HOW HAS THE ROLE OF PATIENTS GOT STRONGER AND WHAT THEY – AND REGULATORS HAVE LEARNT SO FAR

Changes in Regulatory Sciences in the EU

XI Foresight Training Course – Gianni Benzi Foundation

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EURORDIS.ORG

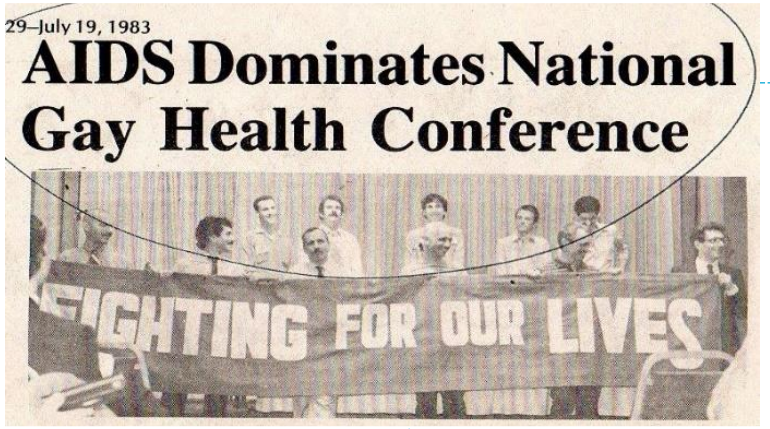
In this presentation

Patients working with regulators

Disclaimer

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

Modern Treatment Activism/Advocacy



LGBT Convention in Denver 9-12 June 1983: dozen met at the National Lesbian and Gay Health Conference in Denver

They enacted the principles of patient advocacy. In particular:

- Form caucuses to choose your own representatives, to deal with the media, to choose your own agenda and to plan your own strategies
- Be involved at every level of decision-making
- Be included in all forums with equal credibility as other participants, to share their own experiences and knowledge

- **Upstream of regulatory momentum**

- Designed the pivotal trial M94-247 that made a sea-change in the AIDS epidemic (Norvir®)

#buildingexpertise

Spencer Cox

- Theater player, AIDS advocate NYC
- The New York Times, 21/12/2012. See documentary *How to Survive a Plague*

Treatment activism

- Participate in the decision-making for all decisions that affect our lives – Denver Principles of Patient Advocacy 1983

• Before M94-247 trial

Trials typically conducted among recently infected individuals

Low risk of AIDS onset or death (3% / year)

Long duration to measure events: "counting dead bodies"

Or complex designs (arm switching, dose changing)

Never clear what the new product would offer

• Spencer proposed

To recruit very advanced patients

With high risk of death (25% / year)

Randomisation ritonavir or placebo

For a short duration (6 months)

• Abbott agreed

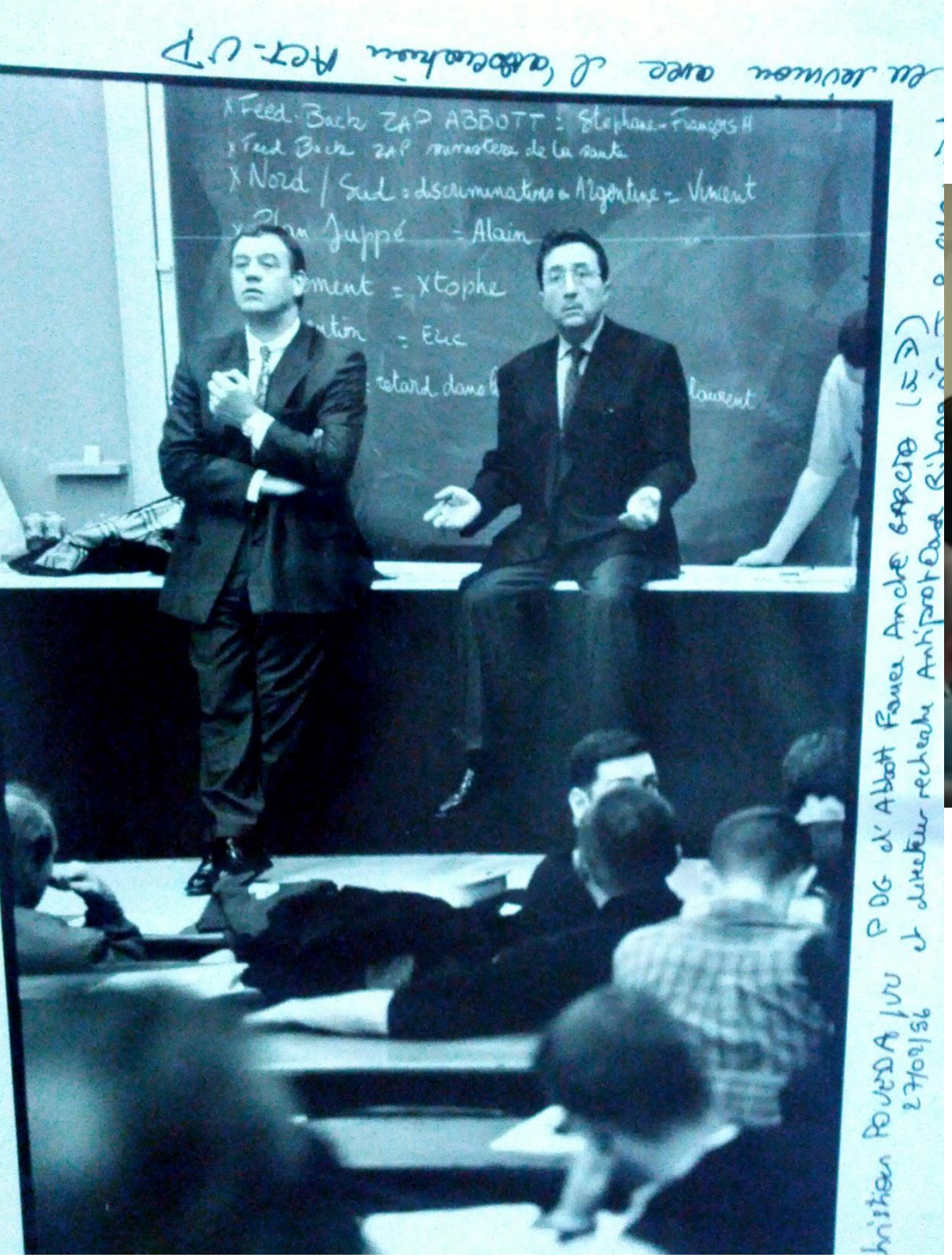
Mortality placebo: 10.1%

Mortality treatment arm: 5.8%

= a 58% reduction

- 28 January 1996 CROI
- 29 February 1996 FDA
- 1 March 1996 ATU
- 23 May CPMP opinion (59 days)
- 26 August 1996 EC authorised

Regulators not aware that trial had been designed by advocates


Feed-Back ZAP ABBOTT : Stéphane-François H
Feed Back ZAP ministère de la santé
Nord / Sud : discriminations - Migration - Vincent
Alain Juppé : Alain
: Xtophe
: Eric
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Laurent

•A.T.U.

- SAINT REMY SUR AVRE (Normandy), **29 February 1996**
- AIDS : ACT UP Paris Commando Action at an Abbott factory
- 60 activists trained by retired soldiers closed the factory (2 km of barbed wire, accessed the manufacturing chain, took control of the fax machines)

29 February 1996, Antiviral Drug Advisory Committee public hearing for Norvir®

- French advocate asked the committee to restrict the indication to the most advanced patients only, to secure enough supply for Europe
- Temporarily restricting the target population rather than granting an indication for all would free enough supply to solve the issue in Europe

•At the FDA hearing

Andre Pernet, vice pdt of pharmaceutical products R&D at Abbott
Paul Clark, senior vice pdt, pharmaceutical operations

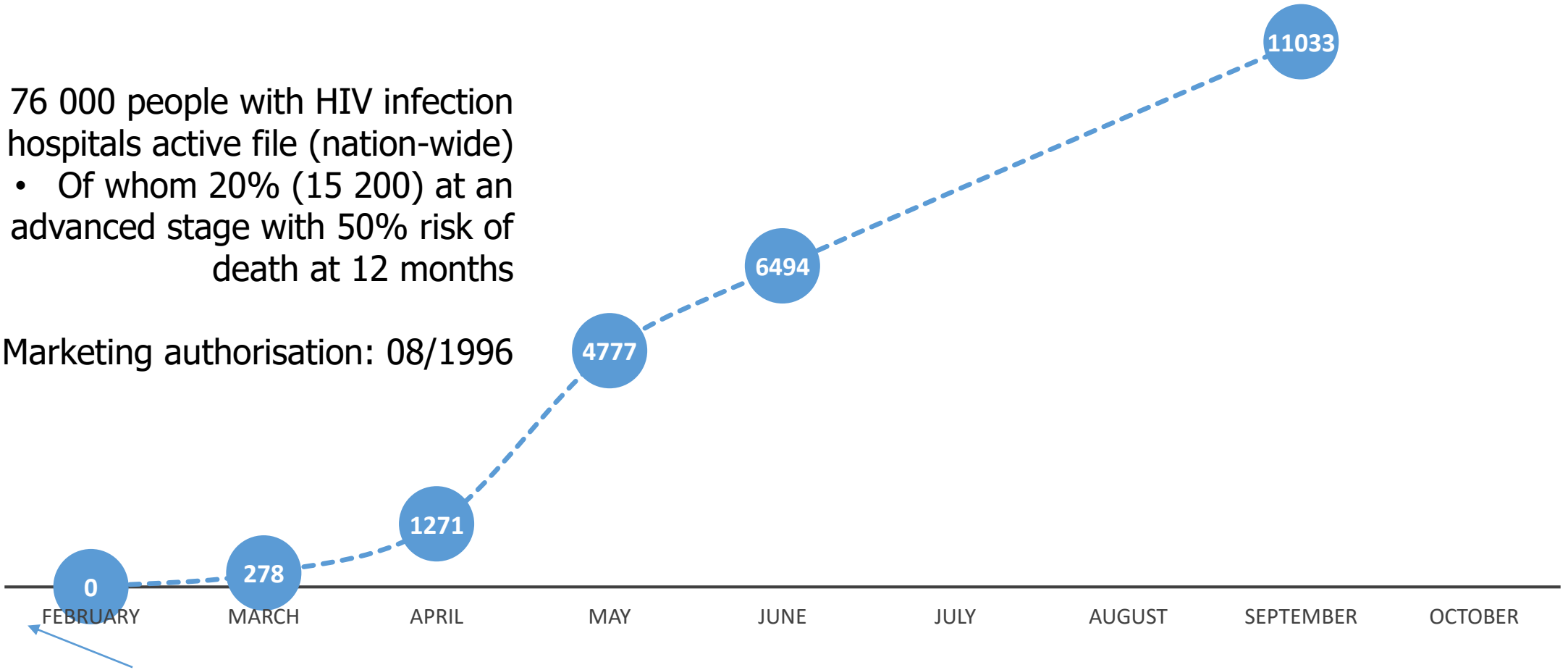
Agreed to sign a letter and to ship 3,000 treatments to France immediately | SOLVED

Unblocked the situation: first patients treated in March 1996, no lottery

(MSD followed a few days later with another 3,000 treatments Crixivan®)

Rapid uptake in France

- > 76 000 people with HIV infection in hospitals active file (nation-wide)
  - Of whom 20% (15 200) at an advanced stage with 50% risk of death at 12 months
- Marketing authorisation: 08/1996



January: results at AIDS conference Washington DC

Dr Marie-Christine Gervais, Merck SD France and
Dr. Jean-Pierre Chauvin, Abbott France

FDA Releases AIDS Drug on Parallel Track

Move Follows Intensive Pressure from Activists

by Cliff O'Neill

WASHINGTON—DDI, an experimental anti-HIV drug, was released into a broad distribution program called a "parallel track," by the U.S. Public Health Service on Sept. 28, after months of intense pressure from AIDS activists.

The drug, a less toxic relative of AZT, which is the only federally approved anti-HIV drug, will now enter broad Phase II clinical trials in which its effectiveness will be tested. In an unprecedented move, the Food and Drug Administration will also allow the drug's manufacturer to distribute the drug to a wide array of people with AIDS and advanced ARC who cannot tolerate AZT or do not qualify for the ddI clinical trials for a variety of other reasons.

DDI has raised hope of AIDS researchers after initial Phase I toxicity trials on 200 people showed that it appeared to be as effective, and less toxic than, AZT. However, clinicians have found that several patients taking high doses of ddI reported bouts of pain

commissioner Frank Young on ddI's release. "Since ddI is still an experimental drug, it must be tested carefully and must demonstrate safety and efficacy before it can be approved. We believe, however, that it is important to offer the drug to people with AIDS for whom the standard treat-

ddI if they don't have to.

"I believe people who are stable on AZT right now would be wisest staying on AZT, unless they've been on it so very long that they and their physicians are virtually certain it's not helping," stated Jim Eigo of ACT UP.

The Public Health Service's announcement comes after months of intense pressure from AIDS activists, which initially came up with the concept of making experimental drugs available to AIDS patients on a parallel track after toxicity levels are established but before its effectiveness is proven.

To implement the new distribution system, the FDA, working with AIDS activists, has broadened its definitions of two existing programs, called "Treatment IND [Investigational New Drug]" and "compassionate use" protocols, to allow for the drug's release as soon as it enters Phase II effectiveness studies.

"This plan offers some additional options for people with AIDS and particularly for the thousands of AIDS patients who cannot tolerate AZT," stated Secretary of Health and Human Services Dr. Louis Sullivan, announcing

AZT OK, TOO
Jim Eigo

Photo: T.L. Litt

- **Tribute**

- To all who negotiated compassionate use schemes with health authorities

High quality dialogue

- Who | What | Where | When | Why can regulators act to help patients

17-May-96 15:43 ⁽0171-627 3101 NAM Publications Keith Alcorn→Rodya Troyke

EMA organised a scientific workshop in September 1996 and changed the evaluation guidelines: HIV RNA as a surrogate marker – no mortality / clinical endpoints anymore. Duration of clinical trials for HIV dropped from **156 weeks (3 years) to 24 weeks (6 months)**

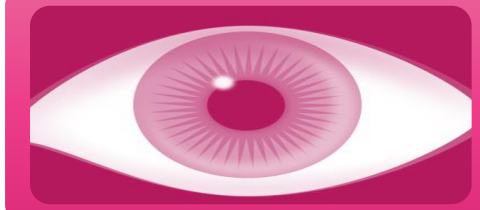
This is an extremely patient relevant outcome (PRO): timeliness

NOTES FROM A MEETING BETWEEN THE CPMP OF THE EMEA AND REPRESENTATIVES OF THE EATG.

London - April 16, 1996

Present for the EATG : Keith Alcorn (National AIDS Manual, London), Raffi Babakhanian (Treatment Action Taskforce, London), Arnulfo Gonsalez (director, EATG, Spain), François Houyez (Treatment Committee, ACTUP Paris), Stéphane Korsia (director, EATG; AIDES, Paris), Hans-Josef Linkens (Executive Director, EATG; Deutsche AIDS Hilfe, Berlin).

Triple objective of patient engagement in regulatory affairs



Eyewitness of the regulatory process

- See regulators at work – guided by science, evidence based
- Report back to the patient community

Contribute to the scientific discussion

- Bring your own perspective as a patient
- No room for political stands, lobbying, confrontation

Propose other approaches to involve patients

- Evaluation: how to best organise the consultation?
- Debrief, and reflection on future consultations

Understanding each other

Often regulators trigger the process

- Patients have their own concerns: how to bring patients' issues in the regulatory process?
  - E.g. When patients think the experimental dose is not the right one?

How to organise patient engagement? Isolated patients, or members of organisations?

- Training programmes – EURORDIS Summer School
- Mentoring: identifying the right patient, explaining the procedure, help in filling-in DoI, confidentiality undertaking, preparing comments/reading documents, accompanying, debriefing…
- Policies to minimise influence by third parties (key opinion leaders, industry, intellectual CoI…)

Impact - outcomes

• Own opinion

- CHMP commented: patients not systematically in favour of authorising the product
- Sometimes even tougher than regulators

• Numbers 2017

- 131 in scientific advice / protocol assistance / HTA
- 46 in scientific advisory groups
- 104 committee consultations

• Methods

- 1 or 2 patients invited among other experts
- Including CHMP oral explanation with applicant
- Public hearings

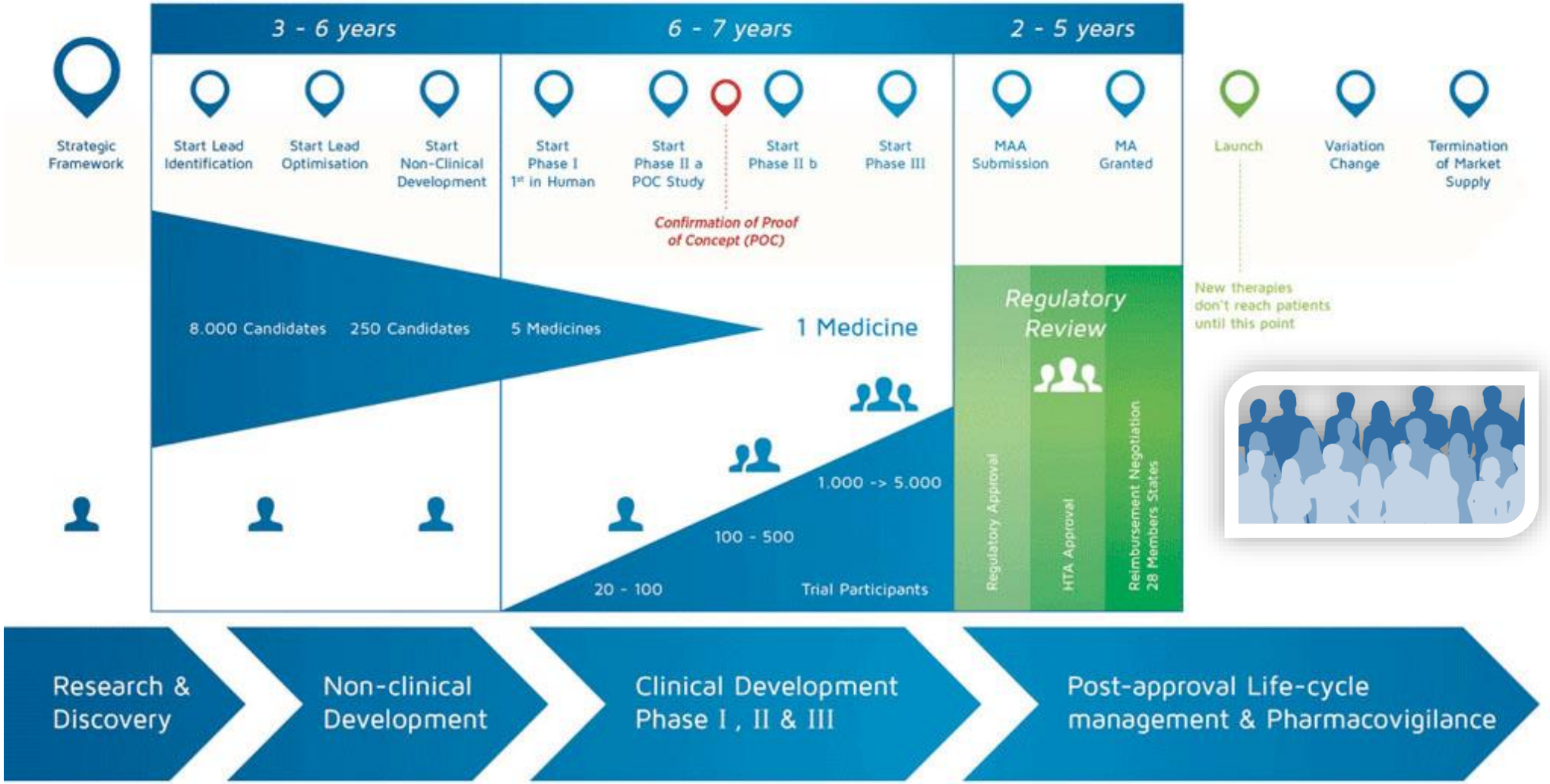
• Evaluation

- Collegial thinking – difficult to highlight the contribution of individual experts
- Confidentiality

• More work needed

- Patient preferences elicitation
- Evaluation guidelines
- Visibility of patient involvement? A condition for trust

Overview of Decision Points and Development Steps in Medicines R&D



Deciding the dose

- CAB meeting with Agouron, 1996 | Nelfinavir, new HIV protease inhibitor | CAB cost: $50,000 | RoI: >10,000 x

• Phase II results, study 510

1.5 g/day: effective
10% loose stools (grade 2)

2.25 g: more effective

3.00 g: even more effective
30% loose stools

• Agouron and clinicians chose 2.25 and 3.00 g or more for phase III

CAB disagreed

1.5 and 2.25 preferred

Finally 2.25 and 2.5 in phase III

#unique_patient_perspective

• Authorised in 1998 at 2.25 or 2.5/day

Children could be treated for 1st time (tolerance). Demand > offer

Patients were staying longer on treatment. Dose adjustment ++

Surplus of 500 Mio$ sales 1st year compared to Agouron's best estimates

Deciding the endpoint

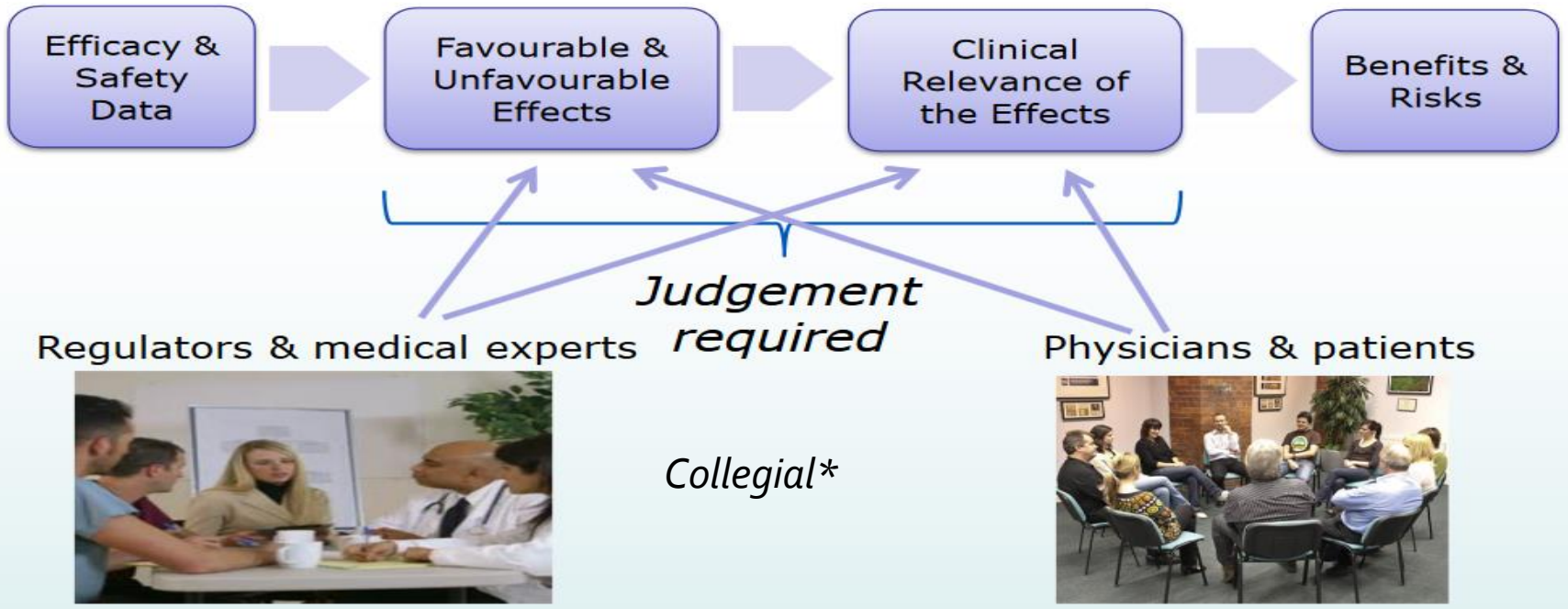
Performance of Upper Limb

Development of the Performance of the Upper Limb module for **Duchenne** muscular dystrophy.
Dev Med Child Neurol. 2013 Nov

*Mayhew A, Mazzone ES, Eagle M, Duong T, Ash M, Decostre V, Vandenhauwe M, Klingels K, Florence J, Main M, Bianco F, Henrikson E, Servais L, Campion G, **Vroom** E, Ricotti V, Goemans N, McDonald C, Mercuri E; Performance of the Upper Limb Working Group*

IMI PROTECT: Lawrence Phillips

Efficacy & Safety ⇒ Benefits & Risks



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

Drug to reduce weight. Which one would you prefer?

Run the test among 30 or 300 patients depending on technics (among many other possible technics. Which one to use?)

EUROCAB in practice: the "patient investigator"

- Group of 10 - 20 trained patients (same disease or similar) committed to follow up the research over time
  - Equivalent of clinical investigators meetings
- Agenda and meetings driven by the patients
  - They advise all developers in their field
  - No company driven advisory boards anymore
- Meet at regular intervals
- Mentor to help with the organisation, governance
- Costs borne by companies/sponsors
- Charter / Memorandum of Understanding (Scope, commitment…)
- Agendas are public (transparency)

Success factors: Deliberative democracy

- A form of democracy in which deliberation is central to decision-making
- It adopts elements of both consensus decision-making and majority rule
- Deliberative democracy differs from traditional democratic theory in that authentic deliberation, not mere voting, is the primary source of legitimacy for the decision
- In domains of high uncertainty: necessity to involve all actors

There are many possible methods to engage patients. Are they all being tested? How to decide which ones to use and when?

Scientific Advice / protocol assistance
- Telephone interviews / semi-guided interviews
- Experts invited to face-to-face meeting

Horizon Scanning
- Surveys
- Questionnaire
- Separate meetings
- Delphi method
- Participation of patients in selection committee
- Patients' jury

Scoping phase (HTA)
- Patients review the literature search results
- Patients review the assessment protocol
- Expert panel
- Development of Questionnaire on the experience of living with the disease, patients' preferences
- Interviews
- Focus groups

Benefit/risks - Information sources
- Expert panel
- Data mining, analysis of social networks / patients forums
- Surveys
- Questionnaire on the experience of living with the disease, patients' preferences elicitations
- Expert panel
- Citizen's panel
- Discussion groups
- Invitation to CHMP discussions / Scientific Advisory Groups

Dissemination of reports
- Review of the documents for the public
- Passive or active dissemination

EURORDIS Summer School (Barcelona)

- Started in 2008. Each year:
  - 40 patients' representatives & 10 academic researchers
- So far, > 400 patient representatives trained
  - from 35 different countries, representing > 75 diseases
- 5-day face-to-face training on:
  - **Clinical Trials & Medicines Development**
  - **EU Regulatory Processes & EMA**
  - **HTA, Reimbursement, Patient Access**
  - **Translational & International Research**
- On line: 7 modules (27 hours)
- 29 faculty members (EMA/regulators (4), EMA committees' members (5), HTA experts (2), ethicists/scientists (5), industry/consultants (5), patients' advocates (8))

In the future: more systematic dialogue between patients' organisations (CABs) and regulators – exchanging minutes

In the future: CHMP public hearings? FDA ones are excellent to learn on b/r of a new product

In the future: patients as members of the CHMP?

In the future: real world data will provide as much information post-authorisation than trials pre-launch? Role of patients organisations?

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RARE DISEASES EUROPE

Thank you for your attention.

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What does the EuroCAB programme consist in

• Guidance

- How to start, how to operate
- Travel and accommodation, compensation time spent
- Declaration of interests
- Insider trading prevention
- Templates++

• Codes

- Code of Conduct for CAB members (individuals)
- Transparency, independence
- Registry "The Gate"

• Mentors

- Patients advocates
- Health professionals
- Experienced with CABs
- Experienced with regulatory affairs / HTA
- To accompany CABs

• Trainings

- EUPATI Patients' Academy
- EURORDIS Open Academy
- Ad hoc trainings (e.g. pricing negotiation, horizon scanning, consent…)
- Online library

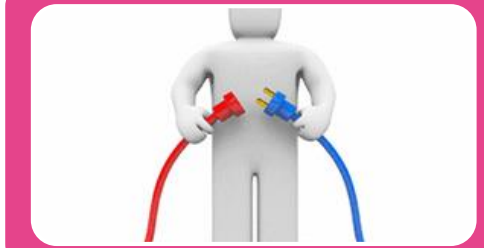
• GPEP

- Good Patient Engagement Practices
- Annual Meeting of CAB chairs and mentors
- Stakeholders (clinicians, ERNs, industry, HTA, regulators…)

The EuroCAB programme: incubator, mentor, advisor

Identification of areas where CABs are needed

- Call to Members
- Feedback from experts (COMP, PRIME…), scanning the horizon
- Webinars to patient networks, meetings, preparatory phase (3-6 months)



Matchmaking with industry

- Contact or help contacting developers /sponsors in relation to horizon scanning
- Receives direct requests from developers

Mentoring

- Preparing/help preparing and running CAB meetings
- Keeping guidelines up-to-date, developing policies, qualification with authorities
- Back-end office, "treatment activist advice"

Success factors

- High quality **dialogue**
  - Patients are considered on the same level as other experts
- A **dedicated unit** at the EMA for stakeholders' involvement
  - Training materials (videos, face to face…)
  - Special needs
- Adequate **resources, time** and budget
  - All costs covered
  - Daily allowance, doubled for volunteers
- Rules for involvement defined **together** with stakeholders
  - For all aspects
  - Revised as often as needed

"*With a high quality dialogue, patients and regulators can only agree.*"

Jean-Michel Alexandre
Former CHMP chair, EMA