AIFA: focus on registries and non-commercial trials

Entela Xoxi

Regional and international trial funding programmes and how they contribute to patient care and healthcare systems

Brussels, October 12th 2016

KCE TRIALS SYMPOSIUM
PUBLICLY FUNDED PRAGMATIC PRACTICE-ORIENTED CLINICAL TRIALS

AIFA Agenzia Italiana del Farmaco

Agenzia Italiana del Farmaco AIFA

Public Declaration of transparency/interests*

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

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious 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

*Entela Xoxi, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (25.03.2015) and published on the Official Journal of 15.05.2015 according to EMA policy /626261/2014 on the handling of the conflicts of interest for scientific committee members and experts.

N.B. I am not receiving any compensation

AIFA is the NCA for the regulatory activity on pharmaceuticals in Italy: from 2004

The mission consists in:

1. Improving human health care through pharmaceuticals products
2. Guaranteeing the economic equilibrium of the system by respecting annually planned pharmaceutical expenditures ceilings
3. Ensuring consistent application of the pharmaceutical system nationwide
4. Promoting pharmaceutical independent research and encouraging research & development investments in Italy
5. Strengthening relations with MSs, EMA and other international bodies

Since 2004, prices of all medicines reimbursed by the Italian NHS are set through Negotiation procedure between AIFA & Pharma companies.

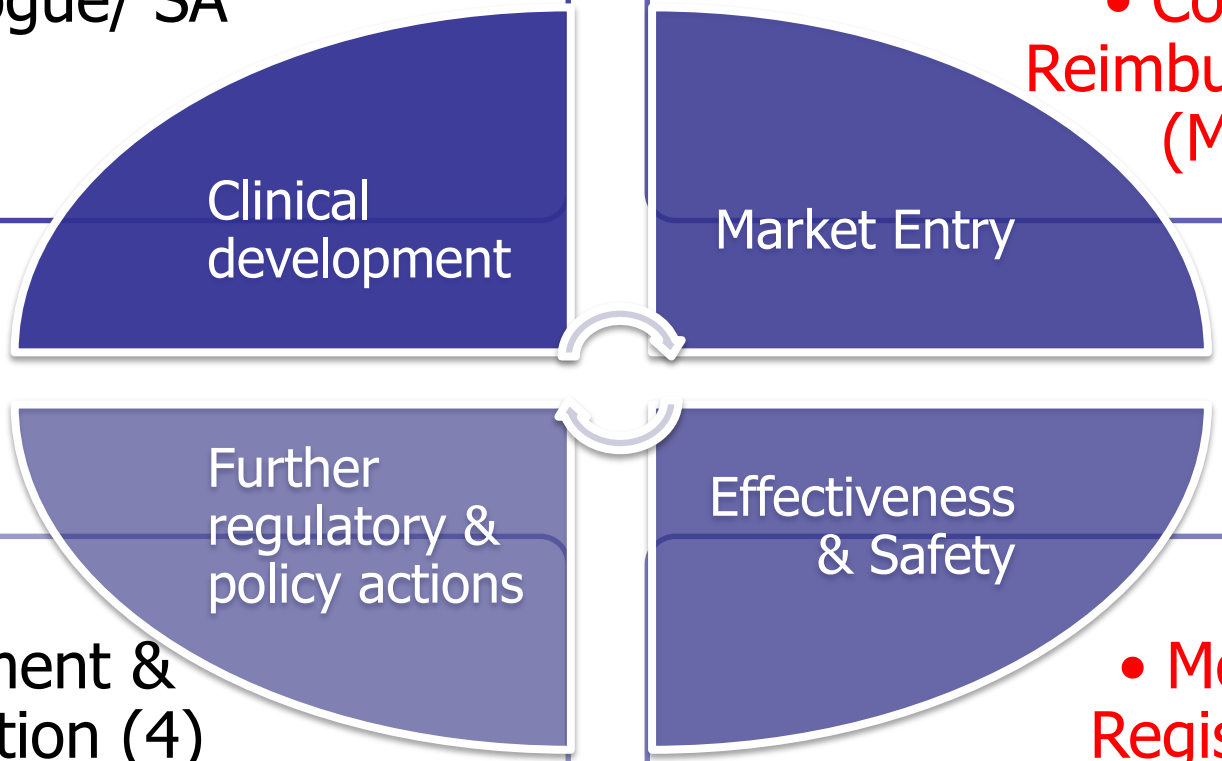
The parameters taken account are defined by Interministerial Committee for Economic Programming (CIPE) Resolution n. 3 of 2001:

1. Economic impact on NHS
2. Prices in other EU countries
3. Cost of treatment per day compared to the cost of medicines with similar effectiveness
4. B/R ratio compared to medicines with the same therapeutic indication
5. C/E ratio when other treatments options are available
6. Innovation level

AIFA's Formula

- Early dialogue/ SA (1)

- Conditional Reimbursement (MEAs) (2)



- Reassessment & Renegotiation (4)

- Monitoring Registries (3)

Strategy based on simple principles

How to achieve better outcomes and control the cost curves? What is the cut-off to be considered between therapeutic utility of a new medicine and its costs?

Registration is mandatory

Reimbursement is the only field for actions: it is here that national regulatory agencies may intervene

An innovative drug should be reimbursed only if effective

The welfare systems cannot take anymore responsibility for the failures in front of such high costs

Identification of responders in order to ensure an effective therapy against the poor prediction of clinical response at the time of recruitment

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

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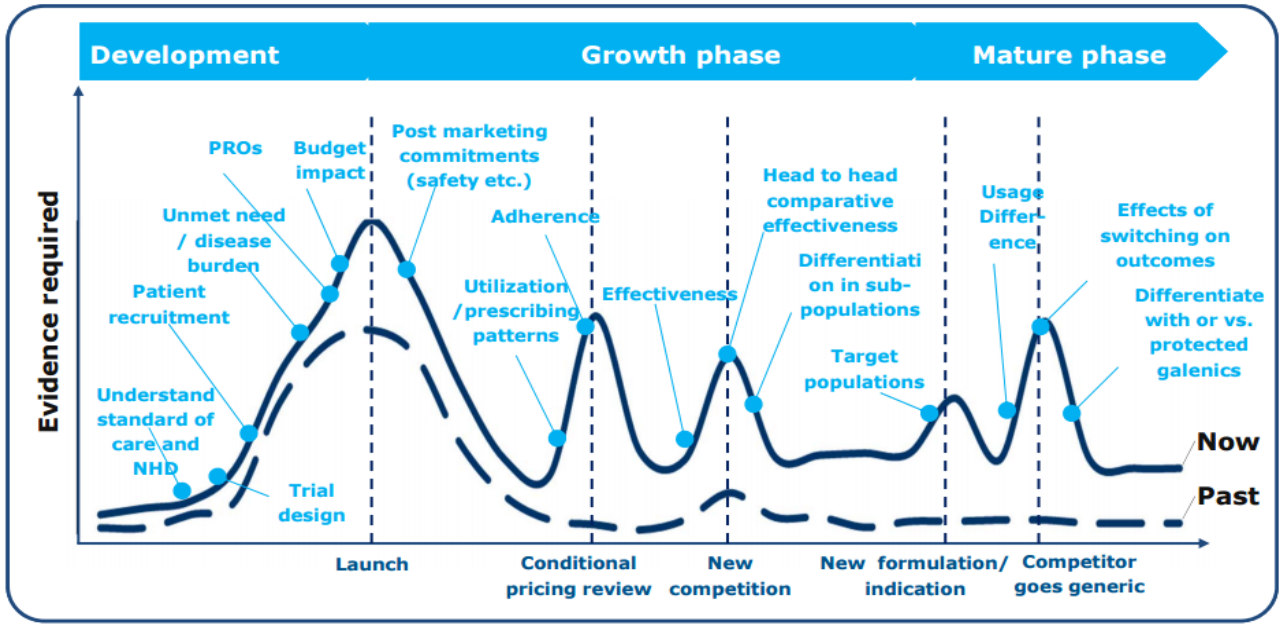
RWE can support access throughout the lifecycle



Source: IMI GetReal

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Registries are one of the many sources of RWD: electronic medical records, observational studies, administrative data, claims databases, health surveys & patient reported outcomes (PROs) are alternative tools.

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AIFA Registries

Are telematic tools @National level AND @patient level (ITS NHS - Law 135/2012), placed in the early phases after MA, in some cases for the 'authorized' off-label use (*early access tools*), designed to:

①Collect RWD on efficacy & safety (implementation of RMP, education on safety concerns & Risk Minimisation Measures, implementation of PPP), broad collection of baseline characteristics: appropriateness

②Capture outcome-health and apply the Managed Entry Agreements

③Govern the public drug expenditure

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Data collected through Registry are owned by AIFA
Maintenance costs are charged by Pharma Companies

Early access tools set by law in Italy

Requirements	Law 648/1996	Law 326/2003	Minister's Decree May 8 2003	Law 94/1998
Lack of treatment alternatives	YES	Not detailed	YES	YES
Scientific evidence	Positive results form Phase 2 studies	Rare diseases Not detailed	Positive results form Phase 3 studies, or Phase 2 for life threatening conditions	Positive results form Phase 2 studies
Authorisation	AIFA	AIFA	Ethics Committees	Ad-hoc hospital commission
Monitoring and data trasmission	Clinical and economic monitoring	-	Limited to safety	-
Payer	NHS	AIFA	Compassionate use - Free supply by Pharma Company	Patient, or NHS in case of hospitalisation

128 registries: all *drug-based*

31 registries: *disease-approach* data collection

48 MAH

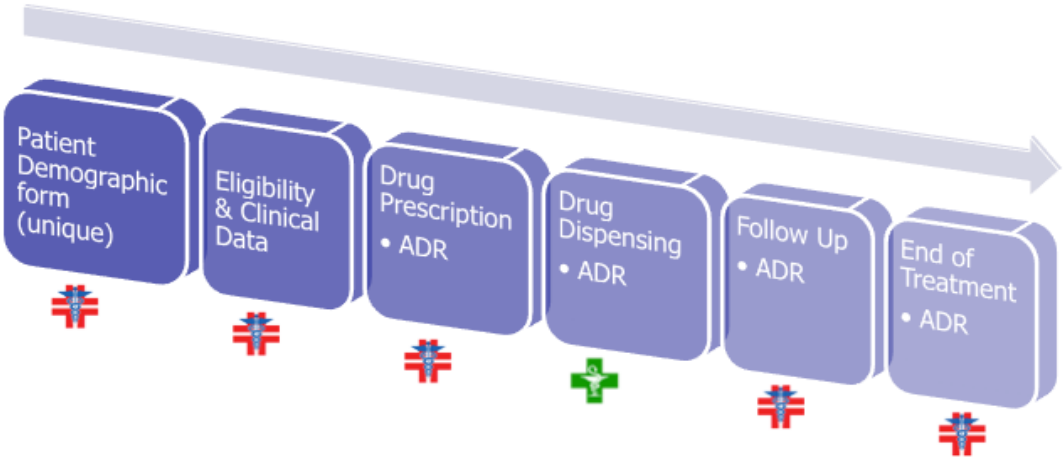
More than 1,000,000 patients

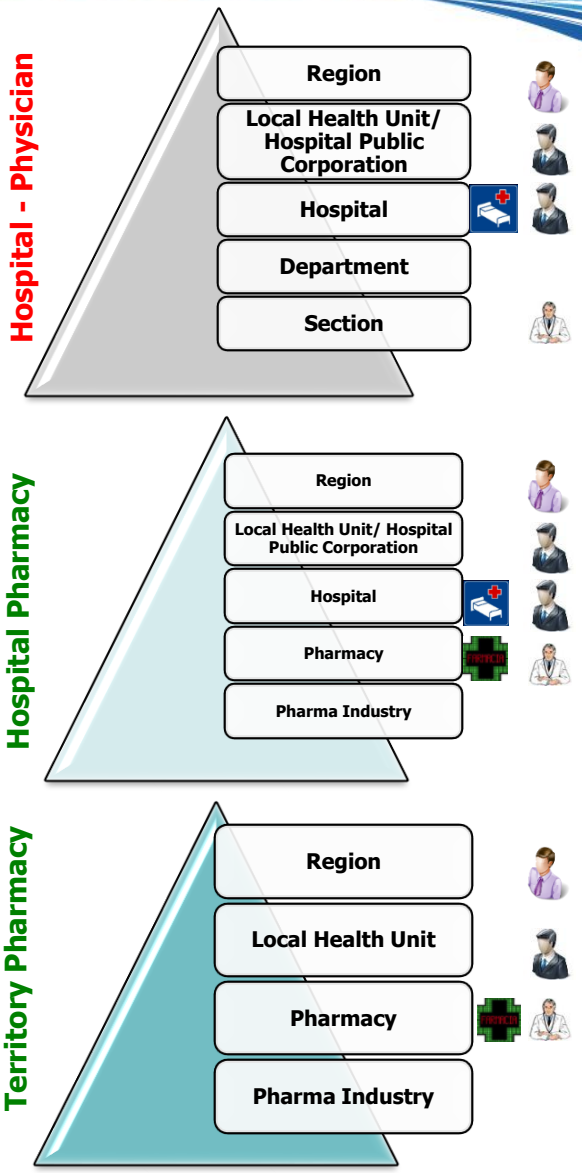
≈29,000 physicians

≈2,000 pharmacists

≈1,700 Health managers

49 Regional referees





Dealing with uncertainty
Managed Entry Agreements

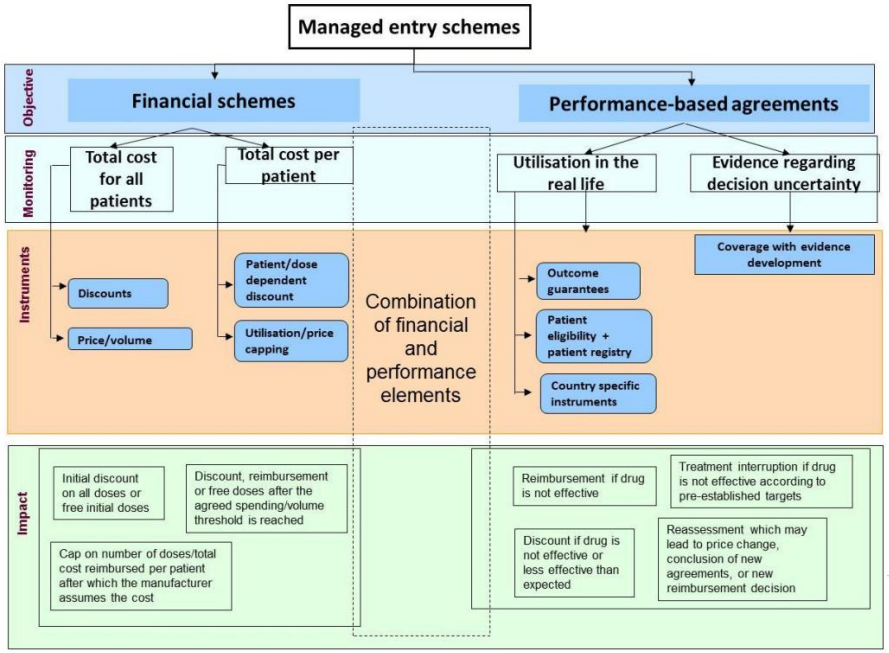
Avoiding exclusion from reimbursement of medicines which could be of some help to some patients

Avoiding unnecessary expenses to NHS helping to optimise allocation of expenditure and system sustainability

A **MEA** is an arrangement between a manufacturer and payer/provider that enables the reimbursement of a medicine subject to specific conditions with the aim to:

- Mitigate the impact of Uncertainty in Cost/Effectiveness & expenditures
- Enable patients to access promising new drugs in a context of uncertainty

PBRSAs are payment schemes – they involve a plan by which the performance of the product is tracked in a defined patient population over a specified period of time and the level of reimbursement is based on the health and costs outcomes achieved



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MEAs in P&R: YES Italian legislation
NO EU regulation & legal framework

TESTO COORDINATO DEL DECRETO-LEGGE 19 giugno 2015, n. 78

Testo del decreto-legge 19 giugno 2015, n. 78 (in Supplemento ordinario n. 32/L alla Gazzetta Ufficiale - serie generale - n. 140 del 19 giugno 2015), coordinato con la legge di conversione 6 agosto 2015 , n. 125 (in questo stesso Supplemento ordinario alla pag. 1), recante: «Disposizioni urgenti in materia di enti territoriali. Disposizioni per garantire la continuita' dei dispositivi di sicurezza e di controllo del territorio. Razionalizzazione delle spese del Servizio sanitario nazionale nonche' norme in materia di rifiuti e di emissioni industriali. ». (15A06371)

(GU n.188 del 14-8-2015 - Suppl. Ordinario n. 49)

Vigente al: 14-8-2015

11. All'articolo 48 del decreto-legge 30 settembre 2003, n. 269, convertito, con modificazioni, dalla legge 24 novembre 2003, n. 326, e successive modificazioni, dopo il comma 33 sono inseriti i seguenti:

33-ter. Al fine di ridurre il prezzo di rimborso da parte del Servizio sanitario nazionale dei medicinali soggetti a rimborsabilita' condizionata nell'ambito dei registri di monitoraggio presso l'Agenzia, i cui benefici rilevati, decorsi due anni dal rilascio dell'autorizzazione all'immissione in commercio, siano risultati inferiori rispetto a quelli individuati nell'ambito dell'accordo negoziale, l'Agenzia medesima avvia una nuova procedura di contrattazione con il titolare dell'autorizzazione in commercio ai sensi del comma 33.».

National Market Authorisation

Web monitoring by registry (timing)

If MEA: analysis of data collection & MEAs after 2 Ys

If the benefits obtained are lower than those expected, AIFA must initiate a process of ri-negotiation with MAH: in order to reduce NHS costs

Italian management in red Ξ Registries

Managing uncertainty relating to clinical benefit & cost effectiveness

Outcome based
- Payment by result
- Risk sharing
- Success fee

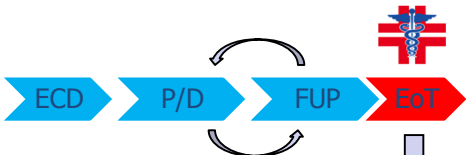
Managing budget impact

Non Outcome based (single or combined)
- Cost sharing
- Capping
- Price volume

Managing utilization to optimize

Appropriateness
- Safety monitoring
- Prescription plans
- AIFA Notes

Payback flow and two main actors: Public Pharmacy & Pharma company



Treatment refundable

Dynamic evaluation

Treatment not refundable

- Data Analysis
- Other conditions.,

Reimbursement Request (RR)

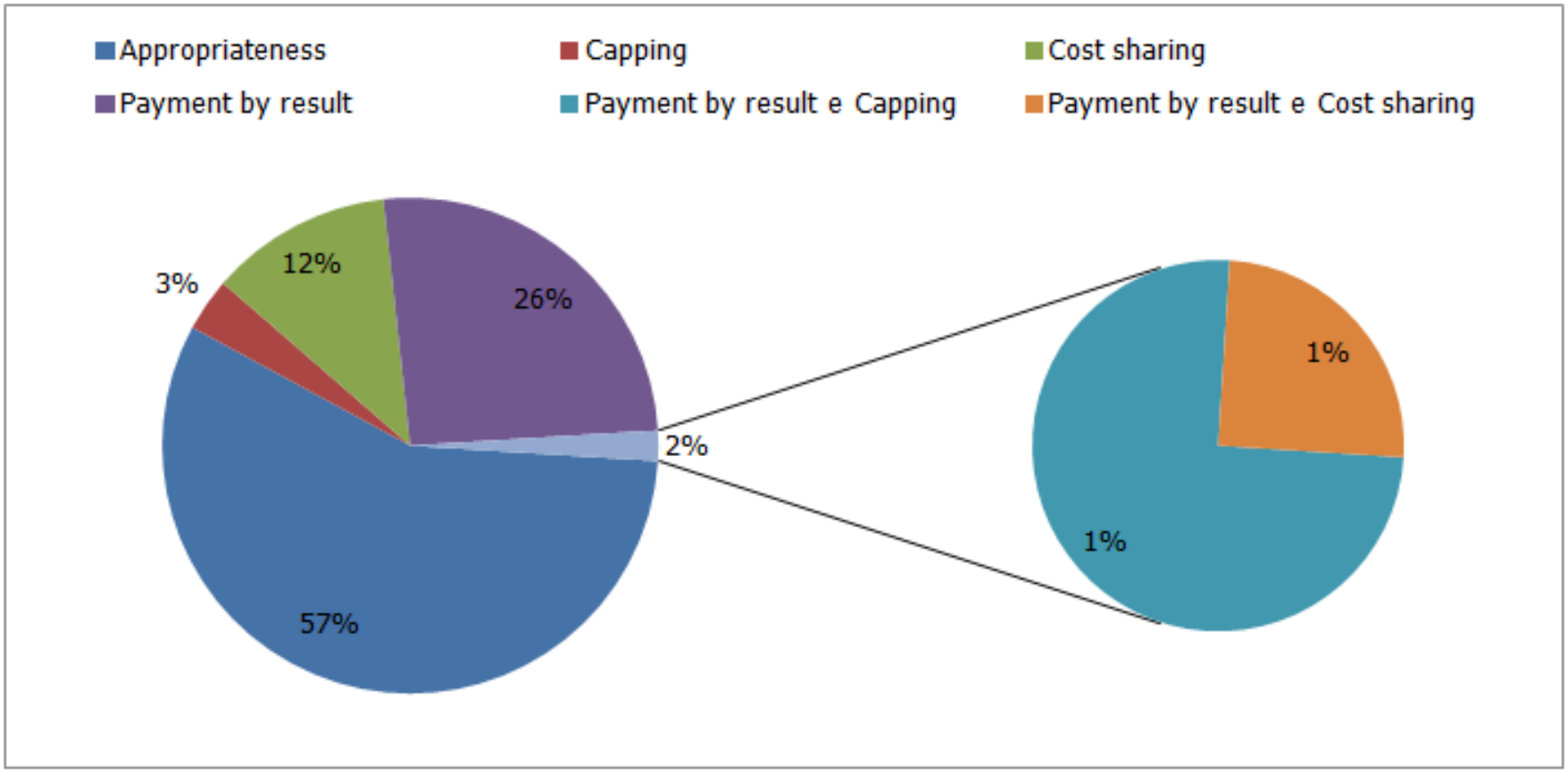
Treatments for the same register for a specific pharmacy

Evaluation of RR by Pharma company

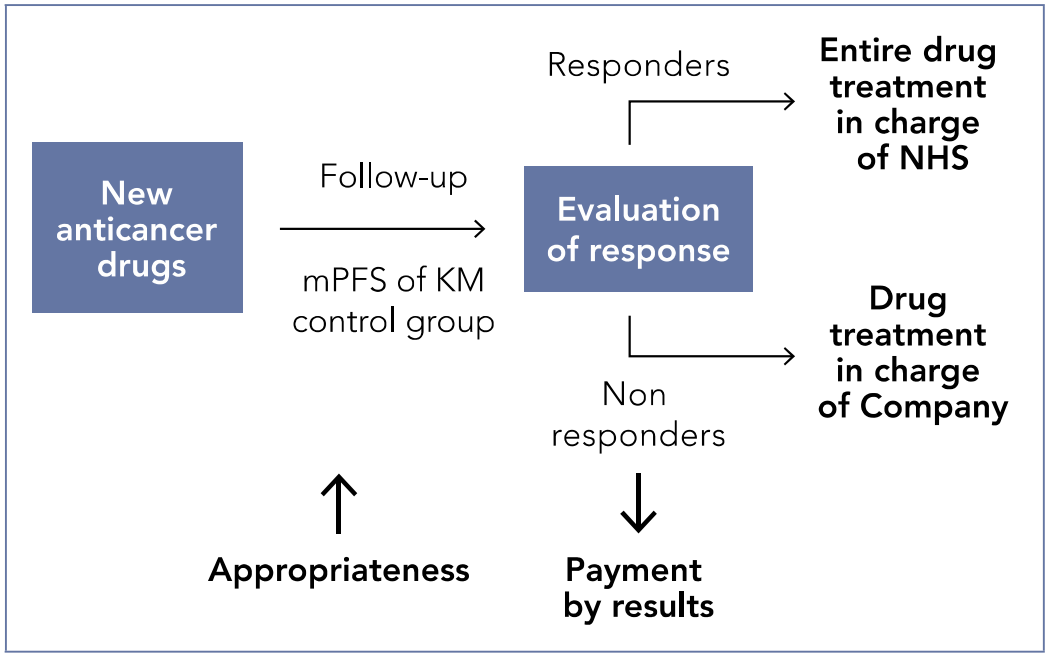
Evaluation of PP by public Pharmacy

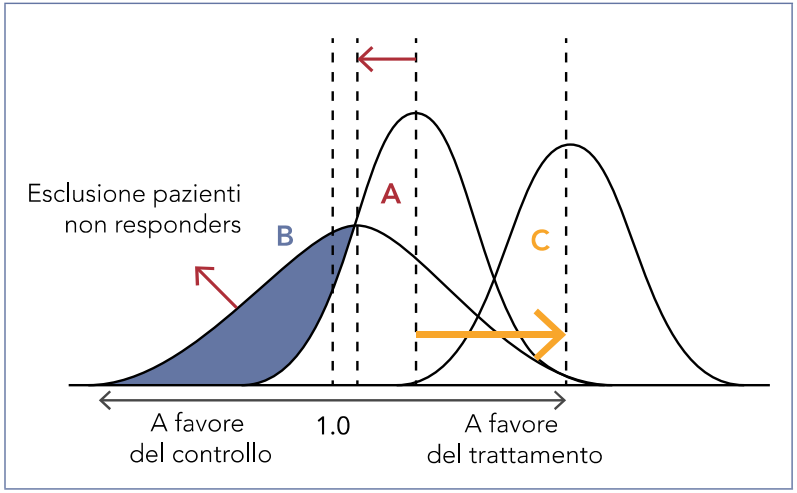
Proposal for payback (PP)

MEAs in Italy



Methodology in cancer area





mPFS of KM: tempo di follow-up calcolato sulla mediana della PFS della curva di Kaplan-Meier nel gruppo di controllo

Time of mPFS in the control group, which expresses the incremental effect of PFS of the new drug compared to control. This value is weighted for the duration of the treatment, on the basis of TToT curve of KM curves.

Relevant variables of outcome-based agreements

A. Definition of non-responders or treatment failure (*disease progression, treatment discontinuation, death*)
   a. Which criteria?
   b. Single or multiple evaluations over time?
B. Percentage of refund (PbR 100%, CS variable discounts.,)
C. Evaluation time
   a. After how many days/months should treatment response be evaluated?

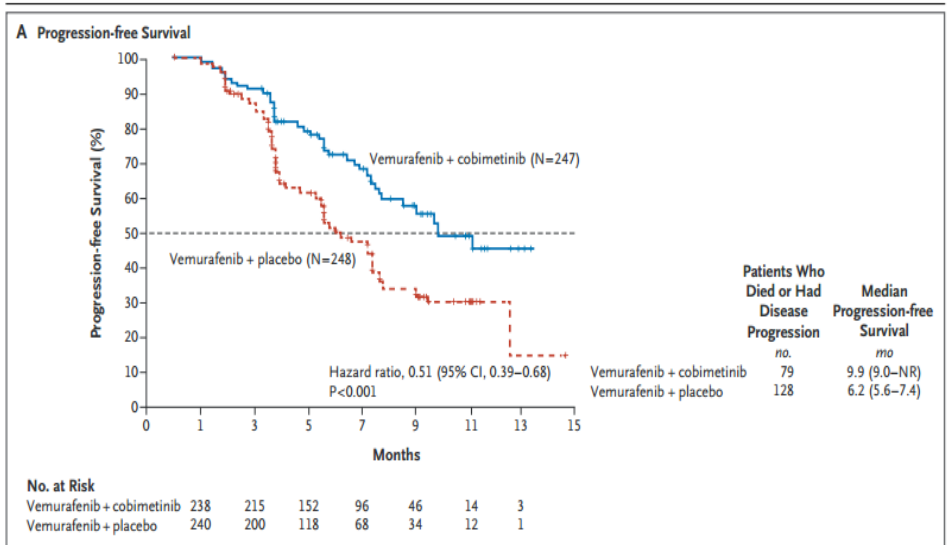
The case for BRAF + MEK Inhibitors: Melanoma

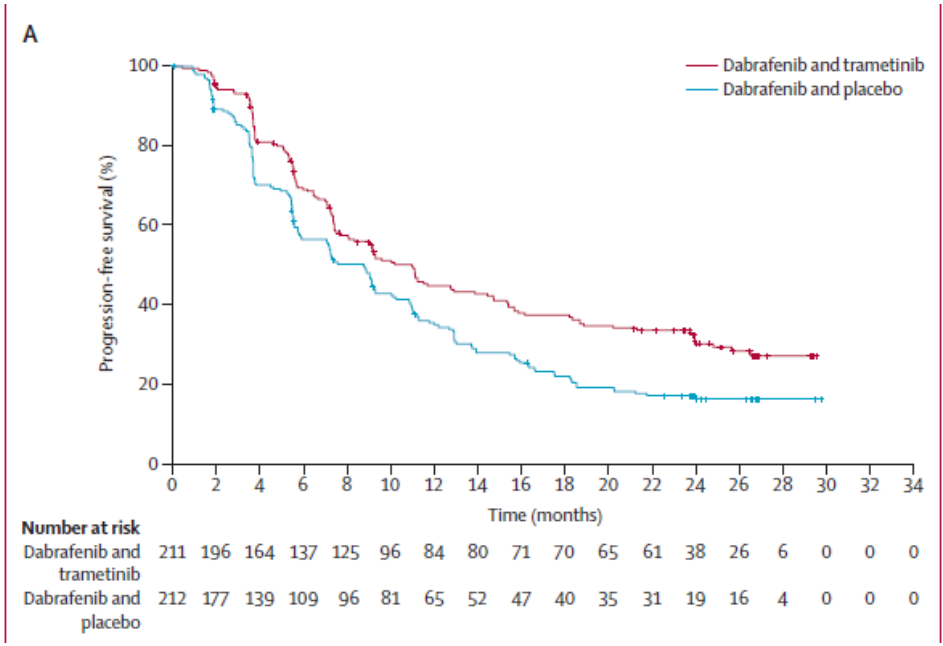
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 13, 2014 VOL. 371 NO. 20

Combined Vemurafenib and Cobimetinib in *BRAF*-Mutated Melanoma

James Larkin, M.D., Ph.D., Paolo A. Ascierto, M.D., Brigitte Dréno, M.D., Ph.D., Victoria Atkinson, M.D., Gabriella Liszkay, M.D., Michele Maio, M.D., Mario Mandalà, M.D., Lev Demidov, M.D., Daniil Stroyakovskiy, M.D., Luc Thomas, M.D., Ph.D., Luis de la Cruz-Merino, M.D., Caroline Dutriaux, M.D., Claus Garbe, M.D., Mika A. Sovak, M.D., Ph.D., Ilsung Chang, Ph.D., Nicholas Choong, M.D., Stephen P. Hack, M.D., Ph.D., Grant A. McArthur, M.B., B.S., Ph.D., and Antoni Ribas, M.D., Ph.D.

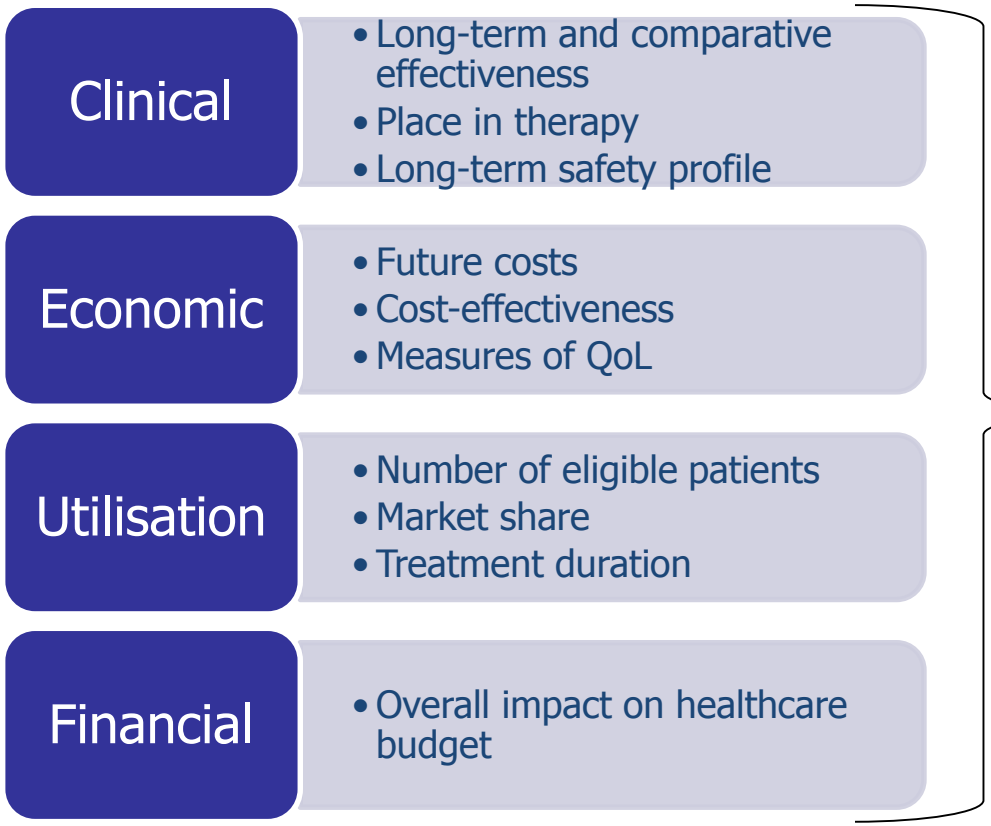




Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial

Georgina V Long, Daniil Stroyakovskiy, Helen Gogas, Evgeny Levchenko, Filippo de Braud, James Larkin, Claus Garbe, Thomas Jouary, Axel Hauschild, Jean-Jacques Grob, Vanna Chiarion-Sileni, Celeste Lebbe, Mario Mandalà, Michael Millward, Ana Arance, Igor Bondarenko, John B A G Haanen, Johan Hansson, Jochen Utikal, Virginia Ferraresi, Nadezhda Kovalenko, Peter Mohr, Volodymyr Probachai, Dirk Schadendorf, Paul Nathan, Caroline Robert, Antoni Ribas, Douglas J DeMarini, Jhangir G Irani, Suzanne Swann, Jeffrey J Legos, Fan Jin, Bijoyesh Mookerjee, Keith Flaherty

Value-based pricing under Uncertainty



Risks for payers

1. To reimburse technologies that turn out to be not cost-effective
2. To exceede annual budget for pharmaceuticals

Even if cost-effectiveness analysis did provide a reliable way forward, there is still a budgetary problem to be considered (Bach, *N Engl J Med* 2015).

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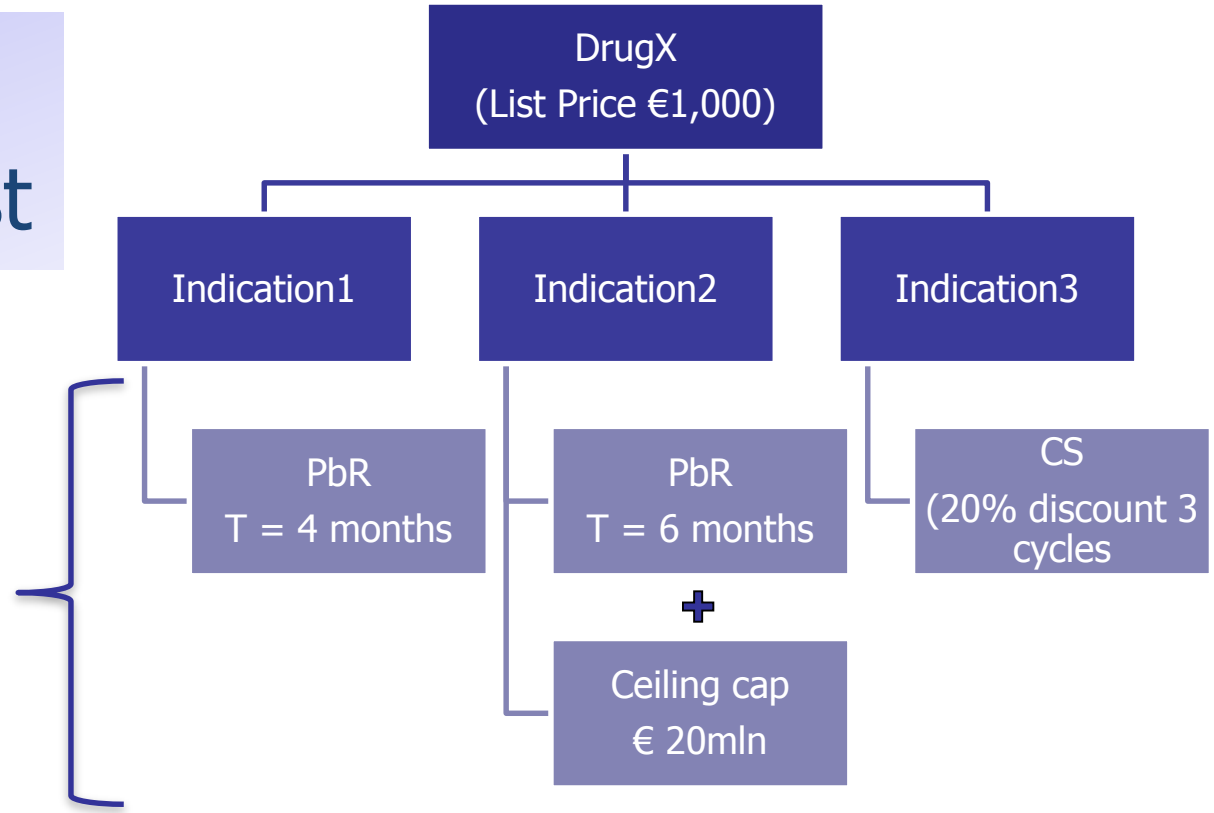
Multiple indications drug: Price discrimination

Same list price, value-based cost



Specific MEA for each therapeutic indication (Bach, *Jama* 2014) 'when costs are essentially the same but benefit differs widely, value is not the same' → crude metric of value: cost per Y of life gained

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Multiple indications: same list price, value-based cost

Active Ingredient	Indication	Type of MEA
Bevacizumab	Ovarian Neoplasms	OBA
	Ovarian Neoplasms	OBA
	Breast Neoplasms	OBA
	Carcinoma, Non-Small-Cell Lung	OBA
	Carcinoma, Renal Cell	OBA
	Colorectal Neoplasms	OBA + FB
Ranibizumab	Myopia, Degenerative	OBA
	Diabetes Complications Macular Edema	OBA
	Macular Edema	OBA
	OBA	OBA
Sorafenib	Carcinoma, Hepatocellular	OBA
	Carcinoma, Renal Cell	FBA

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Source: http://www.agenziafarmaco.gov.it/it/content/lista-aggiornata-dei-registri-e-dei-piani-terapeutici-web-based, update 23/02/2016

When New Cancer Treatments Fail, Italy Wants Its Money Back

by Makiko Kitamura maki_kitamura Johannes Koch

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.

International Journal of Technology Assessment in Health Care, 31:4 (2015), 210–213.

doi:10.1017/S0266462315000446

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

Simona Montilla
Italian Medicines Agency (AIFA)
S.Montilla@aifa.gov.it
Entela Xoxi, Pierluigi Russo
Italian Medicines Agency (AIFA)
Americo Cicchetti
Università Cattolica del Sacro Cuore
Luca Pani
Italian Medicines Agency (AIFA)

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

Nutrition, Metabolism & Cardiovascular Diseases (2014) 24, 1346–1353

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

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

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]

[a] *Italian Medicines Agency (AIFA), Rome, Italy*
[b] *Unit of Metabolic Diseases, S. Orsola-Malpighi University Hospital, Bologna, Italy*
[c] *Dept. Physiology and Pharmacology, University of Rome "La Sapienza", Rome, Italy*

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Available online 6 October 2014

The economic effect will reflect the actual effectiveness and the costs will be lower in indications with a high number of non-responders

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Interaction between the three "worlds" (regulators, payers, HTA) and enabling strategies

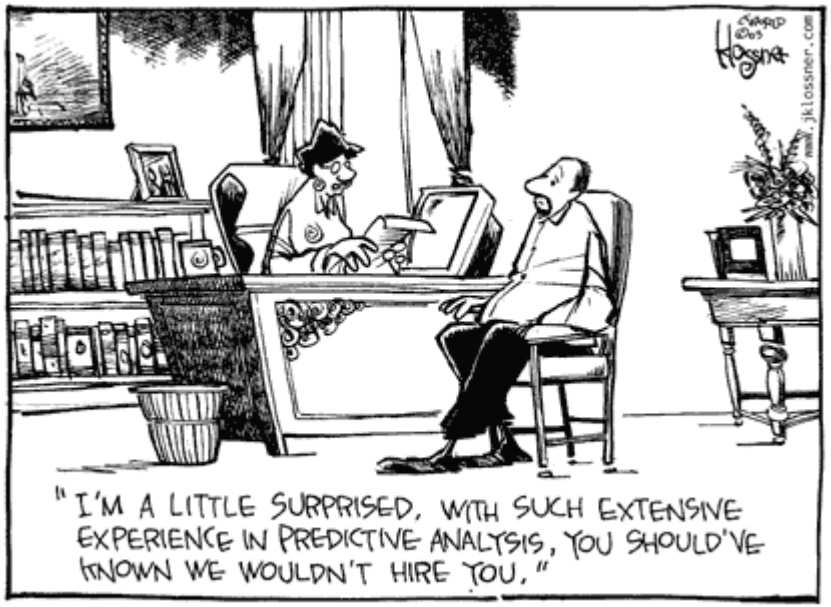
To realise the benefit and smooth the road to access, other stakeholders need to be involved, for planning and implementation. **No benefit to a 'regulator-only' advancement.**

- product prioritisation in a world of limited resources– Who should select the products?
- Selection criteria and meaning of "need" (clinical, public health)
- Entry and exit schemes
- Prescription controls
- Feasibility/desirability of post-authorisation data acquisition vs other risk sharing schemes. Making the most use of available data

BIG DATA means different things to different people and there isn't, and probably never will be, a commonly agreed upon definition out there.

But the phenomenon is real and it is producing benefits in so many different areas, so it makes sense for all of us to have a working understanding of the **concept**.

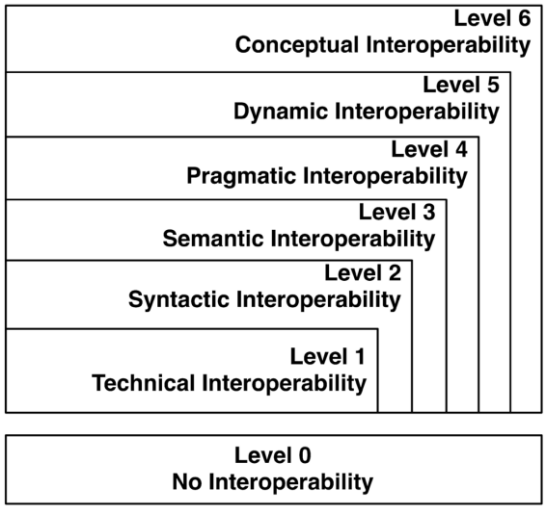
BIG DATA is that everything we do is increasingly leaving a digital trace (or data), which we (and others) can use and analyze.
Big Data therefore refers to that data being **COLLECTED** and our ability to **MAKE USE** of it.



Healthcare data without interoperability = Pain

Interoperability is the ability of different ITS & software applications to **COMUNICATE**, **EXCHANGE DATA**, and **USE** the information that has been exchanged.

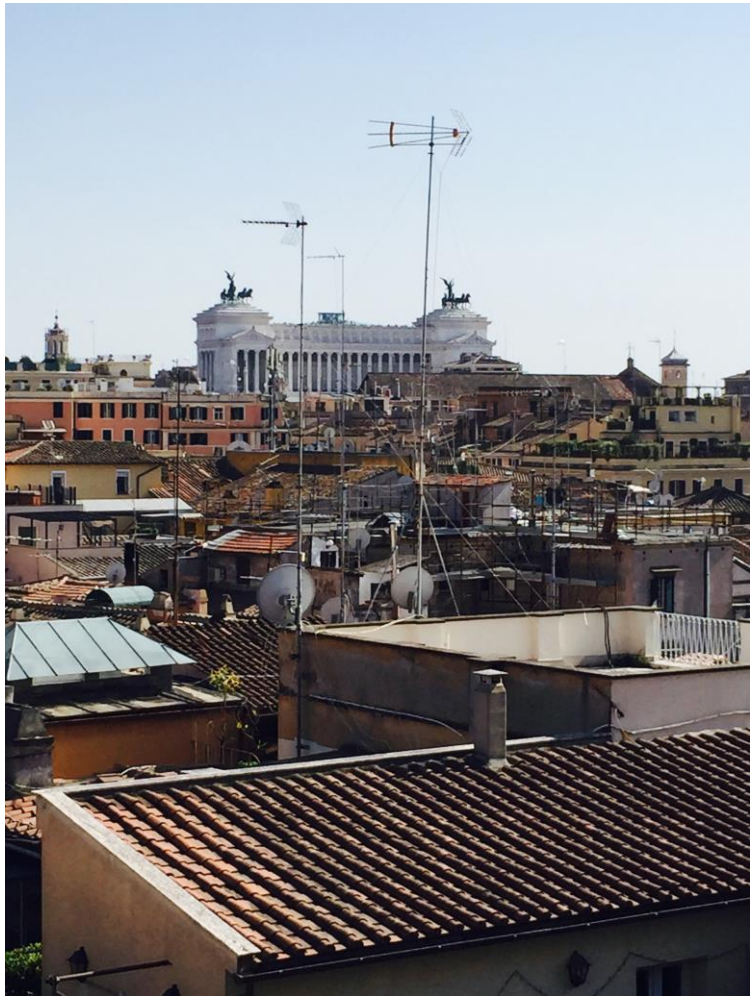
Data exchange schema and standards should permit data to be shared across clinicians, lab, hospital, pharmacy, and patient regardless of the application or application vendor.
Interoperability means the ability of health information systems to work together within and across organizational boundaries in order to advance the health status of, and the effective delivery of healthcare for, individuals and communities



Conclusions

1. Creating synergies with existing initiatives: MAPPs, AP & existing regulatory tools (PAES, PASS)
2. Mandatory early collaboration between EMA and HTAs/payers (and other stakeholders) in a AP approach
3. Changes in law, regulations and procedures may be needed in different countries
4. Patient organizations will have an important role
5. Build on experience with MEAs: *Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States – 17 June 2016*

Thank you for the attention



Entela Xoxi
e.xoxi@aifa.gov.it

http://www.agenziafarmaco.gov.it/it/content/registri-farmaci-sottoposti-monitoraggio