap: a regulator's perspective on addressing variability of drug response. *Nat Rev Drug Discov. 2011 Jul 1;10(7):495-506. Eichler HG, et al.*

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The **I**talian Medicines Agency Strategy

Clinical development	Market entry	Real world effectiveness and safety	Further regulatory/ policy actions
Early dialogue/scientific advice	Conditional Reimbursement (MEAs)	Monitoring Registries	Re-assessment

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Italian Medicines Agency Registries

MONITORING REGISTRIES AT ITALIAN MEDICINES AGENCY: FOSTERING ACCESS, GUARANTEEING SUSTAINABILITY

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Objectives: The AIFA (*Agenzia Italiana del Farmaco*—Italian Medicines Agency) Monitoring Registries track the eligibility of patients and the complete flow of treatments, guaranteeing appropriateness in use of pharmaceutical products, according to approved indications.

Methods: This study describes the Italian pharmaceutical context and the aims and functioning of AIFA Monitoring Registries, focusing on the applications to the Managed Entry Agreements (MEAs) and HTA approaches.

Results: The AIFA Monitoring Registries System has been operational in Italy since 2005. In 2012, the system became part of the NHS Information Technology system, aiming at enhancing appropriate use of pharmaceuticals and efficiency of the administrative activity. Currently, seventy-six medicines are monitored through the system, corresponding to fifty-eight therapeutic indications; individual treatments recorded are more than 515,000, for a population of approximately 505,000 patients. For each monitored product, patients eligible for treatment are registered in the specific therapeutic indication dynamic monitoring database to collect epidemiologic and clinical data, including data on the safety profile, and ex-post information missing at first evaluation stage.

Conclusions: AIFA Monitoring Registries allow the evaluation of the pharmaceuticals' performance in clinical practice and may promote innovation and quicker access to medicines at affordable prices, for the benefit of patients.

Keywords: Drug monitoring, Registries, Real clinical practice data collection, Managed entry agreements

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Registries provide Real World Data (RWD)

RWD is an umbrella term including effects of health interventions that are not collected in the context of conventional RCTs.

Registries are one of the main sources of RWD.
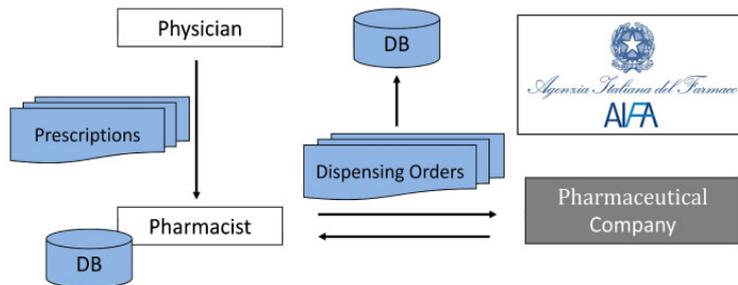
Alternative / Additional tools are:

➢ Electronic medical records

➢ Observational studies

➢ Administrative data

➢ Claims databases

➢ Health surveys & patient reported outcomes (PROs).

AIFA Monitoring Registries are...

AIFA drug-product Registries are web tools placed in the early phases after MA and also for some "authorized" *off label* use.
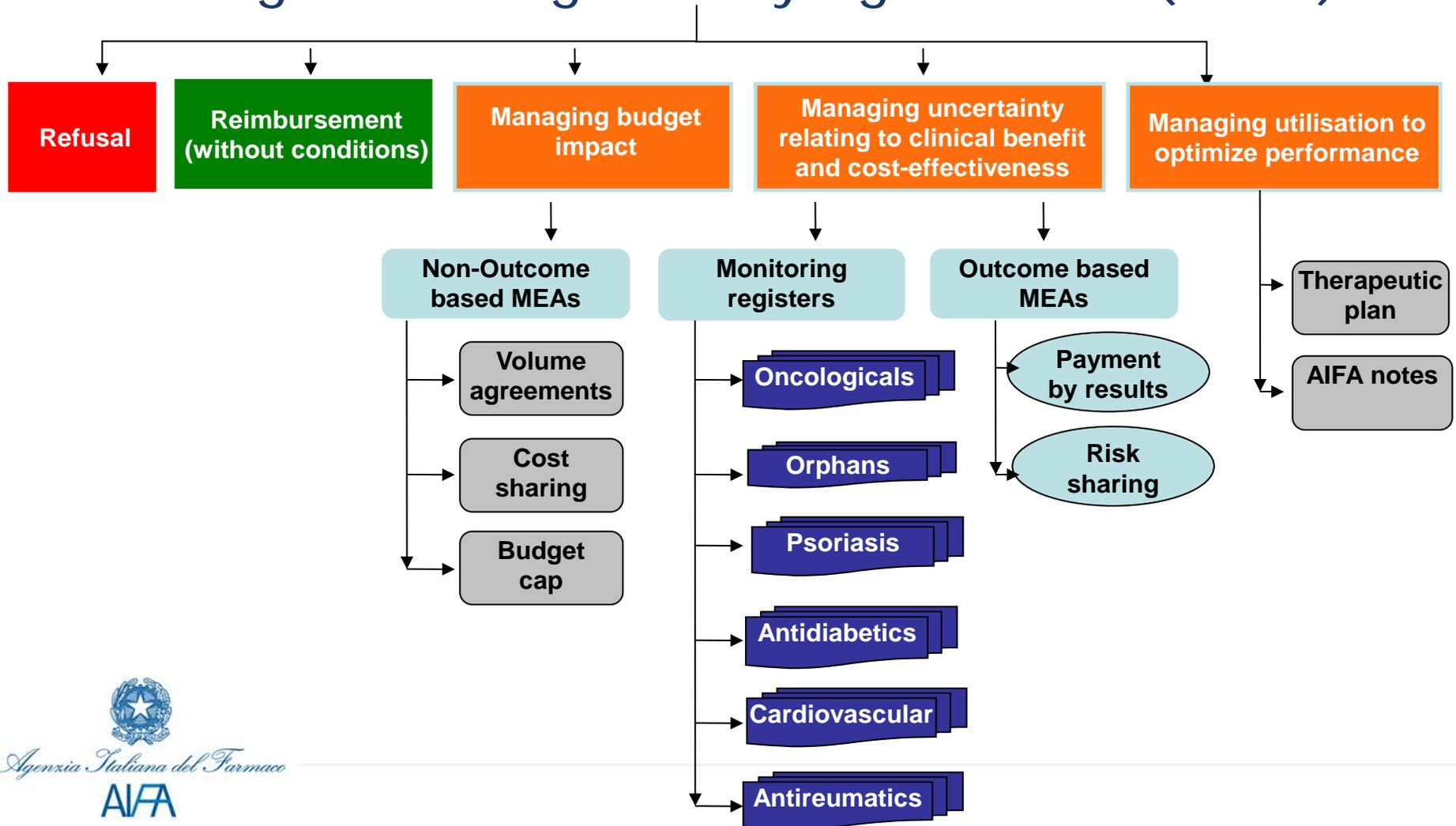
Measure RW safety and effectiveness
and
Apply MEAs procedures.

In 2012 AIFA Registries officially became part of the NHS Information Technology (IT) Law n. 135/2012.

The Italian Medicines Agency Strategy:
A range of Managed Entry Agreements (MEAs)

- **Refusal**
- **Reimbursement (without conditions)**
- **Managing budget impact**
  - **Non-Outcome based MEAs**
    - Volume agreements
    - Cost sharing
    - Budget cap
- **Managing uncertainty relating to clinical benefit and cost-effectiveness**
  - **Monitoring registers**
    - Oncologicals
    - Orphans
    - Psoriasis
    - Antidiabetics
    - Cardiovascular
    - Antireumatics
  - **Outcome based MEAs**
    - Payment by results
    - Risk sharing
- **Managing utilisation to optimize performance**
  - Therapeutic plan
  - AIFA notes

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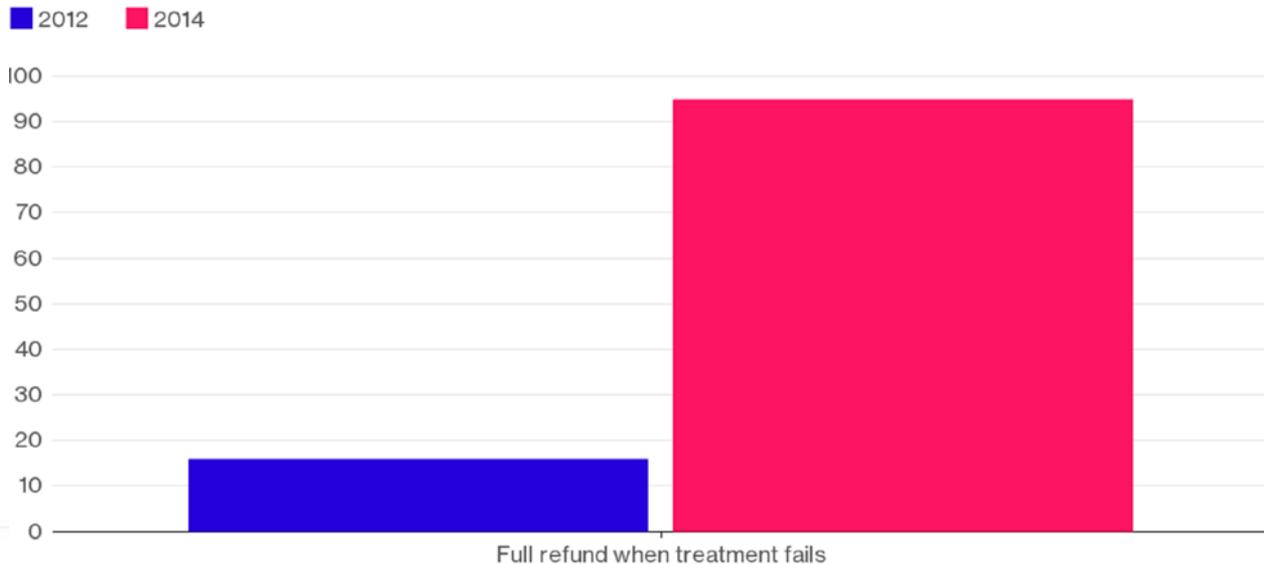# When New Cancer Treatments Fail, Italy Wants Its Money Back

The Italian Medicines Agency has devised deals with pharma companies that set payment based on how well a patient responds to treatment, and in some cases where the medication fails to help, the drugmaker gives a full refund. Italy is signing more such contracts as growing numbers of medications receive regulatory approval after mid-stage trials of fewer than 100 patients rather than awaiting final-stage assessments involving thousands.
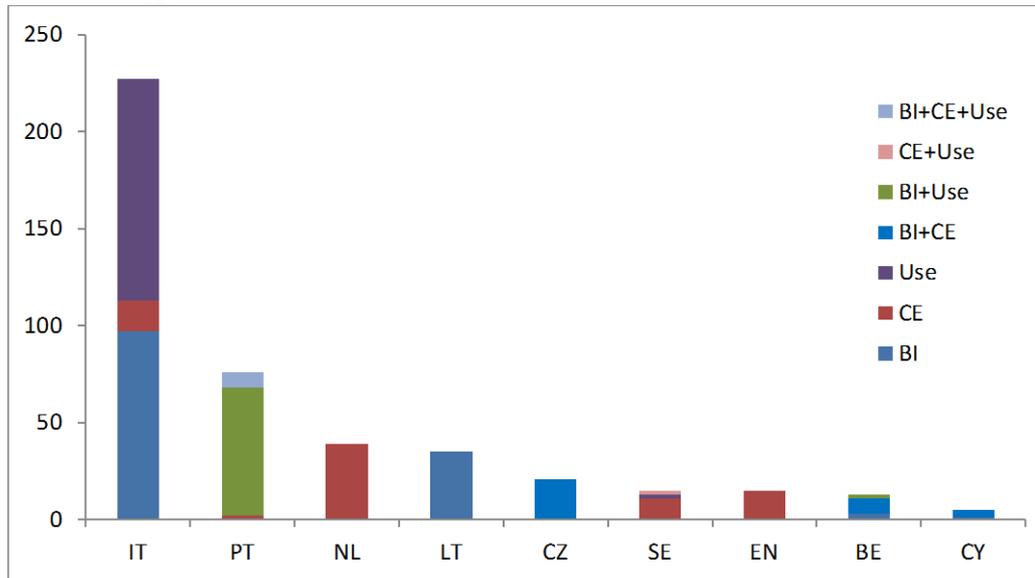
by   Makiko Kitamura   Johannes Koch
🐦 maki_kitamura

January 15, 2016 — 6:00 AM CET

Drug contracts with money-back guarantees

Italy is signing more contracts stipulating refunds when treatments fail, allowing it to take a chance on medicines getting approved with smaller trials
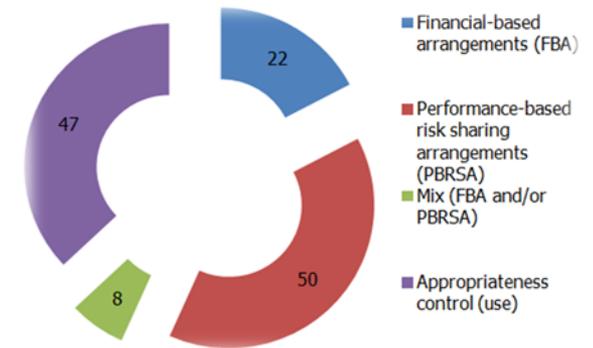
■ 2012   ■ 2014

Full refund when treatment fails

Bloomberg

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MEAs in EU

MEAs in Italy

Legend: BI: Limit budget impact, CE: Address uncertainties regarding the cost-effectiveness, Use: Monitor use in clinical practice, Access+CE: Improve patient access and cost-effectiveness. BE: Belgium, CY: Cyprus, CZ: Czech Republic, EN: England, IT: Italy, LT: Lithuania, MT: Malta, NL: Netherlands, PT: Portugal, SE: Sweden

Legend:
- Financial-based arrangements (FBA)
- Performance-based risk sharing arrangements (PBRSA)
- Mix (FBA and/or PBRSA)
- Appropriateness control (use)

80 of 96 Registries are associated with a MEA; PbR are the most frequently used schemes.

Managed entry agreements for pharmaceuticals: the European experience
Alessandra Ferrario and Panos Kanavos

(R)Evolution

Y 2006
Version 1.0
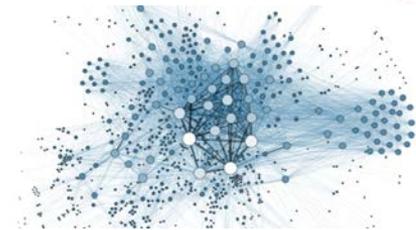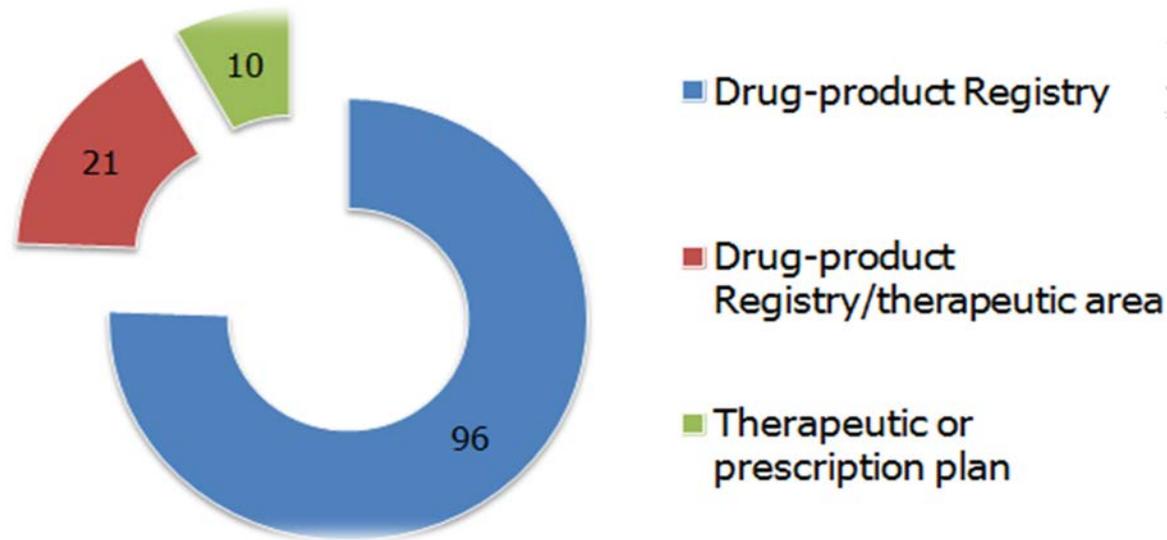

Y 2013
Version 2.0

Data collection & Monitoring

Therapeutic area' approach data collection

Accreditation pyramidal system

Regions

Health managers

Pharma companies

Data collection typologies

- Drug-product Registry
- Drug-product Registry/therapeutic area
- Therapeutic or prescription plan

> 850,000 Patients
> 24.000 physicians and >1,300 pharmacists
32 MAH
~ 900 Health managers & 48 Regional responsible Agents

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The Italian Databases and HCV Treatment Costs

- New treatments DAAs are able to eradicate the infection in almost all patients

- High prevalence of the infection in Italy (about 2.6 to 3%);
- High cost treatment proposed;
- Unsustainability spending for our NHS;
- Although sofosbuvir/ledipasvir results could be cost-effective in several subgroups population, problem of economic sustainability remains!

Italian Medicines Agency Strategy for HCV

- Permanent national working group on HCV
- Compassionate use programs > 2,500 pts treated
- Joint negotiation and procurement initiatives with other European countries
- Prioritization program based on clinical urgency criteria

Safeguarding equity/homogeneity of drug access by guaranteeing the sustainability of the system.

Disease Criteria to access treatments

Criterion 1 - Patients with cirrhosis in Child class A or B and/or HCC with complete response to therapy resettive surgical or locoregional not candidates for liver transplantation in which the liver disease significantly affects prognosis

Criterion 2 - Recurrent hepatitis HCV RNA-positive liver transplant patients in clinically stable and with optimal levels of immunosuppression

Criterion 3 - Chronic hepatitis with severe HCV-related extrahepatic manifestations (cryoglobulinemic syndrome with organ damage, B-cell lymphoproliferative syndromes)

Criterion 4 - Chronic hepatitis with fibrosis METAVIR F3 (or corresponding Ishak)

Criterion 5 - In the list for liver transplantation with cirrhosis MELD <25 and/or HCC within the Milan criteria with the possibility of waiting in a list of at least 2 months

Criterion 6 - Chronic hepatitis after solid organ transplantation (not liver) or marrow fibrosis METAVIR ≥2 (or corresponding Ishack)

Criterion 7 - Chronic hepatitis with fibrosis METAVIR F0-F2 (or corresponding Ishak)

DAAs' treatments/criterion
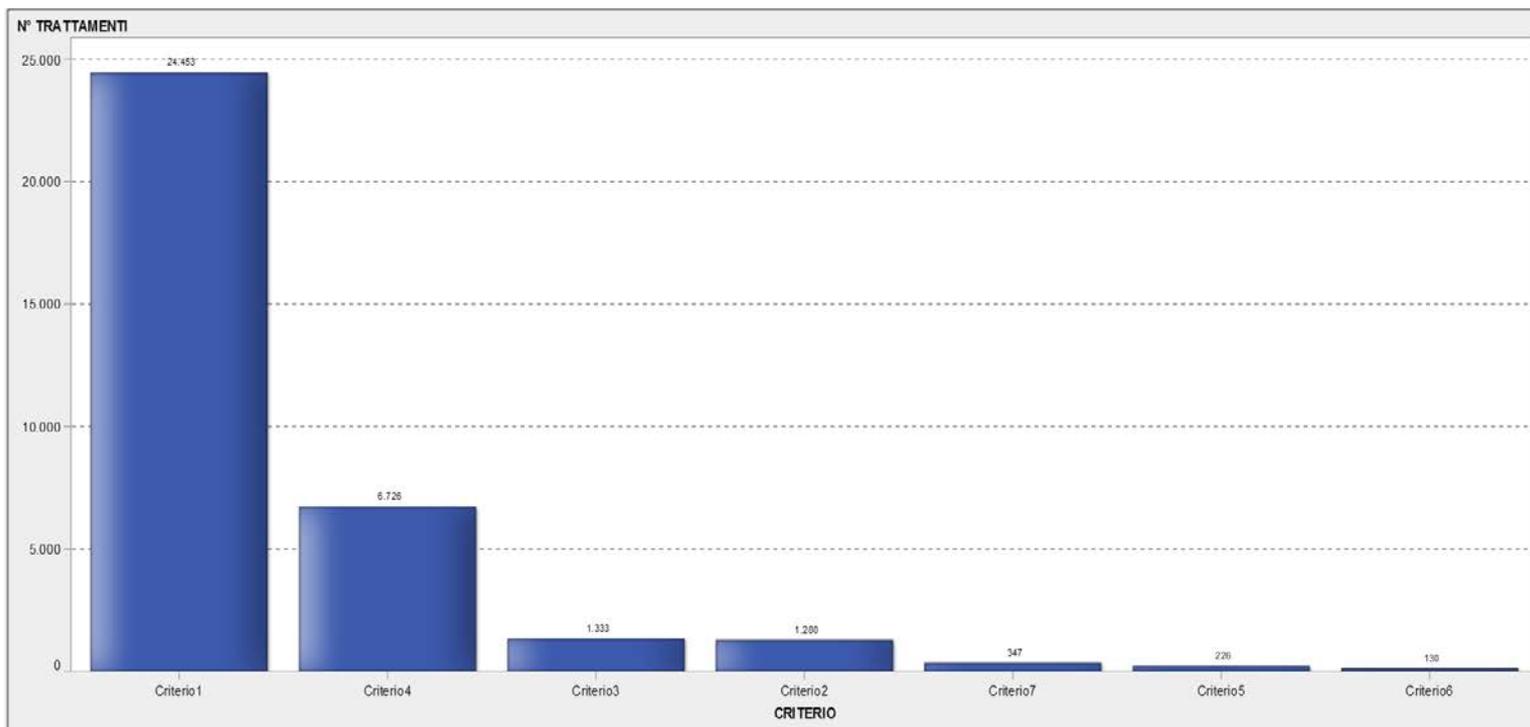
The total number of treatments as of Feb 2016 is **34.487**.
Criterion 1: 24.453; Criterion 4: 6.726; Criterion 2: 1.280; Criterion 3: 1.333;
Criterion 5: 226; Criterion 6: 130; Criterion 7: 347.

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Costs of HCV Drugs in Italy

Monitoring the number of patients at individual level allowed AIFA to negotiate prices by precise price/volume discount confidential contracts. These were linked to product specific managed entry agreements, mainly based on the high prevalence of this pathology in Italy but also on real life payment by result.

Prices obtained are the lowest in the EU, Japan and North America

AIFA Databases of drugs for diabetes

The incretin-mimetic and incretin-enhancer AIFA Registry was the first example of a "dirty" monitoring tool in a highly prevalent disease largely managed by general practitioners (GPs).

Drug utilization, safety, and effectiveness of exenatide, sitagliptin, and vildagliptin for type 2 diabetes in the real world: Data from the Italian AIFA Anti-diabetics Monitoring Registry

CrossMark

S. Montilla [a,*], G. Marchesini [b], A. Sammarco [a], M.P. Trotta [a], P.D. Siviero [a], C. Tomino [a], D. Melchiorri [c], L. Pani [a] for the AIFA Anti-diabetics Monitoring Group[1]

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We analysed 75,283 pts with type 2 diabetes treated with exenatide, sitagliptin, or vildagliptin over two years.

Result: In real world prescriptions, incretins have been mostly used off-label. When appropriately utilized, incretins showed results in line with those in registration trials.

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AIFA Databases of drugs for Multiple Sclerosis

This registry has been active from 2007 to 2012

6.304 patients recorded; 99% evaluated; 97% eligible and 88% treated.

Data of follow up for 3.539 (42%) patients.

Characteristics at baseline, efficacy outcome in the general population and in the highly active MS subcluster are analyzed in comparison to the Affirm study.

12 patients have been diagnosed and confirmed with PML.

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The National Medicines Observatory (OsMed) and the use of Antidepressants

Osmed is the largest data warehouse from unselected population in the world, with almost 40 million people in all age groups.

AIFA started a study in collaboration with MGH (Maurizio Fava et al.) on the evaluation of real-life treatment-resistant depression on approximately 450,000 patients selected from Osmed.
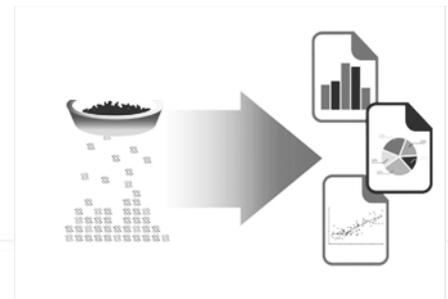
Study on Resistant Depression: Methods

An AD utilization index (resistance class 0, 1, 2, 3 and > 4) was calculated as the number of antidepressants (by ATC codes) treatment courses for at least 6 weeks (1 point = 1 ATC treatment course).

Patients (age range, gender and comorbidity index) for each resistance class have been followed up for two years after the index prescription.

Distribution by comorbidity index as well as costs will be calculated for each resistance class over a 12 months period after the two years of follow up*.

Conclusions: Italian Registries and Clinical Trials

1. Accelerate access of drugs to subclusters of patients;
2. Prevent exclusion of drugs with potential efficacy;
3. Early exclusion of drugs with safety issues;
4. Real world data generation;
5. Contain NHS expenditure optimizing allocation of resources and the sustainability of the system;
6. Use of these resources in clinical trials?