EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Medicines Adaptive Pathways to Patients:
The expected contribution of Real World Data

Köln, IQWiG, November 2015

Hans-Georg Eichler
Senior Medical Officer

An agency of the European Union

In this talk

Do we have a gold standard for evidence generation?

Why do we need adaptive pathways to market?

Can real world data (RWD) fill the gap?

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Exhibit 1: Statins

"We have randomised ~136,000 patients in statin RCTs"

[Quote from a senior biostatistician]

So – why is there heated debate?

- Who should be treated?
- How big is the clinical benefit?
- What dose/substance?

Can RCTs ever show us more than the tip of the iceberg?

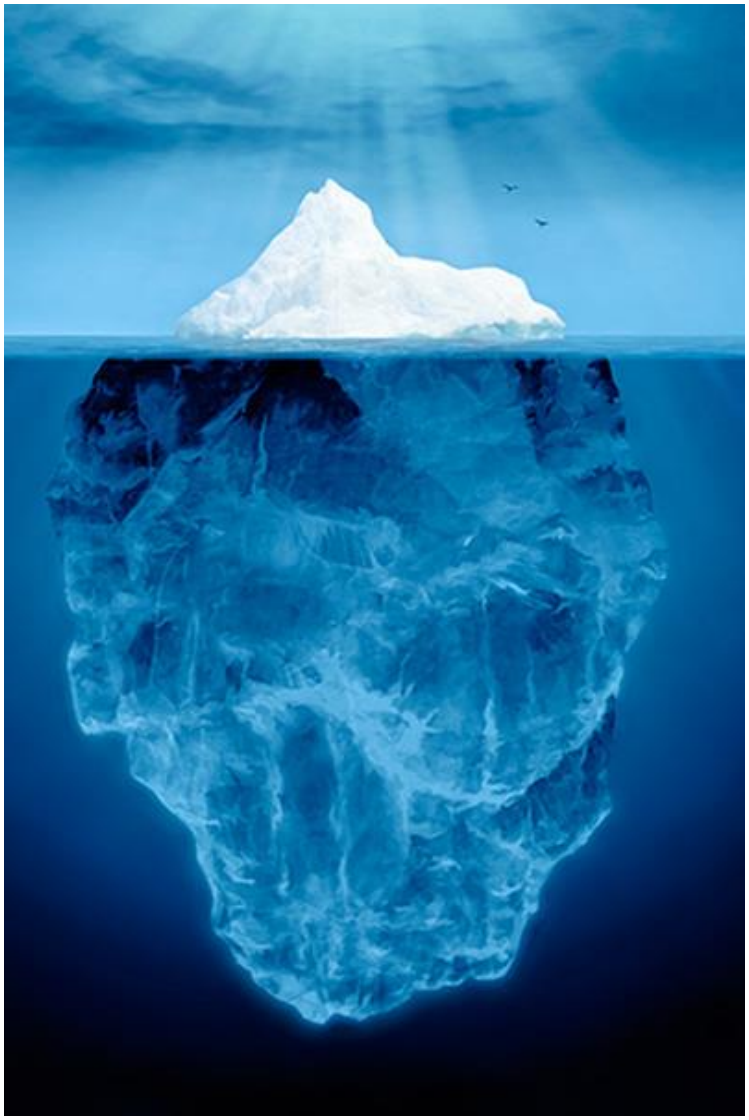


Exhibit 2: Glucose management in ICU patients

- 2001 RCT: intensive insulin therapy for blood glucose management shows improved survival in surgical Intensive Care Unit (ICU) patients
- Subsequent RCTs: ~17,000 patients randomised in different settings and patient sub-populations
- Wide gap between findings (better, neutral, worse)

"This new perception of hyperglycaemia and its management should be assessed in large surveys and observational studies."

Mesotten et al. Lancet Diabetes Endocrinol 2015; 3: 723

Exhibit 3: Rimonabant

- Rimonabant (Acomplia®), licensed in 2006 in EU for weight reduction in a defined subgroup of obese or overweight patients.
- Pre-licensing clinical program: 49 mostly randomised studies; 16,120 subjects or patients - hardly an "under-researched" product.
- On-market observational data: considerably smaller than expected effect size and higher number of adverse events.

Large volume of RCT information → poor predictor of real-world performance → product taken off the market in 2009

Source: EMA EPAR "Acomplia"

Is the RCT truly a Gold Standard?

- As for any test, positive predictive value <100% (depending on pre-study chance of effect probed being non-null)
- Unknown confounders cannot be excluded (though RCTs are best to minimise)
- Many RCTs are *not* perfectly planned, executed and analysed; bias can still occur (e.g. population choice bias)
- RCT results often heterogeneous, sometimes contradictory (reasons sometimes understood, sometimes not)
- External validity often low → relevance for clinical practice?
- Slow and expensive

Is the RCT truly a Gold Standard?

Conclusion 1:

- Maybe there is no “Gold Standard”?
- Maybe we should do away with any metallurgical reference?
- Maybe there is just a spectrum of methodologies on a continuum of internal and external validity?
- Among these, the RCT has the highest level of internal validity.

Is the RCT truly a Gold Standard?

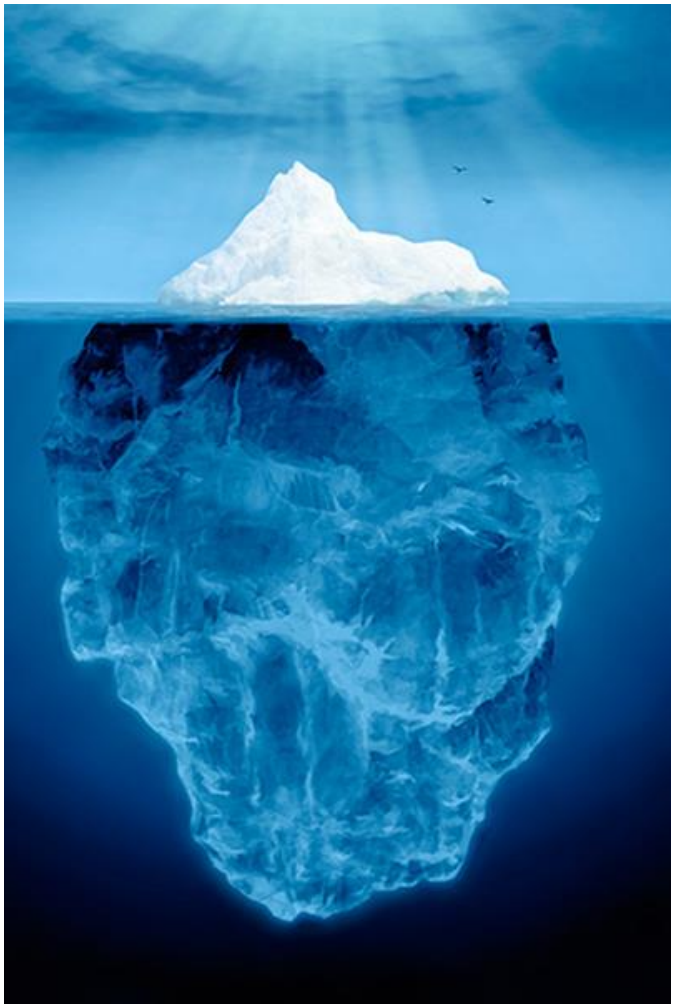
Conclusion 2:

Randomised or not,

adaptive pathways or not,

any evidence requires post-licensing verification:

- by way of a life-span approach to evidence generation,
- including Real World Data,
- to ensure robust information on benefits and harms,
- to see more of the iceberg.



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Why do we need adaptive pathways?

Realisation of competing objectives

Allow timely access for patients to address urgent medical need	⟷	Allow only well-studied drugs on the market
Enable precision medicine, 'difficult' indications	⟷	Rely on robust study methodology and end points
Ensure sustainability of the innovation engine	⟷	Ensure sustainability of health care systems

What will change with adaptive pathways?

Transition from …

Magic moment	→	life-span management
Prediction	→	monitoring
RCT only	→	toolkit for evidence generation
Big populations	→	small populations
Focus on licensing	→	focus on patient access
Open utilisation	→	managed utilisation

In this talk

Do we have a gold standard for evidence generation?

Why do we need adaptive pathways to market?

Can real world data (RWD) fill the gap?

- examples
- reflections
- conclusions

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Dabigatran and Postmarketing Reports of Bleeding

Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.

N Engl J Med 2013; 368:1272-1274 | April 4, 2013 | DOI: 10.1056/NEJMp1302834

Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.*

Analysis	Dabigatran			Warfarin		
	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)
Gastrointestinal hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,599	16	1.6	43,541	160	3.5
Sensitivity analysis without required diagnosis of atrial fibrillation	12,195	19	1.6	119,940	338	3.1
Intracranial hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,587	8	0.8	43,594	109	2.4
Sensitivity analysis without required diagnosis of atrial fibrillation	12,182	10	0.9	120,020	204	1.9

Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis

Hector S Izurieta, Nicole Thadani*, David K Shay, Yun Lu, Aaron Maurer, Ivo M Foppa, Riley Franks, Douglas Pratt, Richard A Forshee, Thomas MaCurdy, Chris Worrall, Andrew E Howery, Jeffrey Kelman*

Lancet Infect Dis 2015; 15: 293–300

Published Online February 9, 2015 http://dx.doi.org/10.1016/S1473-3099(14)71087-4

Summary

Background A high-dose trivalent inactivated influenza vaccine was licensed in 2009 by the US Food and Drug Administration (FDA) on the basis of serological criteria. We sought to establish whether high-dose inactivated influenza vaccine was more effective for prevention of influenza-related visits and hospital admissions in US Medicare beneficiaries than was standard-dose inactivated influenza vaccine.

Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis

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	High-dose cohort (n=929 730)	Standard-dose cohort (n=1 615 545)	Standardised mean difference
Sex			
Female participants	538 380 (57·91%)	959 072 (59·37%)	0·03
Male participants	391 350 (42·09%)	656 473 (40·63%)	0·03
Race			
White	867 552 (93·31%)	1 512 633 (93·63%)	0·01
Black	25 463 (2·74%)	41 714 (2·58%)	0·01
Other race/unknown	16 235 (1·75%)	27 571 (1·71%)	<0·01
Asian	12 973 (1·40%)	21 178 (1·31%)	0·01
Hispanic	6112 (0·66%)	10 328 (0·64%)	<0·01
Native North American	1395 (0·15%)	2121 (0·13%)	0·01

Lancet Infect Dis 2015; 15: 293–300

Published Online February 9, 2015 http://dx.doi.org/10.1016/S1473-3099(14)71087-4

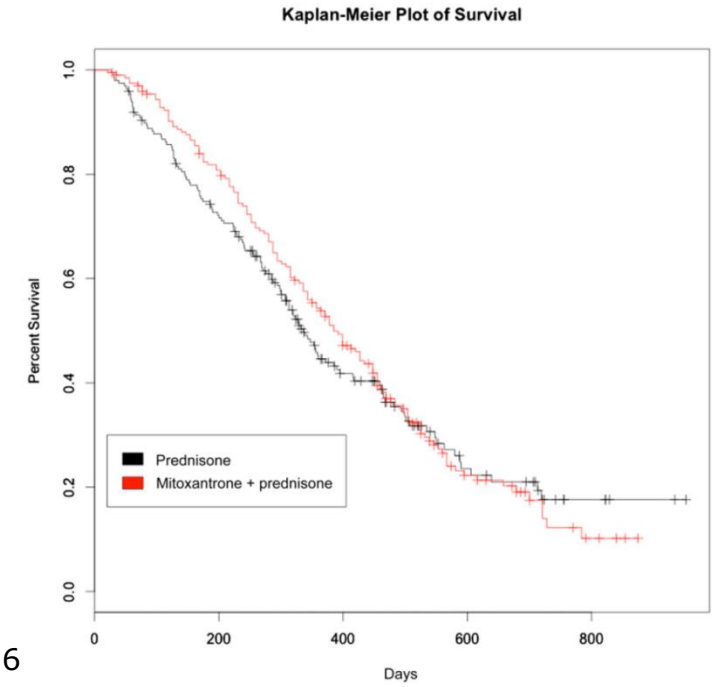
The Oncologist®

Genitourinary Cancer

Comparative Effectiveness of Mitoxantrone Plus Prednisone Versus Prednisone Alone in Metastatic Castrate-Resistant Prostate Cancer After Docetaxel Failure

Angela K. Green,[a,*] Robert W. Corty,[b,*] William A. Wood,[a] Mathew Meeneghan,[a] Katherine E. Reeder-Hayes,[a] Ethan Basch,[a] Matthew I. Milowsky,[a] Stacie B. Dusetzina[c,d]

[a]UNC Lineberger Comprehensive Cancer Center, [b]Division of Hematology and Oncology, School of Medicine, [c]Division of Pharmaceutical Outcomes and Policy, Eshelman School of Pharmacy, and [d]Department of Health Policy and Management, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA



- n=562;
- Not "real-world data"
- Not a single patient was enrolled for this study
- What is it?

Project Data Sphere®

Green, et al. The Oncologist 2015; 20:516-522

How can RWD help?
Minimising realised harm

Inherent risk ≠ realised harm

Let's do a thought experiment:

1950/60s; thalidomide induced phocomelia; high-visibility, low background event:

10.000 cases 'realised'!

How far down can we bring the number with rapid cycle analysis?

How can RWD help?
Monitoring utilisation

- Is use limited to the intended target population?
- Is any off-label or near-label use fully documented?
- Adaptive Pathways relies on appropriate prescribing *and* documentation

How can RWD help?
Monitoring benefits

- Effect size in real world conditions?
- Relative /comparative effectiveness? (example: EUnetHTA assessment of a new diabetes product); RWD *and* patient-level mixed treatment comparisons
- Who benefits? Identifying the 'right' subpopulation for precision medicine

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Monitoring benefits

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Precision medicine (combinations)

A different set of research question

From:

"Is A better than B in a group of patients?"

To:

"If A truly modulates target X, i.e. has pharmaco-dynamic activity, (how) can we identify patients who benefit, combinations that work?"

Precision medicine (combinations)

A different approach to drug development?

- Shift from population focus to individual focus
- Shift from single agent treatment to personalised combinations
- Variance is not noise, variance is the focus of scientific interest
- Can we address by subgroup analysis of RCTs?

Conclusion: the evolution of evidence

- Evidence will be based on a diverse family of data sources and methodologies complementing (not replacing) RCTs.
- Evidence will see a shift from population focus to patient focus.
- Uncertainty cannot be eliminated but …
- Adaptive Pathways seeks to progressively reduce uncertainty – *increasing* the evidence standard over the product life-span

Thank you!