PUBLIC HEARINGS
Product Safety in the therapeutic context

Pharmacovigilance Stakeholders' Forum

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24 September 2018, EMA, London

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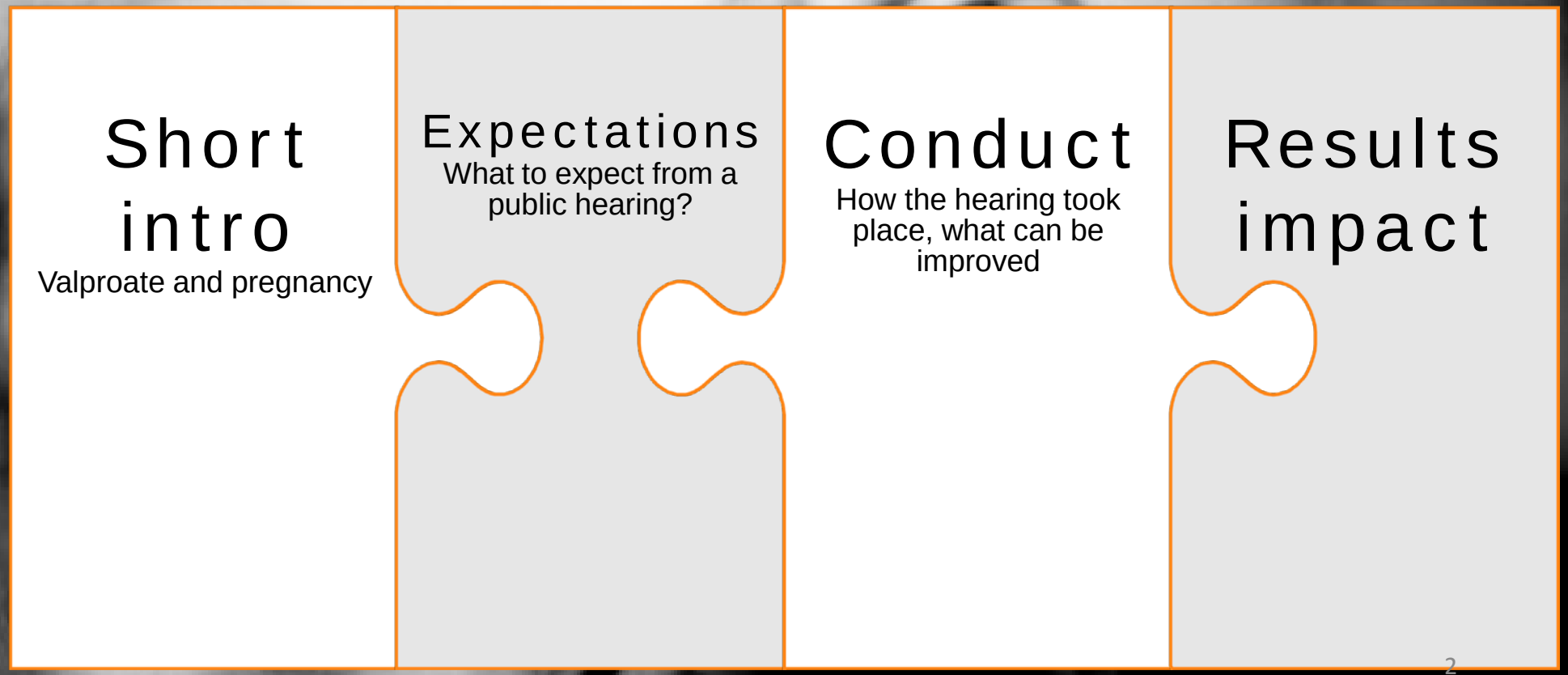
In this presentation

Own views on EMA 1st Public Hearing

Disclaimer

Views and opinions in this presentation are the ones of the author.



1. Expectations and pre-hearing questions

Chronology

•1967-1973

- Valproate sodium marketed (warnings ignored?)

•1980

- Teratogenic potential reported
- Brown March 1980, The Lancet

•1984

- First case of malformation in human
- Bantz 1984 Jun Clin. Pediatr.

?

•2014

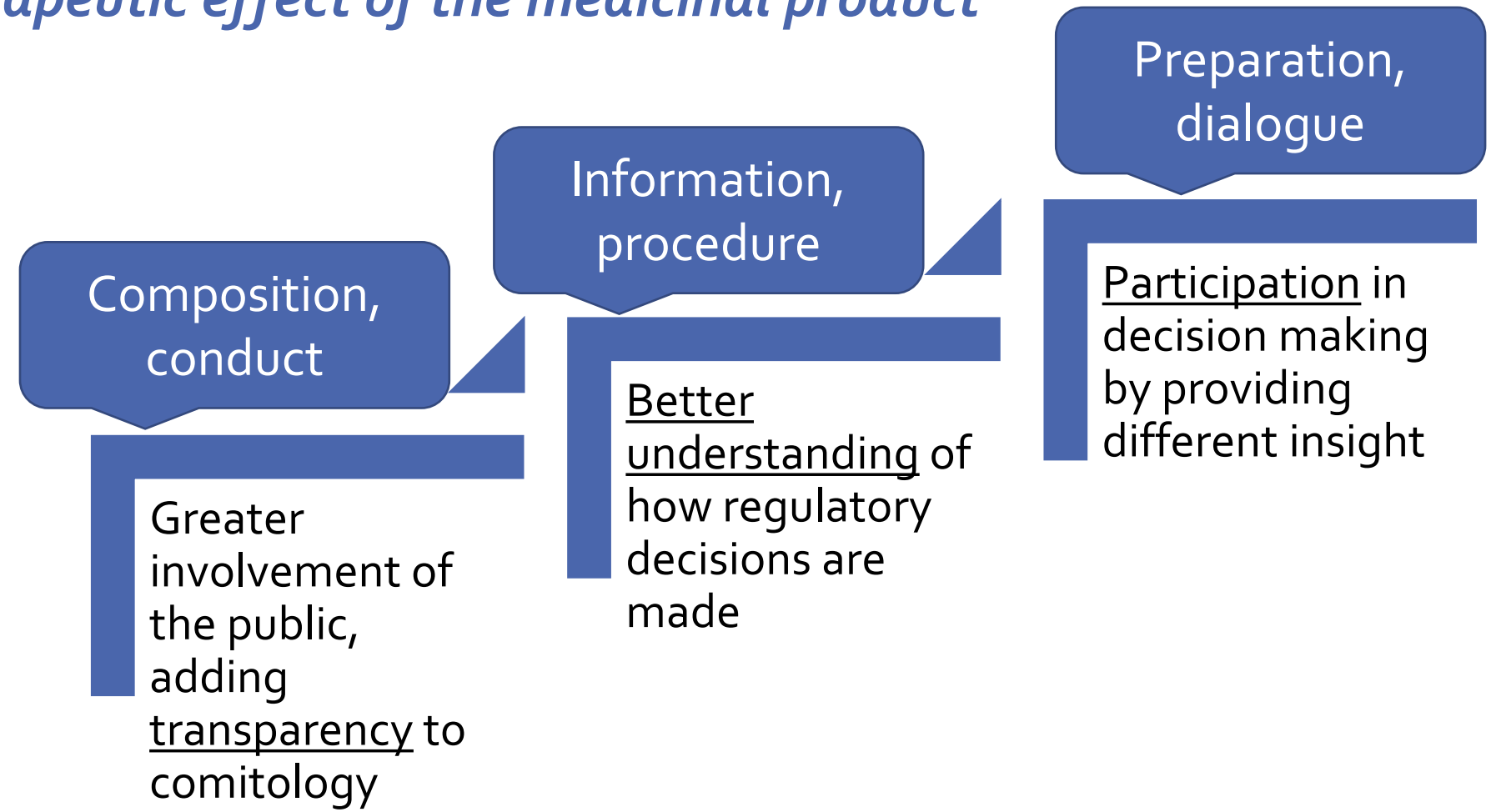
- PRAC updates SmPC & PL

•2017

- EMA public hearing

Pre-hearing expectations

Art 107j "*In the public hearing, due regard shall be given to the therapeutic effect of the medicinal product*"



Prior to the hearing

Questions patients' organisations had

- Will the process be open and transparent?
- A dialogue with PRAC? Or series of stakeholders' statements?
- Will the debates add something to PRAC discussions?
- Will it be confrontational, political?
- Will it contribute to the decision-making? Or post-hoc explanation of an already made decision?
- Will it have an impact? Become the EU-wide reference forum?

Participants

- Different attitudes that reflect different cultures, different stories, different states of mind and psychologies

• Thinking ahead, cold anger

Analysing the problems, suggesting ideas, playing a role in the dissemination of information. How to improve measures taken in 2014?

People living with the condition and acting on the problem

• Complaining, warm anger

Looking for responsible person/entity, bringing case to court, advocating for financial compensation. What happened between 1967 and 2014?

Victims, counting victims

• (mock scientists)

Bringing the patients' perspective but sometimes more with the view point of a scientist, not addressing the experience of those living with.

Talking about "the patients", not "we"

2. Organisation and conduct

In particular

Focus

Systematically asking "What would you recommend?" was key to drive interventions towards the desired objectives

Mutual respect

All participants could feel they could talk with equal credibility as others. The role of the agency conferred solemnity, seriousness, and openness to the process

Freedom of expression, confronting different opinions

All opinions were listened to, and different opinions could be confronted, basis of a democratic debate that ensures trust

Room for emotions and stress

Not all speakers addressed the 3 questions equally

Some expressed their feelings, not just facts or evidence

That's ok, that was expected, that was necessary

Fairness

It was excellent to open the floor to the audience as there was some time left at the end with also interesting comments

Reality check

Different views, showing nothing is black or white, that regulating is not telling the absolute truth, but deciding on what to do

Room for improvement

Attendance, diversity

Perhaps other participants could intervene from the offices of national authorities if equipped with video conferencing services. Brexit: do we loose UK participants?

Webcast

It would be useful to have a larger view of the room, to feel the sense of how large the attendance was

Language barrier

One speaker had interpretation, not sure if the possibility to have interpretation was publicly announced?

Public hearing or debate?

The public is expecting PRAC experts to react, else it could give the impression of a formal exercise. Finally there was a debate

Completeness

Not all questions were answered; e.g. in which countries were materials distributed or not, or the % treated and experiencing long-term remission. Outstanding issues at the end of the hearing?

Multi-stakeholders' debate

In addition to a dialogue between speakers and PRAC, what about a dialogue between all parties? E.g. different parties submitting questions for others in advance? Not just the PRAC preparing questions

About all

High quality testimonies.
Qualifying terms that come to mind:

Powerful (public hearing = ultimate initiative)

"If at the end of this hearing nothing changes, then we would feel this exercise has been a waste of time" Clare Pelham

Courageous / "skin in the game", "connected"

Families struggling for many years

Taking care of their children with little or no support

Having 7 minutes to express themselves on a problem they've been living with for years

Maybe the most important speech of their life as a patient representative. This responsibility was visible

Emotions, the bright side of the Force

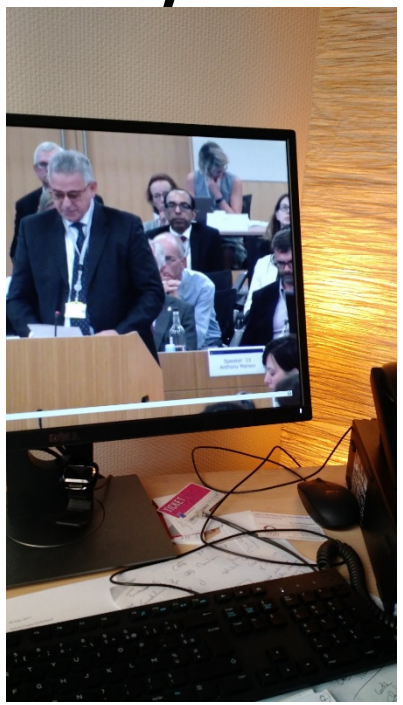
Pragmatic, well **prepared** and informed

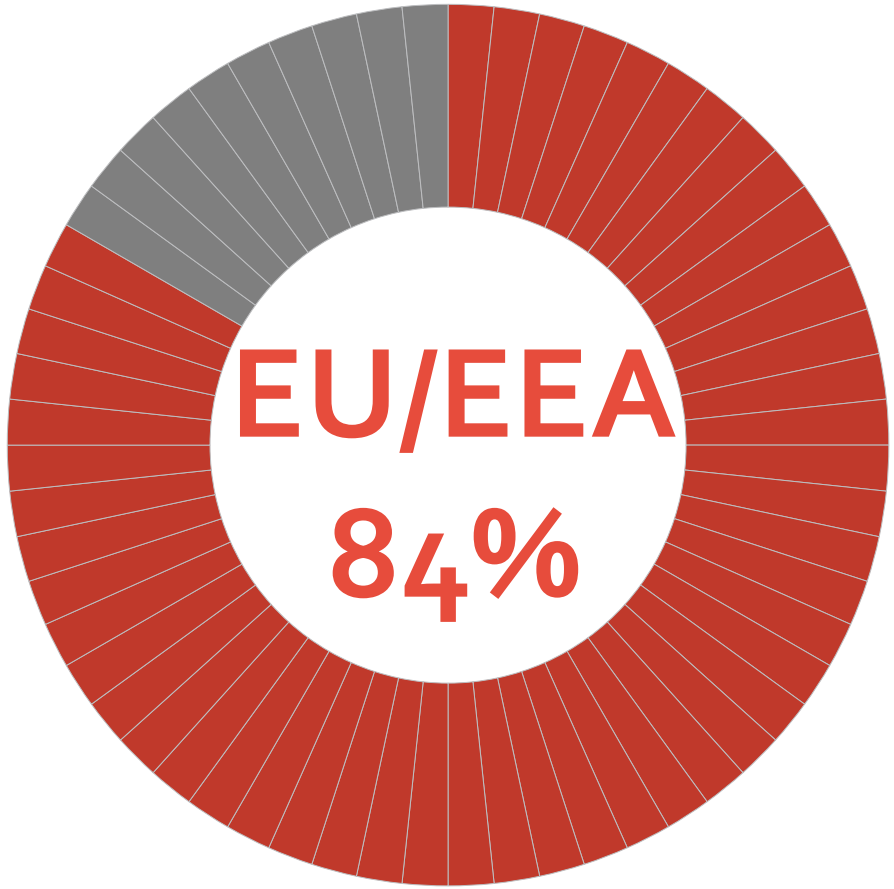
Helped understanding the utility of measures from an end-user's perspective

3. Results, impact

In addition to 65 on-site participants (+ 35 PRAC members)

- 1,801





- 1,800

REC

As of 27/06/2018

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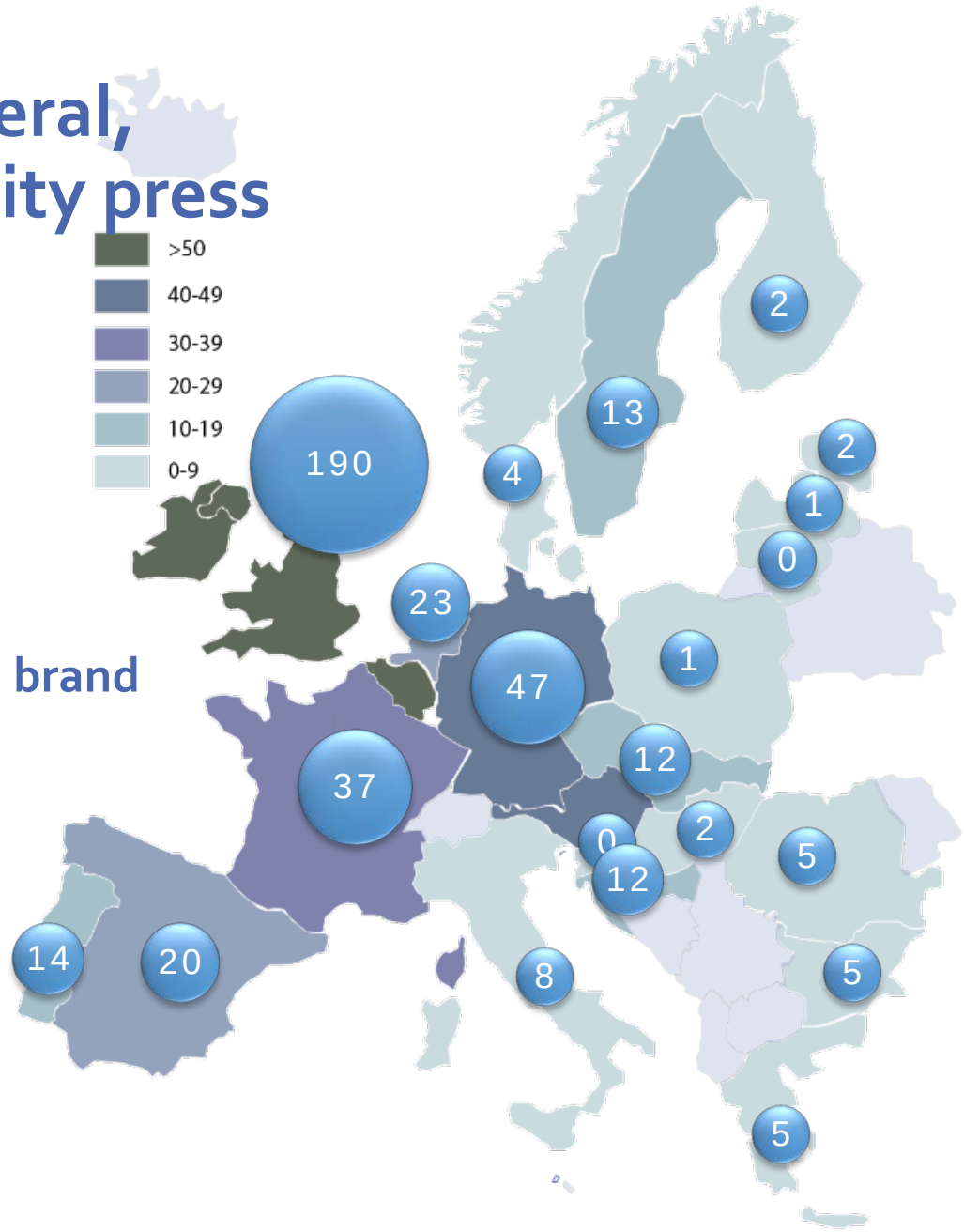
Web search:
403 references, general, medical or community press

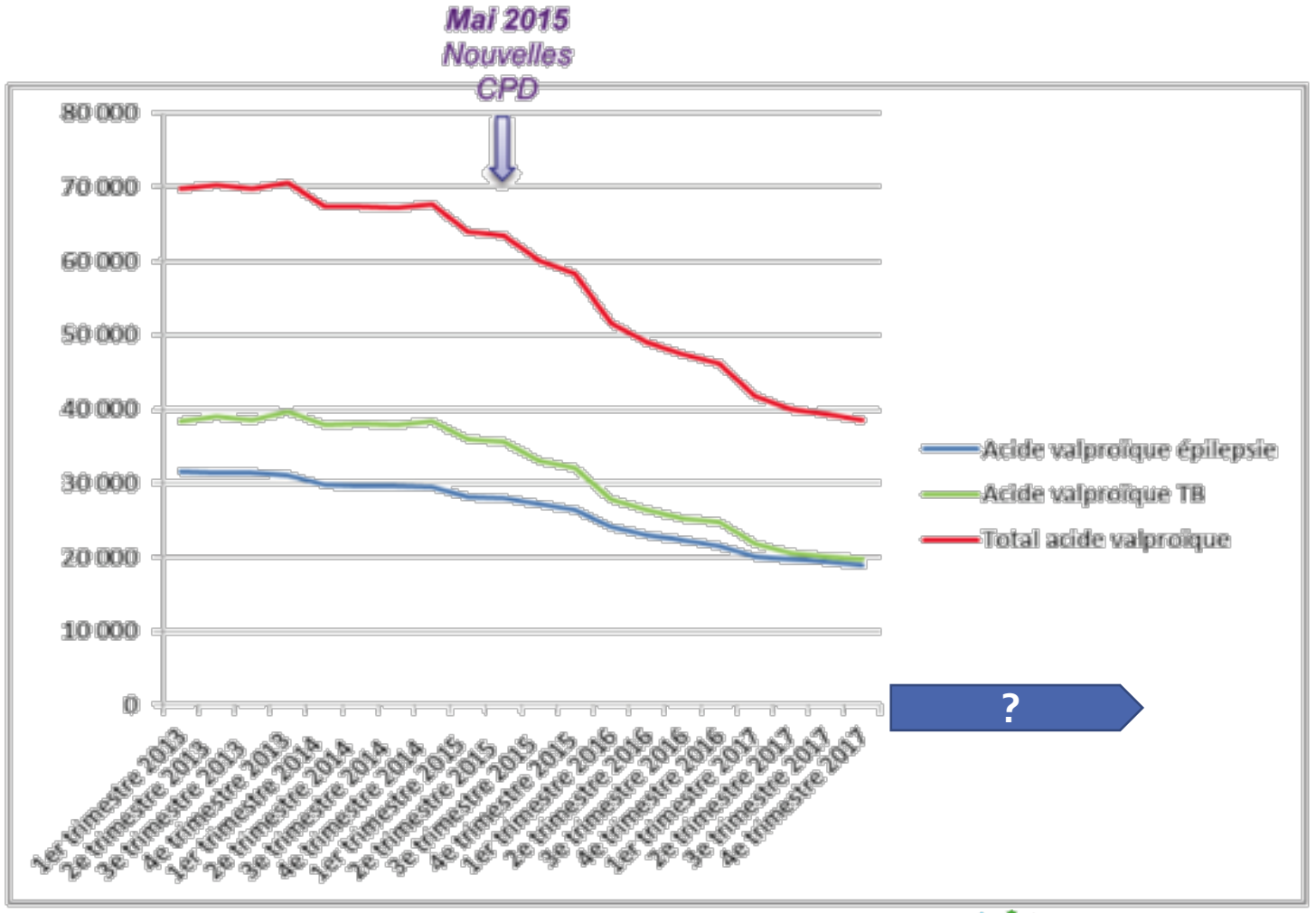
"Valproate"
"EMA"
"public hearing"
in different languages

- Different results when using brand names and not valproate
- When 1 or 2: EMA web site



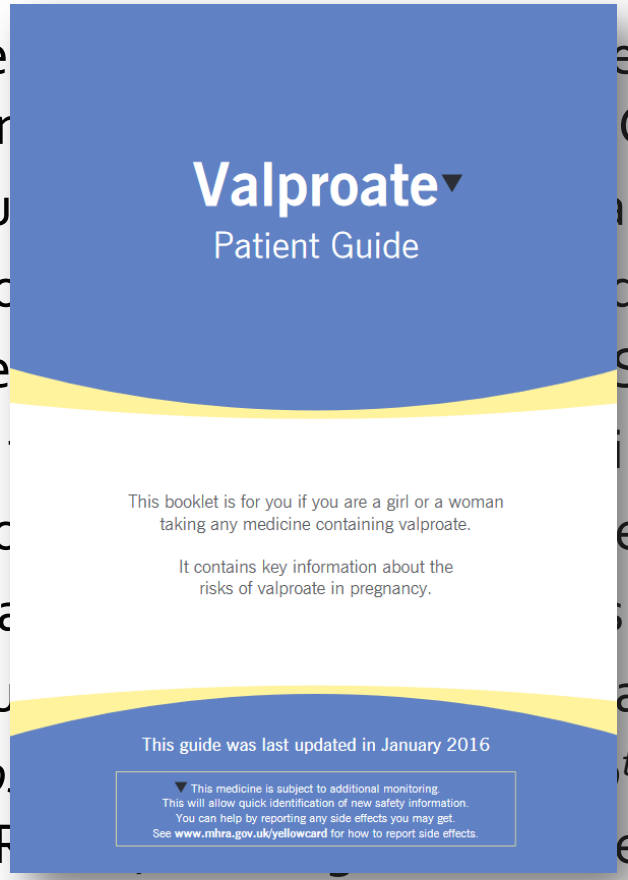
Evolution of Valproate use – France, 2013 to 2017

- 45% global decrease in valproate users
  - Epilepsy: -40%
  - Bipolar disorders: - 49%
- End 2017, used by 38,566 women
  - Epilepsy: 18,987
  - Bipolar disorders: 19,729
- ANSM May 2018



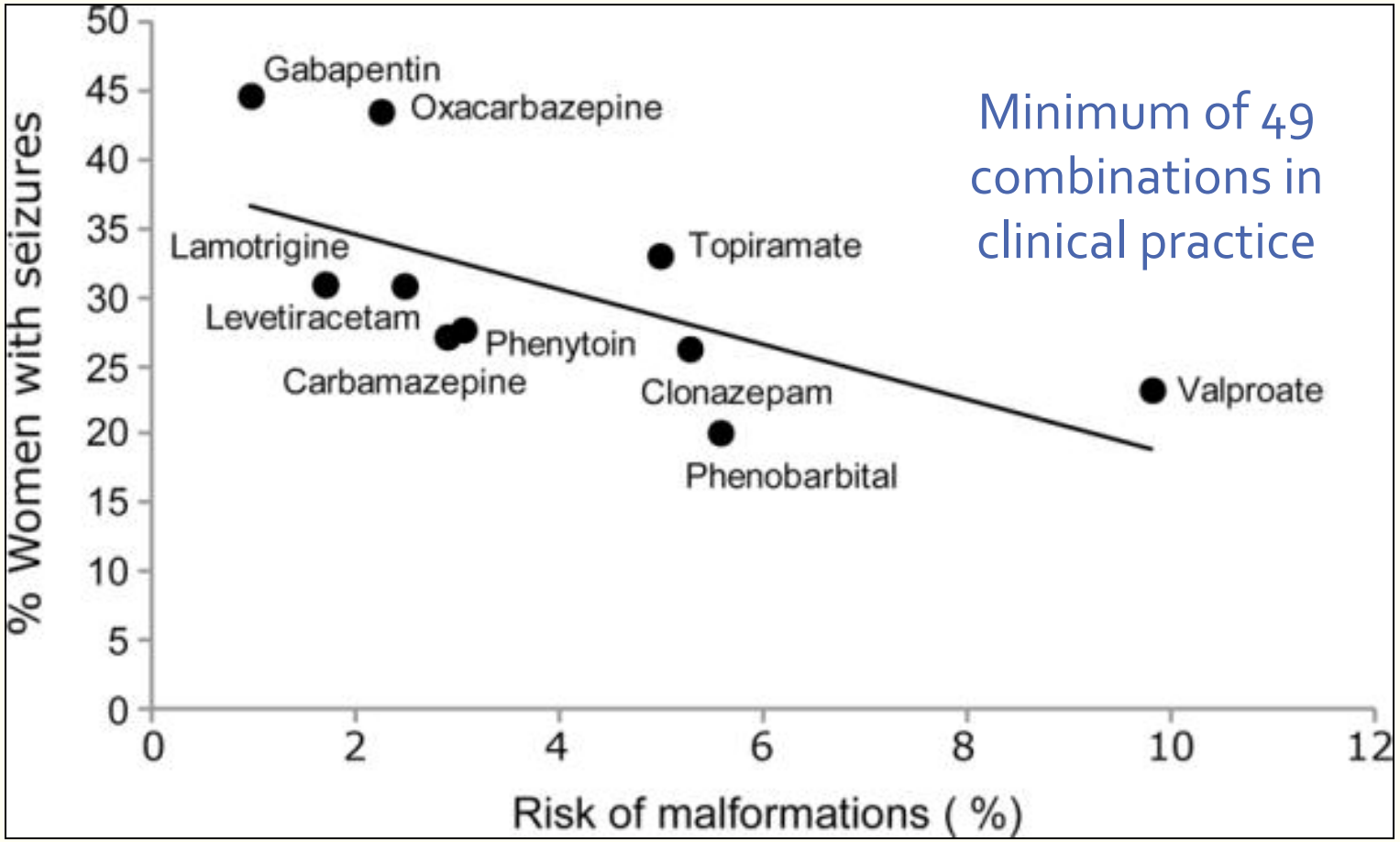
In addition to the hearing's summary

- Not much background information on the therapeutic context (outsiders, press etc.)
- Educational materials produced in 2014 are not used. Risk communication budgets?
- Need for stronger synergie eties, patients' organisations to work together on Treatmer Guidelines
  - EMA regulates one produ asses
  - Therapeutic context: to lo d relative safety (i.e. RWD) →
- Generics: no pictogram (ye SmPC generics versus brand?
- Congenital malformations irth / autism years after birth
  - Causality more difficult to equences on compensation
  - Does PRAC consider socia (here compensation)?
    - Consider "how to docu ational materials?
  - Cf Theory of *Causal Dispo th Anniversary, Uppsala 17 May 2018*. Rani Anjum, Elena F e Sciences



Background information & therapeutic context

The challenge to balance teratogenic risk against seizure control



Hernandez-Diaz Neurology 2012;78:1692-99

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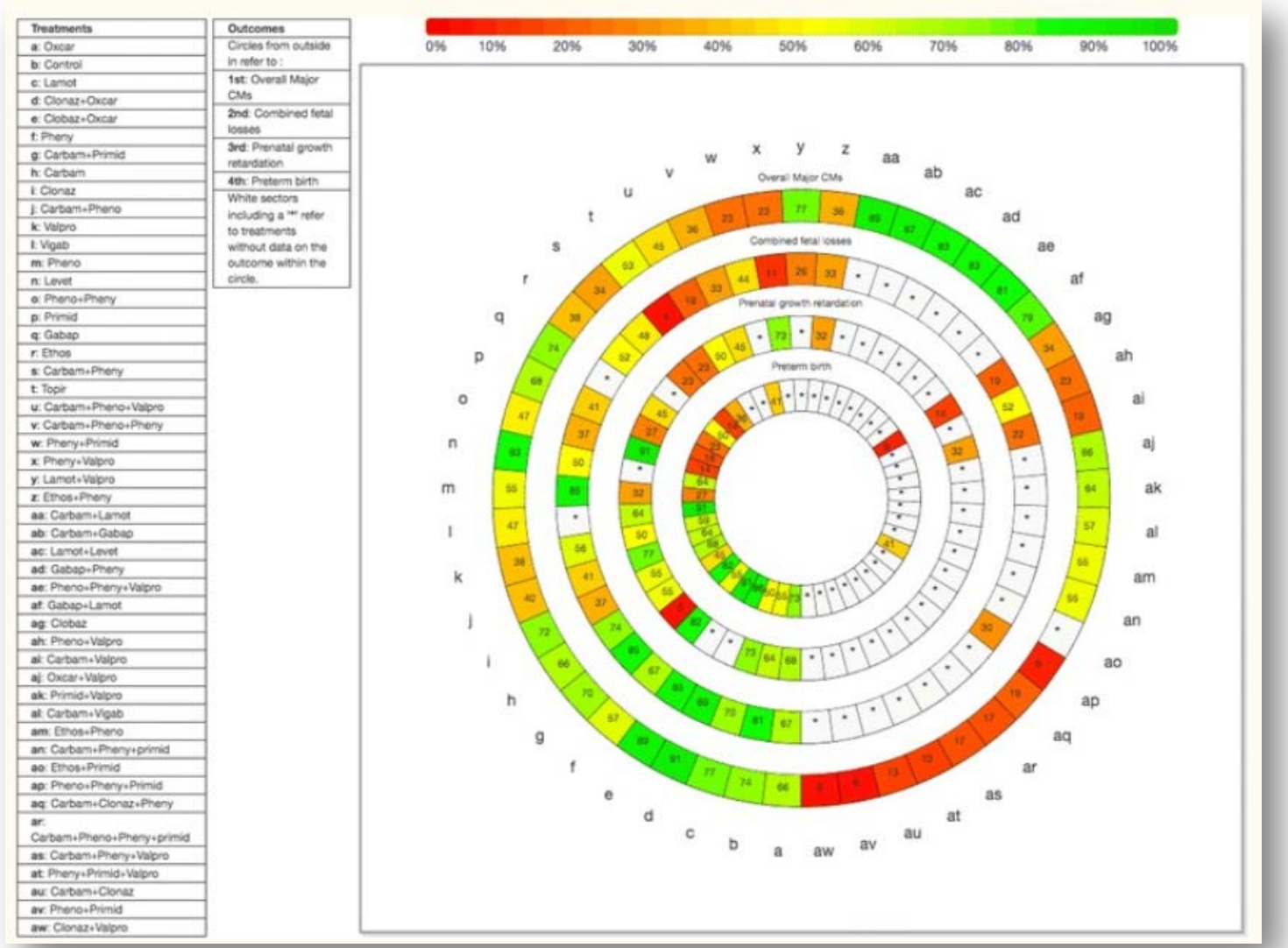
Counselling / pregnancy + epilepsies

published in 2017
49 treatments / combinations
96 eligible studies (58,461 patients)



Rank heat plot for overall major congenital malformations (CMs), combined fetal losses, prenatal growth retardation, and preterm birth. Rank-heat plot of 49 treatments (presented in 49 radii) and four outcomes (presented in four concentric circles). Each sector is colored according to the SUCRA value of the corresponding treatment and outcome using the transformation of three colors: red (0%), yellow (50%), and green (100%). *carbam* carbamazepine, *clobaz* clobazam, *clonaz* clonazepam, *ethos* ethosuximide, *gabap* gabapentin, *lamot* lamotrigine, *levet* levetiracetam, *oxcar* oxcarbazepine, *pheno* phenobarbital, *pheny* phenytoin, *primid* primidone, *topir* topiramate, *valpro* valproate, *vigab* vigabatrin

Veroniki AA, Cogo E, Rios P, et al. Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. BMC Medicine. 2017;15:95. doi:10.1186/s12916-017-0845-1

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Outstanding issues – Valproate is only one part of the armamentarium for epilepsy. Not the end of the story

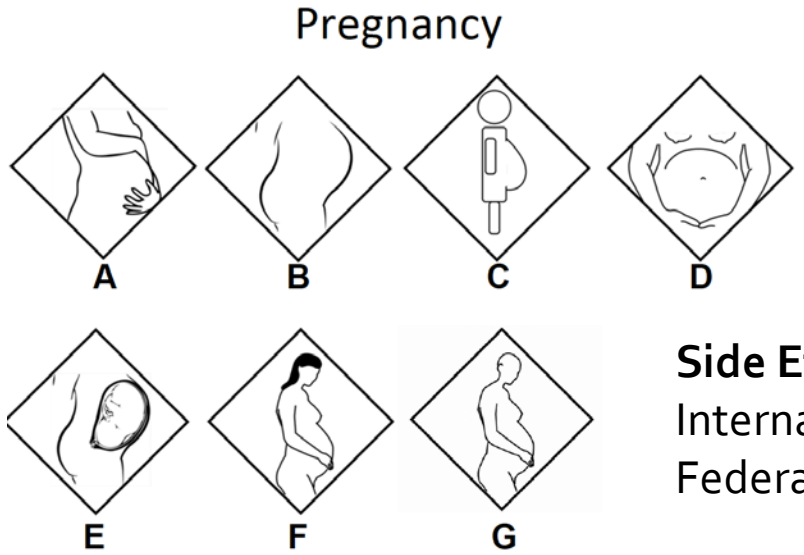
- Dr Renzo Guerrini*, Prof. Child Neurology and Psychiatry, Uni. of Florence
  - *Effects of new anti-epileptic drugs on the developing nervous system: neural excitability, synaptogenesis, dendritic arborisation? May result in lower IQ scores that would take many years to be shown*
  - *When treatment is absolutely necessary during a planned pregnancy: to keep the patient at the lowest possible effective dose whatever drug is used (Valproate: risk reduction of 80% when <700mg compared to >1500 mg)*
- PRAC Assessment Report February 2018
  - *For valproate as well as for other treatments, the lowest effective dose should be established before conception*
- But no recommendation on dose in these documents
  - *PRAC recommends strengthening the restrictions on the use of valproate in women and girls (10/10/2014)*
  - *New measures to avoid valproate exposure in pregnancy endorsed EMA/375438/2018*
- Laura Yates*, Consultant in Clinical Genetics & Head of Teratology (UKTIS)
  - *Foetal risk with use of sustained release preparations or divided dose regimes versus single daily dose?*

* European Conference "Safety of Medication Use in Pregnancy" , 2-4 February 2015, Poznan, Poland **EuroMediCat** http://www.euromedicat.eu/publicationsandpresentations/europeanconference,poznan2015

Recommendations from patients 'organisations, EMA 2004

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/12/WC500018493.pdf

- As part of the general review of the Package Leaflet Guideline, the following points should also be addressed:
  - *The inclusion, in the PL, of clear and unambiguous signs/symbols/pictograms harmonised across the whole EU to aid visual navigation and highlight important sections or statements should be investigated.*



Side Effects Pictogram Survey
International Pharmaceutical Federation

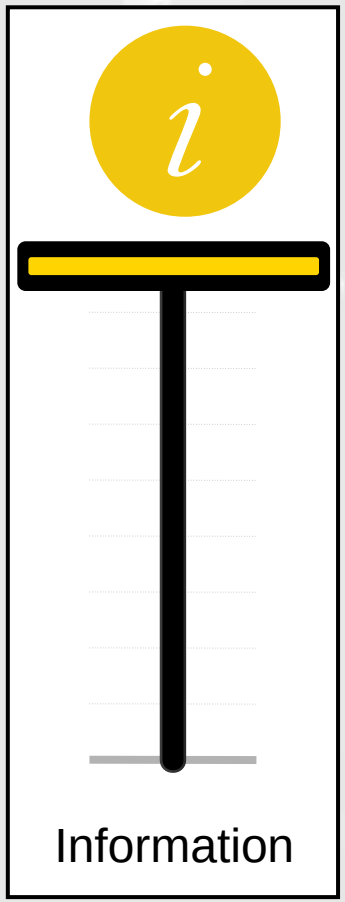
Too many? Good ones? Understandability of pictogram alone: 54% correct answers

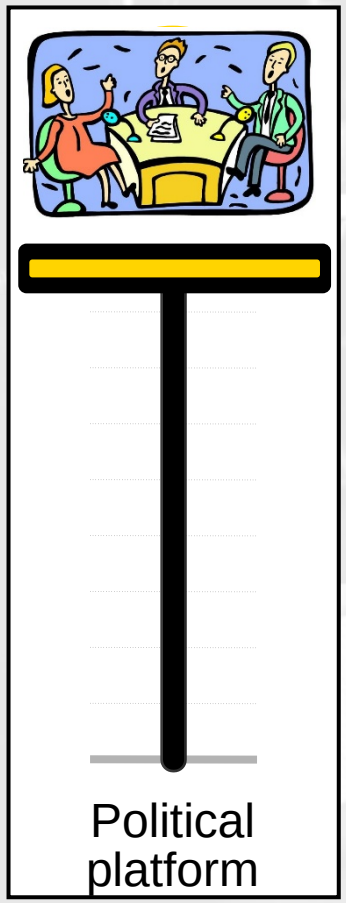
Plus black triangle etc.

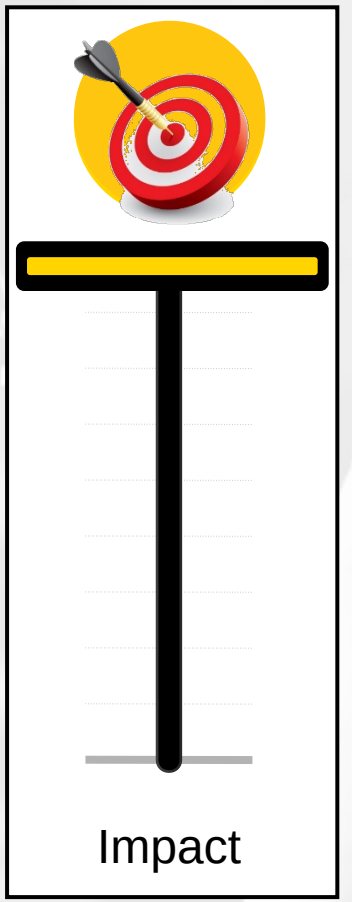
Label	Standard	Simplified Text	+Icon
1	SHAKE WELL BEFORE USING	Shake well before stirring.	
2	FOR EXTERNAL USE ONLY	Use only on your skin.	
3	IT IS VERY IMPORTANT THAT YOU TAKE OR USE THIS EXACTLY AS DIRECTED. DO NOT SKIP DOSES OR DISCONTINUE UNLESS DIRECTED BY YOUR DOCTOR.	Do not stop taking unless directed by your doctor.	
4	TAKE WITH FOOD OR MILK	Take with food or milk.	
5	DO NOT TAKE THIS DRUG IF YOU BECOME PREGNANT	Do not use if you are pregnant, think you are pregnant, or breast feeding.	
6	MAY CAUSE DROWSINESS. ALCOHOL MAY INTENSIFY THIS EFFECT. USE CARE WHEN OPERATING A CAR OR DANGEROUS MACHINERY.	May cause drowsiness. Be careful when driving a car or using machinery.	
7	DO NOT DRINK ALCOHOLIC BEVERAGES WHEN TAKING THIS MEDICATION	Do not drink alcohol.	
8	YOU SHOULD AVOID PROLONGED OR EXCESSIVE EXPOSURE TO DIRECT AND/OR ARTIFICIAL SUNLIGHT WHILE TAKING THIS MEDICATION.	Limit your time in the sun.	
9	OBTAIN MEDICAL ADVICE BEFORE TAKING NONPRESCRIPTION DRUGS. SOME MAY AFFECT THE ACTION OF THIS MEDICATION.	Talk to your doctor before using any over-the-counter drugs.	

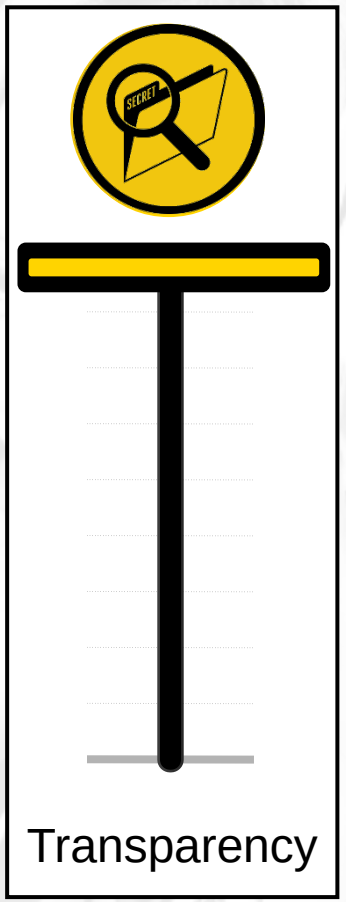
Necessity to focus on pictograms that really make a difference, and forget those that are just nice to have "Imaginary prevention": effect to be measured

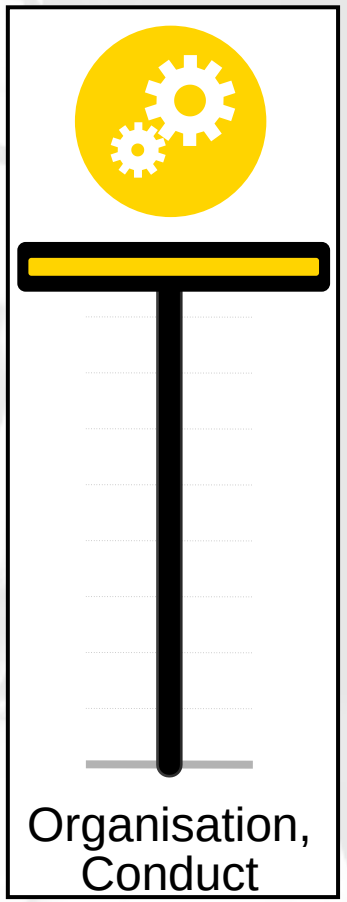
USA
Improving Prescription Drug Warnings to Promote Patient Comprehension
Michael S. Wolf et al
Arch Intern Med. 2010;170(1):50-56.
doi:10.1001/archinternmed.2009.454











overall

Other possible indicators: interaction between participants, added value for PRAC opinions, organisation…

To conclude

A habit cannot be tossed out the window; it must be coaxed down the stairs a step at a time (Mark Twain).

More rapid detection of a problem, action takes time

- National hearings in MS where topic is hot?
- Vigil: To further disseminate the outcomes

This case illustrates the efficacy of Regulation (EU) No 1235/2010: *black triangles, no black holes anymore*

Excellently organised and chaired.

Other committees, public hearings?

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Thank you for your attention.

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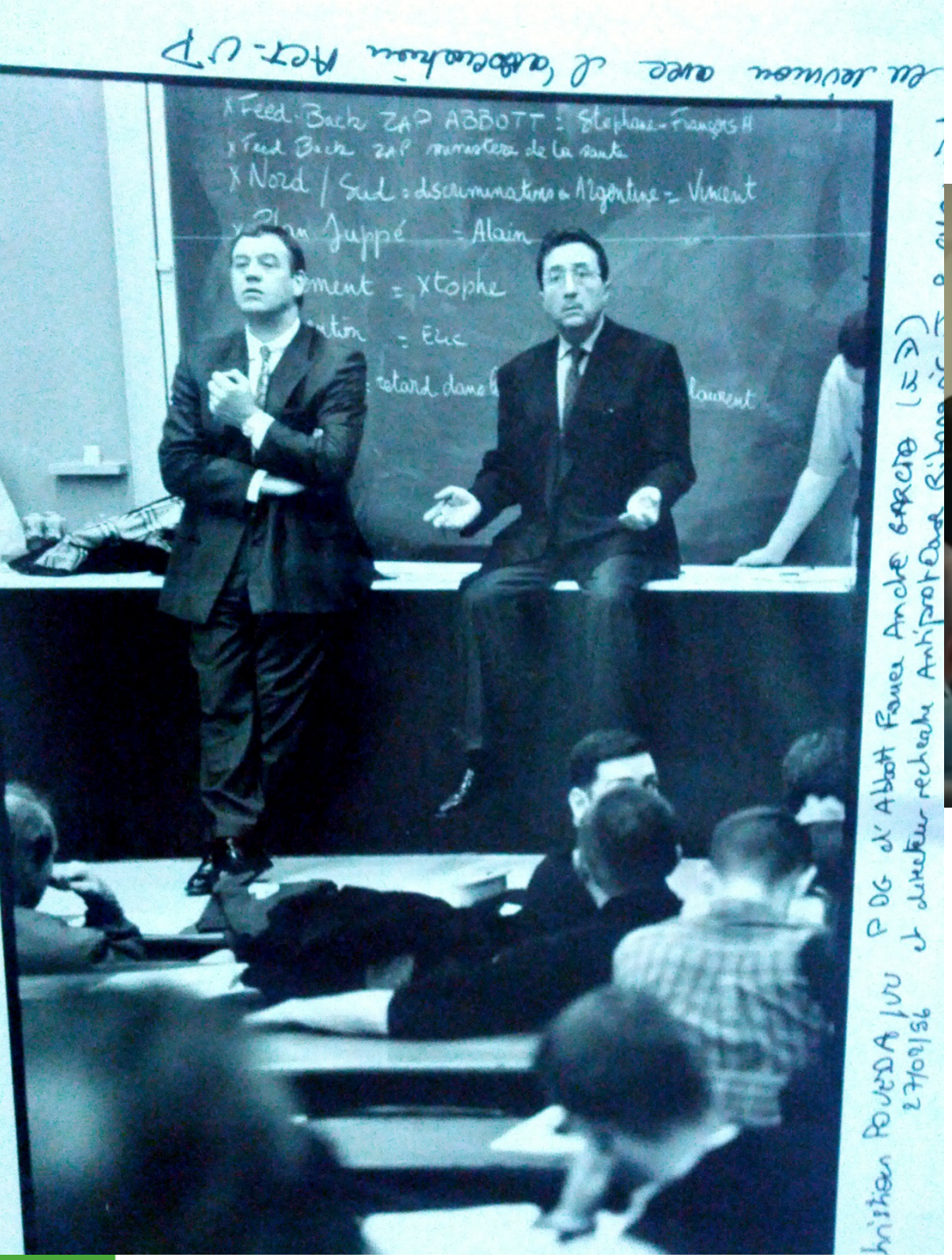

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