Engaging patients: CHMP Benefit Risk Evaluation and HTA Early Dialogues

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EMM 2015, Madrid (30 May, Workshop 2 -11:00-13:00. Room Cibeles)

EURORDIS roles in EMA and in HTA

European Medicines Agency

- Working group with patients and consumers (2002) and Framework of interaction (2005)
- EURORDIS volunteers/staff members of scientific committes (decision making): COMP(2000) /CAT/PDCO
- Agreement between EMA and EURORDIS for the identification of experts (patients/professionals) for OMP procedures
  - Diseases guidelines
  - Orphan drug designation
  - protocol assistance/scientific advice
  - CHMP consultations
  - product information review…

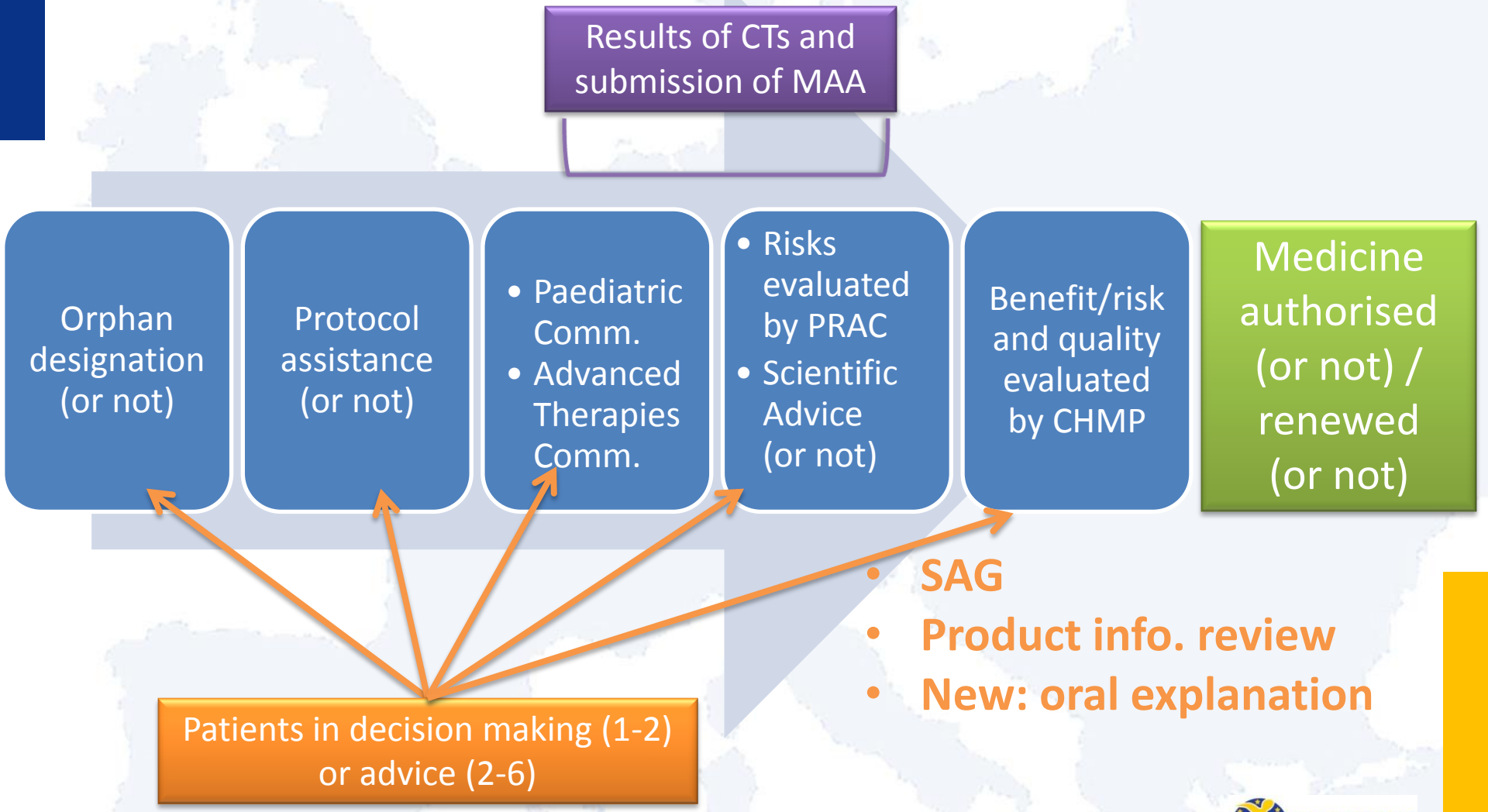
HTA

- Member of EUnetHTA Stakeholders' Forum (since 2010)
- Experts in EUnetHTA Scientific Advisory Groups
- Represent stakeholders at the HTA Network (EC+MS)
- Volunteers and staff at EUnetHTA trainings
- Agreement with SEED consortium and EMA where EURORDIS helps to identify patients for early dialogue meetings
  - Explain the procedure, their role
  - Prepare for the meeting (briefing doc.)

1-CHMP consults patients

At oral explanation with the company

The regulatory process and where we jump in



The CHMP momentum

+/- 2 months to organise it

Day 0
- Submission of marketing authorisation application (MAA)
- 2 rapporteurs appointed

Day 120
- Rapporteurs' report
- Comments from CHMP members
- List of Questions

Day 121
- Submission of responses by applicant

Day 150
- Rapporteurs' report on responses
- Day 180: CHMP outstanding issues

Day 180-210
- Final opinion +/- hearing of the company (oral explanation)

Early detection that the dossier is a difficult one. Scientific Advice can be envisaged

If concerns or doubts within CHMP members: an oral explanation can be proposed
If relevant : to invite 2 patients and a mentor

Do you know where to find information on a MAA for your own disease?

2014: Patients' and Consumers' Working Party and CHMP agreed on participation in oral expl.

- a pilot phase which would explore how this could occur to maximal effect
  - To demonstrate our participation **adds value** to the scientific discussion
- The Rapporteurs and EMA team leaders will decide on a case-by-case basis when this will be needed
  - When the CHMP is likely to recommend the refusal of a MA for a new medicine where there remains an unmet medical need
  - When the PRAC/CHMP are likely to recommend the withdrawal, suspension, revocation or restriction of an indication for a medicine for which a significant impact in patient population is expected

The patients will be accompanied by a ‘mentor’ (likely a PCWP member)

- During pilot phase (1st years)
  - PCWP volunteers
    - François Houÿez (EURORDIS)
    - Hildrun Sundseth (EIWH)
    - Richard West (EURORDIS)
    - Erik Briers (Europa Uomo)
- Their role: more to explain the procedure, to remind them some rules, and to make them comfortable than to intervene in the discussion/content

How should patients join the discussion?

- CHMP can send questions (or not)
- Patients may join the meeting for the briefing by the rapporteurs, followed by the company presentation (20 min) and subsequent Q&A session. They may also remain for the discussion and conclusions
- Patients give their views on these questions and may participate actively in the discussions
- Patients can also ask questions to the company
- Patients do not take part in any decision - making process (no voting rights). Leave before the vote

Concerns

- This is a pilot. Crucial to make it right from the beginning. Can stop at any time
- There are formal rules, need to be fully compliant with them
  - The form is as important as the content
  - As soon as invited by CHMP, and until the EMA announces the opinion on its web site:
    - You can't talk with anyone else except the other invited patient, the EMA staff/rapporteurs and the mentor
    - Refrain from talking with other patients, or clinicians
    - Refrain from talking with the company
- Confidentiality +++, prevention of insider trading +++

Recommendations

- Adapt your practices
  - When meeting with the developer of a medicine, even years before the CHMP momentum, make the agendas of your meetings public
  - Provide EMA with the dates when you met with the company, and the agenda of the meetings
- Sign the “Code of Practices guiding the Relations Between the Healthcare Industry and Patients’ Organisations”
  - And implement it in your organisation
  - Conflicts of interests / revenues from pharma: follow EURORDIS practices

Main drawback

- 1 or 2 patients often (always) feel embarrassed not to reflect the opinion of more patients
- Yet, all discussions are confidential

- How can we capture the views of more than 1 or 2 invited patients?

- Response → next slide

2-Patients' preferences elicitation

What is changing – PROTECT project

Future IMI2 call5

Francesco Pignatti, EMA

EUROPEAN MEDICINES AGENCY

Challenges

A number of methodologies are available, from informal methods (expert opinions) to more formal methods (little experience so far)

- Whose values: Patients? Carers? Both?
- Individual *v.* group?
- How robust?
- How feasible in the context of a MAA?
- How informative for the assessment?

Francesco Pignatti, EMA

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Feasibility study under discussion

- Pilot under discussion (Melanoma Patient Network Europe; Myeloma Patients Europe).
- Online survey, v. decision conferencing.
- Elicit values that can be generalised to different drugs.
- How informative for the benefit-risk assessment?

(Links to Benefit-Risk Methodology project, IMI PROTECT output, Univ. Groningen ADDIS, …)

Consider the following two treatments:

Treatment 1:

Probability of surviving the first 12 months = 40%

Probability of severe side-effects = 10%

Treatment 2:

Probability of surviving the first 12 months = 50%

Probability of severe side-effects = 35%

Which of these treatments would you prefer:

[] Treatment 1

[] Treatment 2

[] Both treatments are equally desirable

Previous Next

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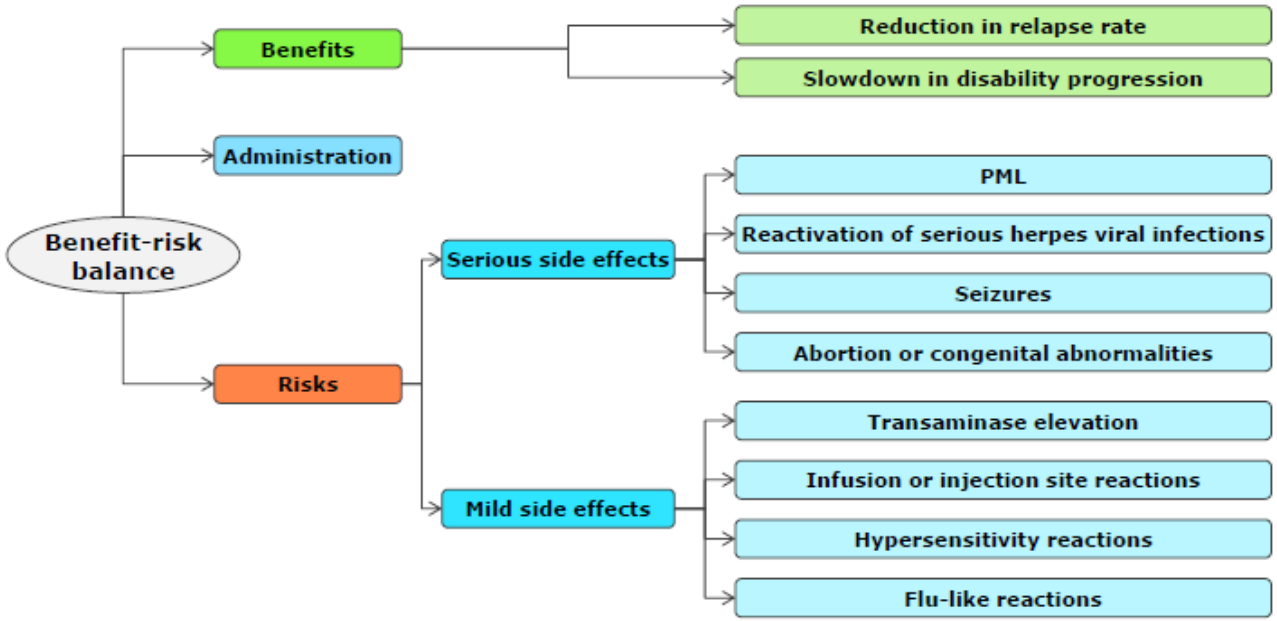
Which favourable and unfavourable effects?

- Which outcome measures to use?



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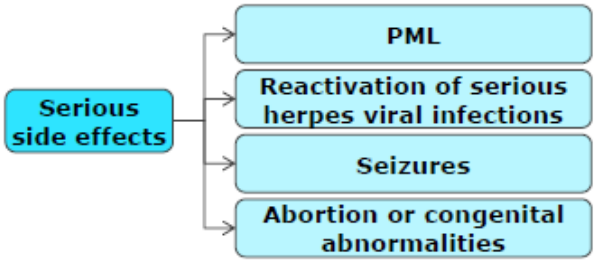
Swing-weighting

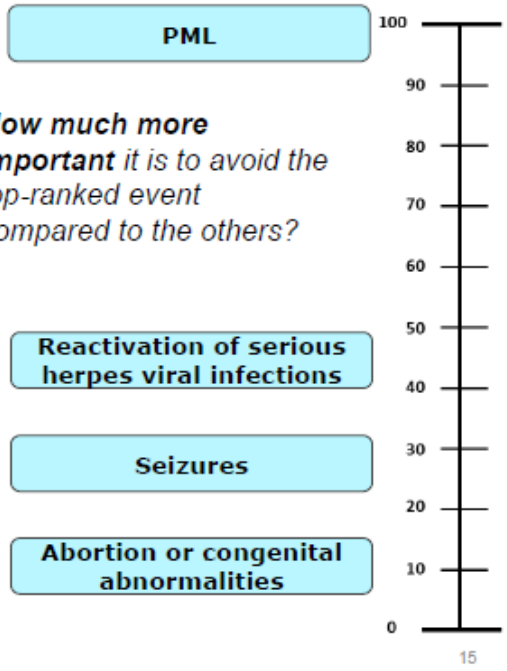
1. For each outcome category



2. Rank outcomes

Outcome	Rank
PML	1
Reactivation of serious herpes viral infections	2
Seizures	3
Abortion or congenital abnormalities	4

3. Relative importance



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Analytic Hierarchy Process

- *Which of the two mild to moderate risks would you prefer to avoid? (Please tick one)*

	Flu-like reactions
	Mild allergic reactions
	They are equally important to avoid

- *If you did not tick "They are equally important to avoid", how much more important is it to avoid the risk you selected compared to the other risk? (Please tick one)*

	Extremely more
	Very strongly more
	Strongly more
	Moderately more

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Discrete choice experiments

Mild allergic reactions	0 patients out of 1000			500 patients out of 1000
Serious allergic reactions	0 patients out of 1000			0 patients out of 1000
Depression	200 patients out of 1000			100 patients out of 1000
Which would you prefer? *(Please tick one)*	☐ **Treatment A**		☐ **Treatment B**	

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3-HTA early dialogues

Started with patients 18 September 2014

HTA early dialogues in one word

- The objective of an early dialogue is to reduce the risk of inadequate data when products are presented for evaluation in aim of reimbursement by national health insurance.

From SEED consortium project description

SEED /EUnetHTA/EMA Early Dialogues with patients

Date	Condition	Type	Technology
16 May 2014	Relapsed/refractory multiple myeloma RD	-	16 May 2014
10 July 2014	Solid tumors	-	10 July 2014
18 Sept. 2014	Advanced Non-small Cell Lung Cancer	SEED	Medicine
8 Oct. 2014	Confidential on company's request RD	EMA-HTA	Medicine
3 Dec. 2014	Myasthenia Gravis RD	EMA-HTA	Medicine
15 Jan. 2015	Management of Heart Failure	SEED	Implantable device
22 Jan. 2015	Confidential on company's request RD	SEED	Medicine
12 Feb. 2015	Asthma	SEED	Medicine
13 Feb. 2015	Thyroid Cancer RD	SEED	Diagnostic test
10 Mar. 2015	Treatment of Discogenic Back Pain	EMA-HTA	Medicine
14 Apr. 2015	Implantable Heart RD	SEED	Implantable device
29 June 2015	Sanfilippo Syndrome RD	EUnetHTA	Medicine
7 July 2015	Haemophilia A RD	EMA-HTA	Medicine
7 September	Insulin dependent diabetes	EUnetHTA	Device

10 patients invited (56% success), 28 contacted, 48 organisations, 126 emails (+ phone)

Date	Condition	Patients	Patients' org
18 Sept. 2014	Non-small C lung cancer	0 / 1	1 (LNCC France)
8 Oct. 2014	confidential	1 / 2	1
3 Dec. 2014	Myasthenia Gravis	0 / 3	2 (MG Romania, MG Germany)
15 Jan. 2015	Heart failure	2 / 2	2 (EU Heart Network, HTAP Fr)
22 Jan. 2015	confidential	2 / 5	5 (EU, Ire, UK, Swe and Summer School Alumni)
12 Feb. 2015	Asthma	1 / 4	11 (EFANET, At, Be, Dk, Fr, Ie, Nl, No, Sw, UK, Orphanet)
13 Feb. 2015	Thyroid cancer	2 / 5	10 (At, Dex2, Frx4, Sp, UKx2)
10 Mar. 2015	Discogenic back pain	1 / 4	14 (EULAR, AFLAR, At, Ch, Cz, Dk, Fi, Hr, Ie, Is, No, Ro, Sw, UK)
14 Apr. 2015	Implantable heart	1 / 2	2 (EU, Fr)
29 June 2015	Sanfilippo syndrome	/ 4	4 (EURORDIS members contacts + RareConnect)
7 July	Haemophilia A	/ 2	2 (EU, Ire)
7 September	Insulin dependent diabetes	/ 1	1 (IDF)

Briefing document: 4 parts

Description of	Clinical development plan	Questions to HTA experts	Responses
• The disease • The technology	• Completed studies • Planned trials (phase III)	• Questions the developer may have to the HTA experts from several countries +/- EU regulators	• As proposed by the developer

Patients comment on PICO

Clinical trial (usually phase III)

- What can you suggest to improve the trial?

Patients' population for the target indication P

- All stages? Advanced stages? If some stages not included, risk of off-label?

Possible impact of the technology in their life (constrains, efficacy… I O

- e.g. implantable devices. Important to select relevant outcome measure

Diversity of healthcare in Europe C

- Usually confirming HTA experts' information. Impact on the comparator choice

Regulatory aspects

- Unavoidable, even if not expected

And much more…

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Issues (1): timing and proceedings

- HTA experts have 90 days to become familiar with the dossier, and are experienced
- Patients, even when trained (EUPATI, EUnetHTA training) have no or little knowledge on HTA
  - Briefing book sent only 7-10 days ahead of the meeting
- One day meeting is just enough to start understanding what it is about and to contribute
- More time would be better
  - Pre-meeting with the developer or one HTA expert
  - Or possibility to send comments, remarks, questions that come to our mind the minute or the day after

Issues (2): training and preparation

- EUPATI and other initiatives to train patients on HTA
  - Hundreds of patients trained already
- Yet, in most cases patients invited to SEED/EMA Early Dialogues will not have been trained
  - Training must be ad hoc, few days before the meeting
  - Need for training materials, e-learning, webinars, videos
- Patients may find it intimidating or difficult to express themselves
  - Meeting very “intense”. “Take the floor as soon as you can”
  - Chair could ask for their input more pro-actively
  - Some express a high degree of frustration
    - “not having the opportunity to express my thoughts”
    - or being told “this is not what we expect from you”

Other Issues

- Exact stage of the disease to be discussed at the meeting not always know when patients are first contacted – varies during the 90 days
  - Difficult to say “sorry but no” to those who said yes already
  - Patients who participate may not be the most appropriate ones
- Travel and accommodation expenses need to be prepaid
  - Can represent a third or a half of a person’s monthly income
  - Else authorise reimbursement to the patient’s organisation
- Patients do not receive written answers or minutes
- A pre-meeting questionnaire on special needs would be useful

Conclusions

- Patients highly appreciate having the possibility to participate.
- "A learning by doing" phase. A great thank you to SEED/EMA ED coordinators
- Difficulties realising the impact of their contribution

IMI PROTECT project (K. Hockey)

Whose Preferences?

Patient and Public:

Clinical trial participants, patients and potential patients, disabled people, parents and guardians, people who use health and/or social care services, carers, members of the public, and the organisations who represent the interests of these consumers.

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