François Houÿez
EURORDIS Summer School 2017, Barcelona

Which benefits for which risks?

A committee conclusion

welcome to the world of collegial thinking

If I could speak for the committee, and please feel free to interrupt if you disagree, although I think there was split opinion, I think the consensus of the committee is that there truly is something here with this drug; that the desire of this committee was to actually believe that there were efficacy data there and to see the data in a fashion that one could feel absolutely comfortable with….

…Some of us tried to see it but it was not fully clear to us.

The CHMP momentum

+/- 2 months to organise it

Day 0
- Submission of marketing authorisation application (MAA)

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

Day 121
- Submission of responses by applicant

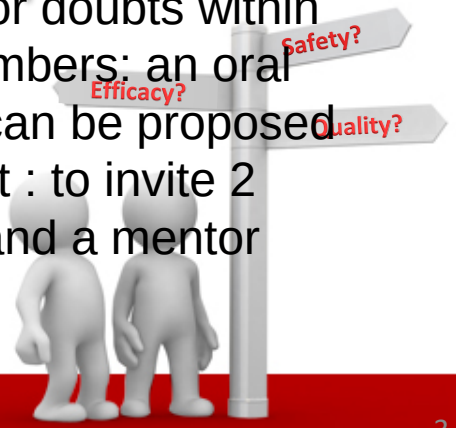
Day 150
- Rapporteurs' report on responses
- Day 180: CHMP outstanding issues

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

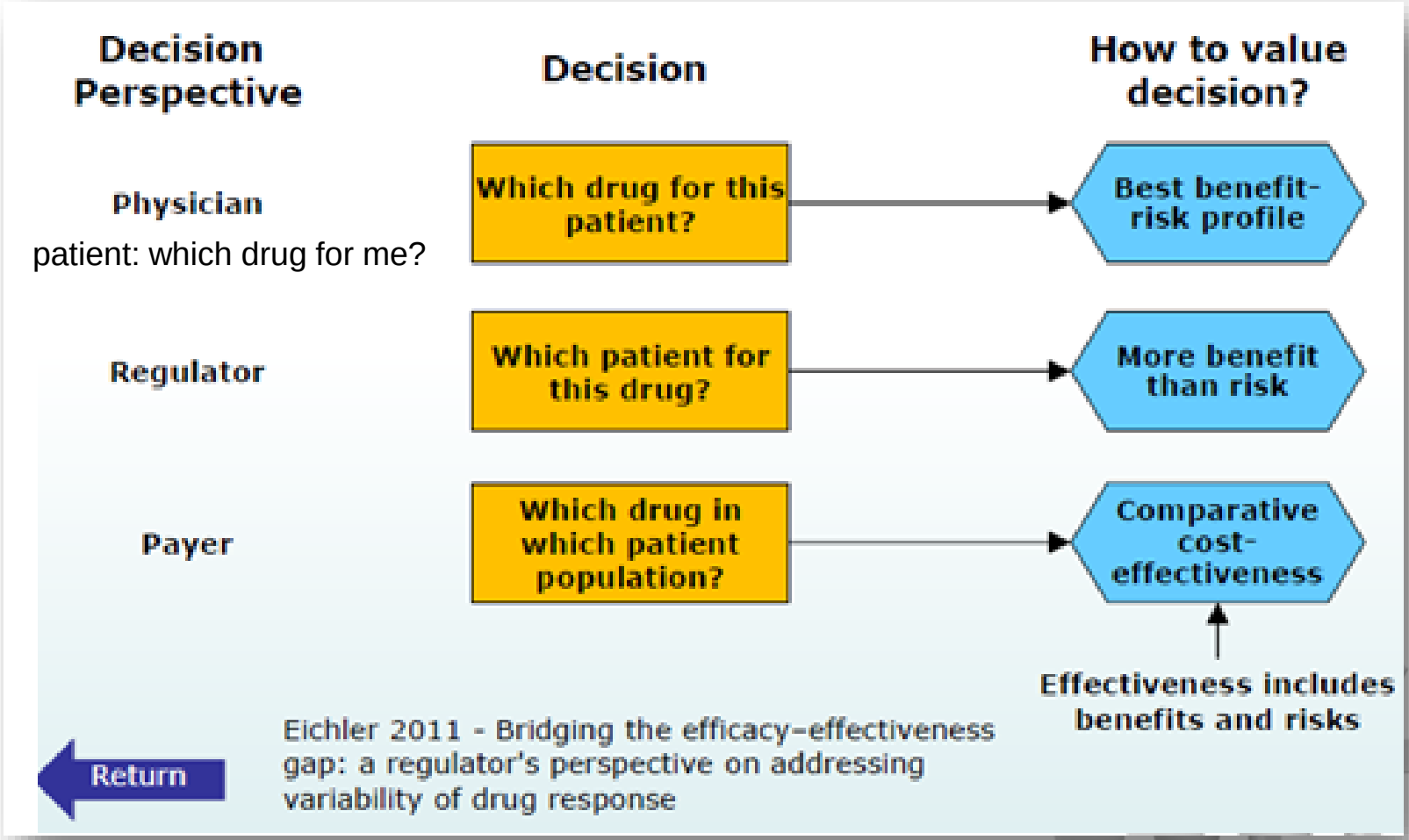
Do you know where to find this info?

Early detection that the dossier is a difficult one. Scientific Advisory Group 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

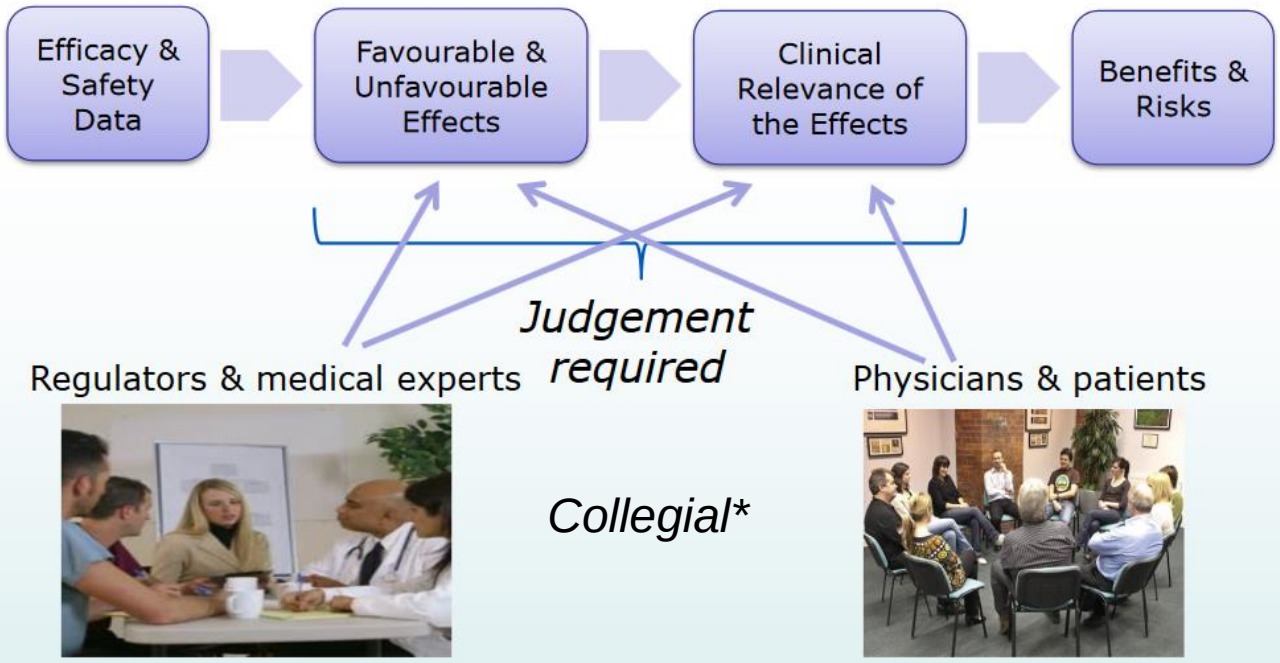


From who's perspective?



IMI PROTECT: Lawrence Phillips

Efficacy & Safety ⇒ Benefits & Risks



* *Relative to a group of persons of equal importance*

EMA announces

Press release

26/09/2014

Patients to discuss benefit-risk evaluation of medicines with the Committee for Medicinal Products for Human Use

EMA launches pilot project to integrate patients' unique and critical views into CHMP discussions

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/09/news_detail_002172.jsp&mid=WC0b01ac058004d5c1

For the moment, patient' input requested in CHMP final discussions if:

- For an initial authorisation application:
  - Decision likely to be negative
  - Impact of the new treatment for the patients is unclear
  - Toxicity/risk profile, and how patients see the risks and weigh the risks/benefits themselves
  - Post authorisation obligations to be discussed: what else could be measured that hasn't been so far?
- For the renewal or a marketing authorisation: conditional approval
  - As the condition been fulfilled? (full authorisation? Renewal of the conditional authorisation? Withdrawal?)
  - Is it likely to be fulfilled in the future? Can the objective be reasonably achieved?

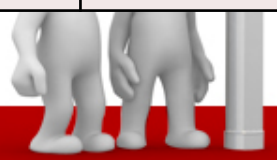
And also (potentially):

- Marketing authorisation suspension/withdrawal
  - Tysabri case study
    - Patients preferences, UK, PL
  - Cf PRAC public hearings (September 2017, Valproate)
- Compassionate use, when CHMP opinion requested
  - Is a compassionate use relevant at this stage (presumed efficacy, early safety)?
  - For which patients?
  - Which data could be collected and how?
- Shortages and their management
  - Which medical criteria to select patients who could continue treatment?

And in general

- To witness the process, to ask questions yourselves, e.g. Ataluren

Timetable	Planned dates	Actual dates
Start of procedure:	29 February 2016	
CHMP and PRAC Rapporteurs Joint Assessment Report	29 March 2016	06 April 2016
CHMP Request for Supplementary Information (RfSI)	28 April 2016	28 April 2016
MAH responses to (RfSI) received on	31 May 2016	31 May 2016
Scientific Advisory Group meeting	16 June 2016	16 June 2016
An Oral explanation took place on	20-23 June 2016	21 June 2016
CHMP Request for Supplementary Information (RfSI)	23June 2016	23June 2016
MAH responses to (RfSI) received on	28 June 2016	28 June 2016
CHMP Request for Supplementary Information (RfSI)	21 July 2016	21 July 2016
MAH responses to (RfSI) received on	20 September 2016	20 September 2016
Scientific Advisory Group meeting	29 September 2016	29 September 2016
An oral explanation took place on	10-13 October 2016	11 October 2016
CHMP Request for Supplementary Information (RfSI)	13 October 2016	13 October 2016
MAH responses to (RfSI) received on	19 October 2016	
Oral explanation	7-10 November 2016	
Final CHMP assessment report adopted on	10 November 2016	



2 risks we're all facing when authorising/rejecting a medicine

To authorise an unsafe or not effective medicine

To reject a yet effective or safe medicine

Tuberculosis treatment: none of them work individually.

- Isoniazid
- Rifampin (Rifadin, Rimactane)
- Ethambutol (Myambutol)
- Pyrazinamide

Uncertainty!

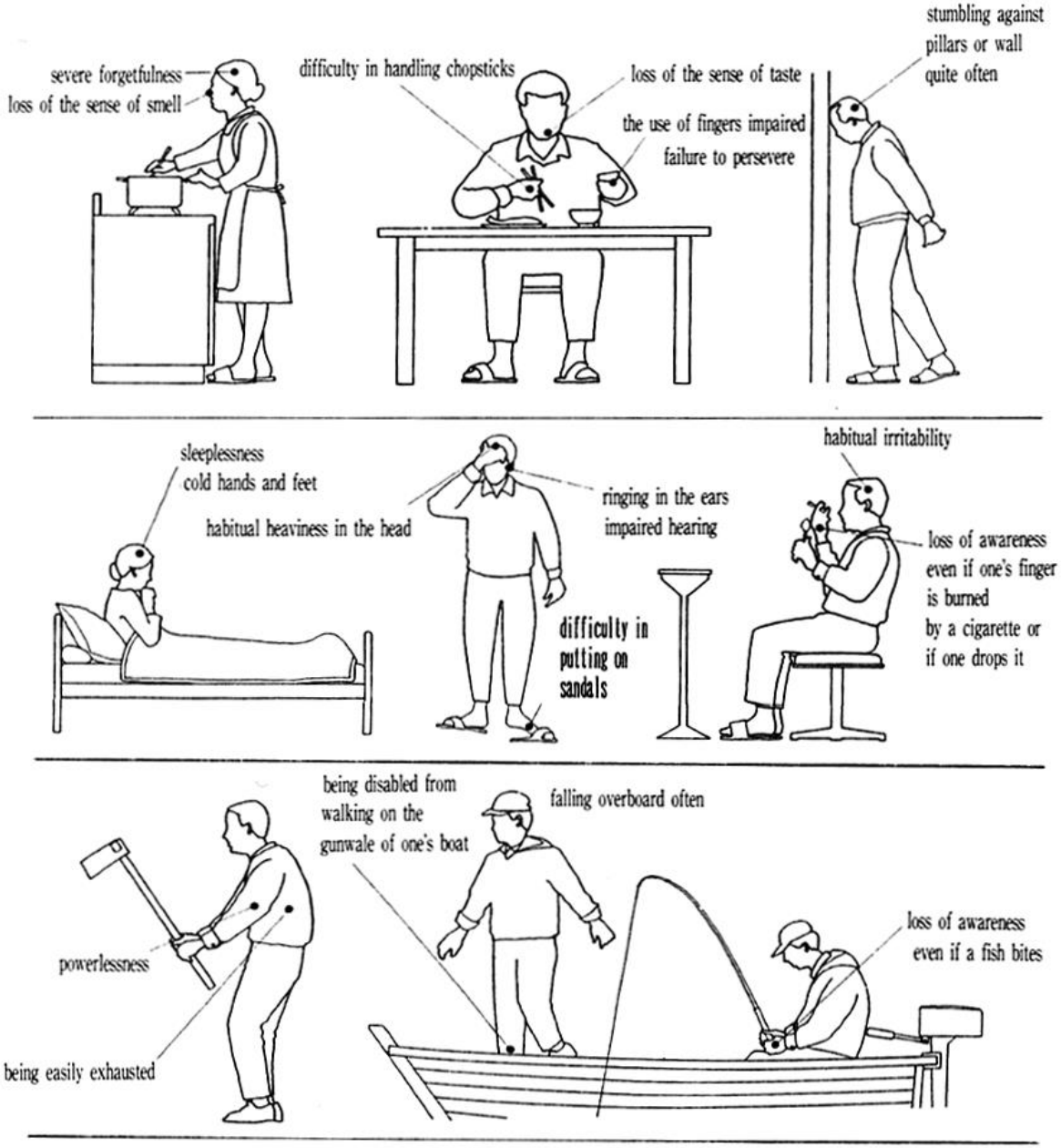
How can you contribute?

- Your own experience, your own opinion on the questions you might receive from the CHMP
- The opinion of a larger group of patients on these questions (even better)
- But you cannot share the confidential information/questions

- So you need to anticipate
- And being member of an organisation

To anticipate? Typical CHMP questions that you can prepare together with others

- What has the medicine changed in the life of patients enrolled in clinical trials?
  - E.g. an enzyme replacement therapy: beyond the normalisation of the enzyme levels in the body, which impact in daily life?
- What else could have been measured in terms of efficacy, and which hasn't?
- Which patients do you think benefit the most?
- How do you see the risks in light of the benefits?


severe forgetfulness
loss of the sense of smell
difficulty in handling chopsticks
loss of the sense of taste
the use of fingers impaired
failure to persevere
stumbling against
pillars or wall
quite often
sleeplessness
cold hands and feet
habitual heaviness in the head
ringing in the ears
impaired hearing
habitual irritability
loss of awareness
even if one's finger
is burned
by a cigarette or
if one drops it
difficulty in
putting on
sandals
being disabled from
walking on the
gunwale of one's boat
falling overboard often
powerlessness
being easily exhausted
loss of awareness
even if a fish bites


Safety?
Quality?

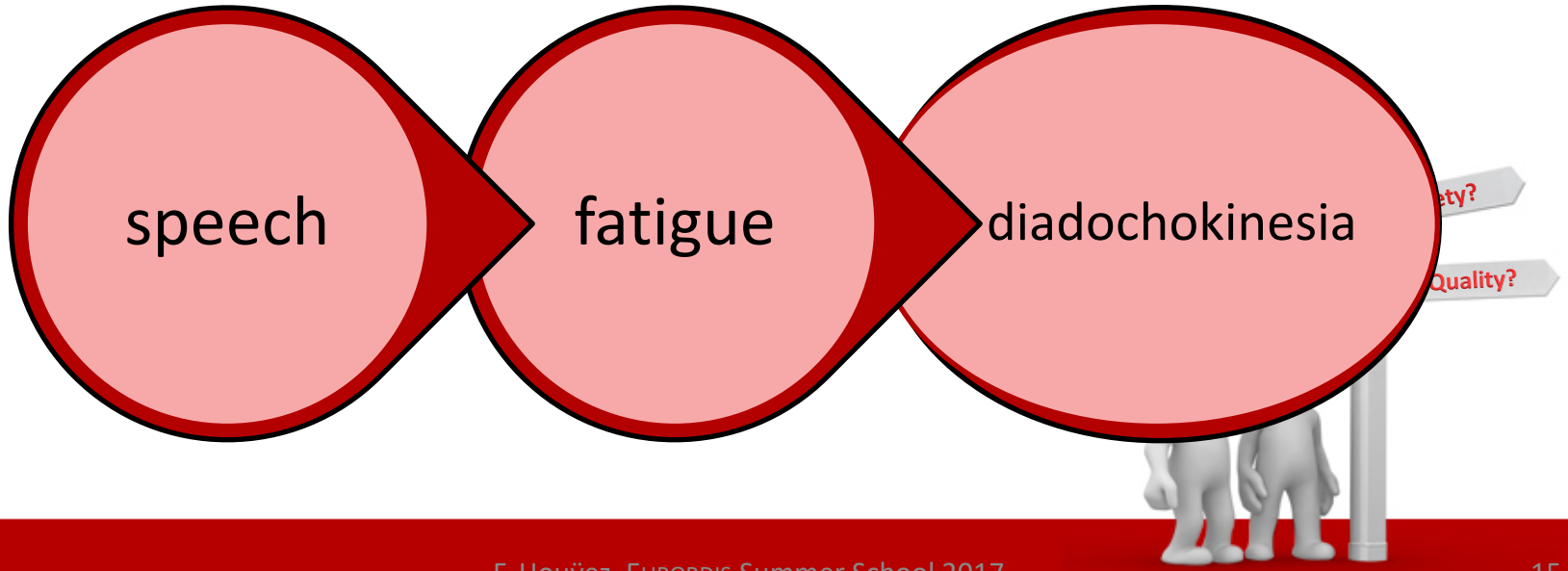
Friedreich Ataxia (degeneration of nerve tissue in the spinal cord, in particular sensory neurons due to reduced expression of the mitochondrial protein frataxin)

A new product was tested:

- Primary Endpoint
  - level of the oxidative stress marker 8 - Hydroxy - 2' deoxyguanosine (a biomarker, not a surrogate though)
- Secondary endpoints:
  - movements control (standard scales for ataxia symptoms), impact on daily activities (using a questionnaire)
  - effect on heart function
- Negative CHMP opinion as no endpoint was conclusive

Yet, patients were reporting improvements

- 40% of patients treated in compassionate use programme decided to continue taking the product after the rejection of the marketing authorisation
- They purchase it off-label, on line, paying out of pocket
- Placebo effect? Or real effect?
- Difficult role of the patient @ CHMP to explain back to all



Friedreich Ataxia: possible outcomes methods
(National Institute of Neurological Disorders and Stroke)

Activities of Daily Living/Performance
Acoustic Analysis of Speech
Activities of Daily Living and Gait
Barthel Index
Functional Independence Measure
Jebsen-Taylor Hand Function Test
PaTaKa Speech Test
Stride Analysis and Gait Variability

Ataxia and Performance Measures
Assessment of Intelligibility of Dysarthic Speech (AIDS)
Bladder Control Scale (BLCS)
Boston Diagnostic Aphasia Exam (BDAE-III)
Bowel Control Scale (BWCS)
Delis Kaplan Executive Function System
Friedreich's Ataxia Impact Scale (FAIS)
Friedreich's Ataxia Rating Scale (FARS)
Impact of Visual Impairment Scale
International Cooperative Rating Scale (ICARS)
Modified Fatigue Impact Scale (MFIS)
MOS Pain Effects Scale (PES)
Nine Hole Peg Test
Phonemic Verbal Fluency (PVF)
Scale for the Assessment and Rating of Ataxia
Sloan Low Contrast Letter Acuity
Tardieu Scale

Quality of Life
Pediatric Quality of Life Inventory (PEDSQL)
Short Form 36-Item Health Survey (SF-36)
Short Form Health Survey 10 for Children (SF-10)

See:
http://www.commondataelements.ninds.nih.gov/FA.aspx#tab=Data_Standards

Ideally

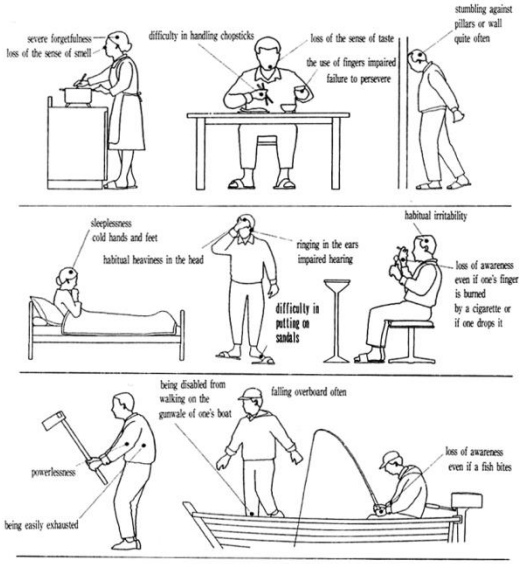
- There is a Community Advisory Board (CAB) for your disease community where you discuss these aspects with all researchers involved, public or private
- You’re able to select Patient Relevant Outcomes

Patient Reported Outcomes: one development PRO-active here

- COPD, IMI project over 5 years
- To develop, validate and approve a new patient reported outcome capturing the experience of Physical Activity (PA) by patients
- Evaluated 104 PA instruments with ≈ 500 publications, 2000 items, 16 qualitative studies, 91 validation studies → draft conceptual model
- Validated the model based on available evidence and 23 one-to-one interviews + 8 focus groups of 55 patients in 4 different countries
- Completed investigation of 6 activity monitors in laboratory, field and usability study– 2 monitors selected
- Completed initial validation of PRO tools - 5 centers, 280 patients

Efficacy: asking patients to feedback on what matters to them? Individualised Efficacy Assessment

- Mixed-methods research can help identifying the most relevant outcomes
- When there are many different outcomes:
  - Ask each patient to select the 3 that matter the most to him/her prior to entering the trial / starting treatment
  - Monitor how these 3 outcomes evolve
  - Analyse how many patients had 3, 2, 1 or 0 outcomes improved on treatment



Try not to make

- A statement on how severe the disease is
  - The CHMP and COMP experts know it
  - To describe your own experience living with the disease doesn't provide much information in the benefit/risks discussion
- A more political statement
  - "This" product is very much needed (if it doesn't really work, is it really?)
  - Versus "a product"
- Comments on the price / reimbursement: not the EMA mandate

IMI PROTECT: visualisation of B/R?

Importance of Patients' Perception for Treatment Decisions

Regulators' view:
An increased cure rate in cancer, a potentially life-saving treatment will always outweigh a grade 1 or 2 AE (e.g. (permanent hair loss) - positive regulatory decision

Some patients' view:
This permanent hair loss is important, severe enough for me to decline the potentially curative and life-saving adjuvant therapy – negative treatment decision

"The mastectomy and loss of breast are NOTHING compared to the loss of my hair."

"Not a day goes by that I don't regret doing the NN (therapy). Oh, if we could only turn back the hands of time!"

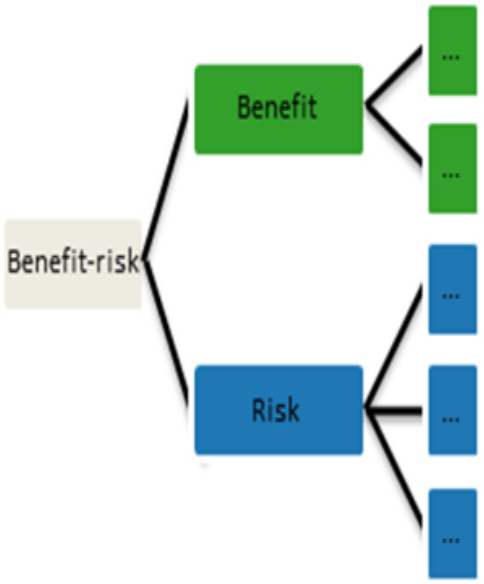
"I* never, never, never *would have agreed to take NN if I was informed of this 6.3% risk; even a 3% risk…or any risk…"

IMI PROTECT: visualisation of B/R? I found the visual easy to read, I found the visual trustworthy, and I found the visual helpful for my decision making

Table shell

	Criteria	Descriptio
Benefit	Weight loss	Number ...
	Improved cholesterol	Number ...
Risk	Stroke and Heart attack	Number ...
	Depression	Number ...
	Constipation or diarrhoea	Number ...

Value tree diagram



List

Benefit criteria:
- Number of people with min. 10% weight loss in one year
- Number of people with significant improvement in cholesterol in one year

Risk criteria:
- Number of people experiencing stroke or heart attack in one year
- Number of people experiencing stroke or heart attack in one year
- Number of people experiencing nausea or diarrhoea in one year

Preferred by 54% **by 21%** **by 25%**

See http://www.protectbenefitrisk.eu/PPI6.html

Thank you!

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1 November 1999 adefovir for HIV infection

FDA CENTER FOR DRUG EVALUATION AND RESEARCH, ANTIVIRAL DRUGS ADVISORY COMMITTEE MEETING

PARTICIPANTS

- Scott M. Hammer, M.D., Acting Chairman, Rhonda W. Stover, R.Ph., Executive Secretary

Committee Members:

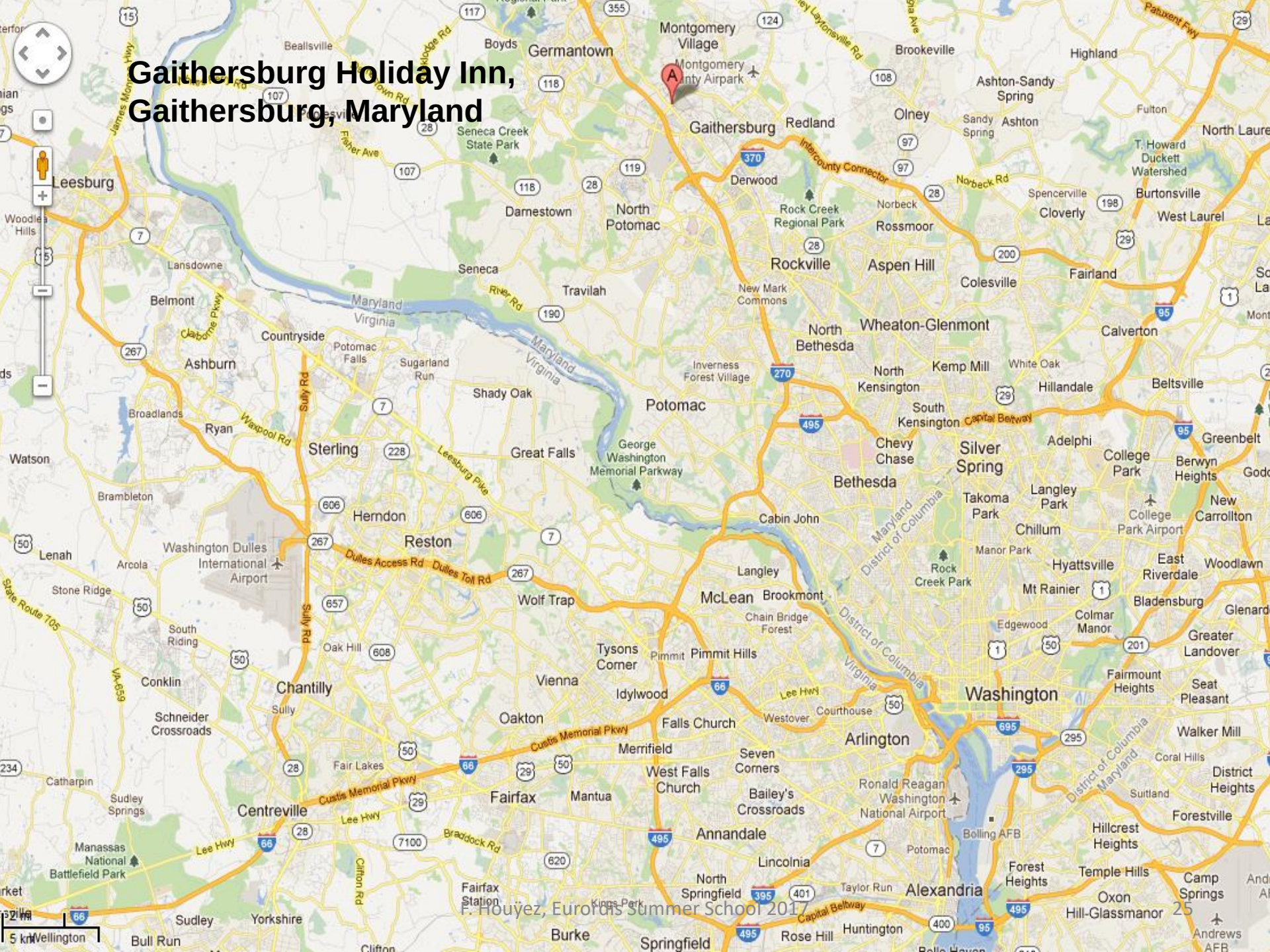
- Henry Masur, M.D., James J. Lipsky, M.D., Roger J. Pomerantz, M.D., John D. Hamilton, M.D., Brian Wong, M.D.

Consultants:

- Joseph S. Bertino, Jr., Pharm. D., Consumer Representative, Wafaa El-Sadr, M.D., M.P.H., Judith Feinberg, M.D., Jeffrey B. Kopp, M.D., Christopher Mathews, M.D., M.S.P.H., Sharilyn K. Stanely, M.D., Joel I. Verter, Ph.D., Ram Yogev, M.D.

Guests: Paul Kimmel, M.D., Jeffrey Schouten

FDA: Douglas Throckmorton, M.D., K. Struble, Pharm. D., Jeff Murray, M.D., Heidi Jolson, M.D., M.P.H., Sandra Kweder, M.D., Greg Soon, Ph.D.


Gaithersburg Holiday Inn,
Gaithersburg, Maryland
Montgomery Village
Germantown
Boyds
Beallsville
Gaithersburg
Redland
Olney
Brookeville
Highland
Ashton-Sandy Spring
Leesburg
Seneca Creek State Park
Derwood
Intercounty Connector
Rock Creek Regional Park
Norbeck
Rossmoor
Spencerville
Cloverly
Burtonsville
West Laurel
Damestown
North Potomac
Rockville
Aspen Hill
Colesville
Fairland
Lansdowne
Belmont
Seneca
Travilah
River Rd
Maryland
Virginia
New Mark Commons
Wheaton-Glenmont
North Bethesda
Calverton
Countryside
Potomac Falls
Sugarland Run
Ashburn
Inverness Forest Village
North Kensington
Kemp Mill
White Oak
Hillandale
Beltsville
Shady Oak
Potomac
South Kensington
Capital Beltway
Broadlands
Ryan
Waxpool Rd
Sterling
Great Falls
George Washington Memorial Parkway
Chevy Chase
Silver Spring
Adelphi
College Park
Berwyn Heights
Greenbelt
Watson
Leesburg Pike
Bethesda
Takoma Park
Langley Park
New Carrollton
Brambleton
Herndon
Cabin John
Chillum
College Park Airport
Lenah
Arcola
Washington Dulles International Airport
Reston
Dulles Access Rd
Dulles Toll Rd
Manor Park
Rock Creek Park
Hyattsville
East Riverdale
Woodlawn
Stone Ridge
Langley
McLean
Brookmont
Wolf Trap
Chain Bridge Forest
Mt Rainier
Bladensburg
Glenarden
South Riding
Oak Hill
Tysons Corner
Pimmit
Pimmit Hills
Edgewood
Colmar Manor
Greater Landover
Conklin
Chantilly
Vienna
Idylwood
Lee Hwy
Washington
Fairmount Heights
Seat Pleasant
Schneider Crossroads
Sully
Oakton
Falls Church
Westover
Courthouse
Arlington
Walker Mill
Custis Memorial Pkwy
Merrifield
Seven Corners
Coral Hills
Fair Lakes
West Falls Church
Ronald Reagan Washington National Airport
District Heights
Catharpin
Sudley Springs
Centreville
Fairfax
Mantua
Bailey's Crossroads
Suitland
Forestville
Lee Hwy
Annandale
Bolling AFB
Hillcrest Heights
Manassas National Battlefield Park
Braddock Rd
Potomac
Lincolnia
Forest Heights
Temple Hills
Camp Springs
Fairfax Station
North Springfield
Taylor Run
Alexandria
Oxon Hill-Glassmanor
Sudley
Yorkshire
Kings Park
Capital Beltway
Huntington
Andrews AFB
Wellington
Bull Run
Burke
Springfield
Rose Hill
5 km

Participants

Function	#
Committee members & guests	17
FDA staff	6
Applicant	4+10
Speakers at public hearing	17
Stock analysts	20-25
Public, other	5
Total	80-85

Public hearing introduction

Chair:

- Each person: three minutes
- “Please also disclose any financial interest in the product at hand today, and also any travel support to this meeting”.
- “If you have specifically no financial interest to report, please so state for the record”.

- Unlike other public hearings, this one was not video-recorded / live streaming

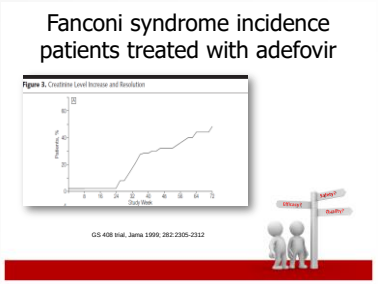
Public contributions

Individual	Opinion	Interest disclosure	As	Contribution
Dr Burchett	In favour	Support for travel	Treating physician	10 children in EAP, 1 Fanconi syndrome
Dr Jones	In favour	Support for travel	Treating physician	24 adults in EAP, 4 stopped for nephrotoxicity
Dr Cimoch	In favour	Support for travel	Treating physician, researcher	55 adults in EAP, 2 stopped for severe nephrotoxicity
Dr Farthing	In favour	Support for travel, investigator and advisory board	Treating physician	130 adults in EAP, nephrotoxicity manageable
Dr Grossman	In favour	Support for travel, investigator	Treating physician	56 adults in EAP, nephrotoxicity = main reason to stop
Dr Hardy	In favour	Investigator	Treating physician, researcher	85 adults in EAP, 52 in CT. 1 Fanconi syndrome
Dr Margolis	In favour	Support for travel	Treating physician	82 adults in EAP, 5 with moderate renal toxicity
Dr McGowan	In favour	Support for travel	Treating physician	68 adults in EAP
Peter Hale	In favour	Undisclosed	Patient	Own experience with drug
William Bahlmann	In favour	Support for travel	Patient group	Let people have the choice
Max Delgato	In favour	Support for travel	Patient	Own experience
Timothy Christy	In favour	Support for travel	Patient	Own experience
Hosam Chreim	In favour	Support for travel	Patient	Own experience
Amy Sullivan	In favour	Support for travel	Investigator	27 in EAP
François Houÿez	against	Support for travel	Patient group	Unanimous vote in EATG membership
Michael Marco	against	none	Patient group	Statement explaining why
Jules Levin	Decided not to talk			

During the day

- Before 8.30 am
  - According to stock analyst: 50/50
- After Applicant presentation
  - 66% in favour / 33 % against
- After FDA analysis
  - 33% in favour / 66% against
- After Committee Discussion
  - 50/50
- After public hearing
  - Half of the public left the room to make phone calls: “sell”
- Questions and vote
  - 1 yes
  - 13 no

My points



- Weak antiviral activity
  - -0,3 log RNA reduction, just in the limit of assay detection
  - Very limited immune restoration (+20 CD4+ cell/mm3)
- Failure to show any clinical benefit
  - Putative niche where adefovir could be interesting
  - But only evaluated in an post hoc analysis
- Up to 60% lab abnormalities (related to proximal renal tubular dysfunction)
- In one of the trials: discontinuation rate, 40-50 % at week 48.
- Next HIV products to come
  - Look much more promising in terms of efficacy and risks
  - Are metabolised by kidney
  - Need fully functioning renal function

Public hearings: how?

The « inquirers »	The « judges »	The « witnesses »	The « defendant »
Rapporteur and co-rapporteur Explain the issue Counter-analysis	10-15 experts e.g. from SAG All express their opinion	The public Patients Consumers Media Healthcare professionals	e.g. pharma. company, research institution, medical journal…