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RARE DISEASES EUROPE

COMMUNITY ADVISORY BOARDS

Council of European Federations

27 October 2017, Paris

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today

intro	• What's a Community Advisory Board? • How can EURORDIS help you setting a CAB
experience	• With existing CABs • Suggestions how to best operate them
example	• A CAB in creation: CF-Europe CAB
your needs	• Your own Horizon Scanning results (8)
practice	• Discussion with all, on the next steps
conflicts?	• EMA policy on conflicts of interests

- Rob Camp
  - EURORDIS consultant and volunteer
- Experience with CABs:
  - Spain:
  - Europe
    - 1995-2002 E-CAB founder and member (EATG)
    - 2009 – today: mentor for e-TSC, SS-ILD, CF-Europe…
  - USA: NIH-ACTG, ATAC
  - Africa:

- Hilde de Keyser
  - CF-EUROPE
- Experience with CABs:
  - CF-Europe Community Advisory Board
    - Created: 2017

- François Houÿez
  - Director of Treatment Information and Access at EURORDIS
- Experience with CABs:
  - France: 1995-2002 TRT5 (reviewed all clinical trials sponsored by ANRS/Inserm)
  - Europe: 1995-2002 ECAB (EATG)
    - One of the ECAB founders – Chair of ECAB 1998-2001
- Total
  - 77 clinical trials reviewed
  - 18+ products followed-up

Experts patients advising researchers

1- Principles

Principles of treatment activism (1983)

- 4th principle: *be involved at every level of decision-making for all decisions that affect our lives*
- 5th principle: *be included in all forums with equal credibility a other participants*

Case study 1 – Consequences of not having a CAB

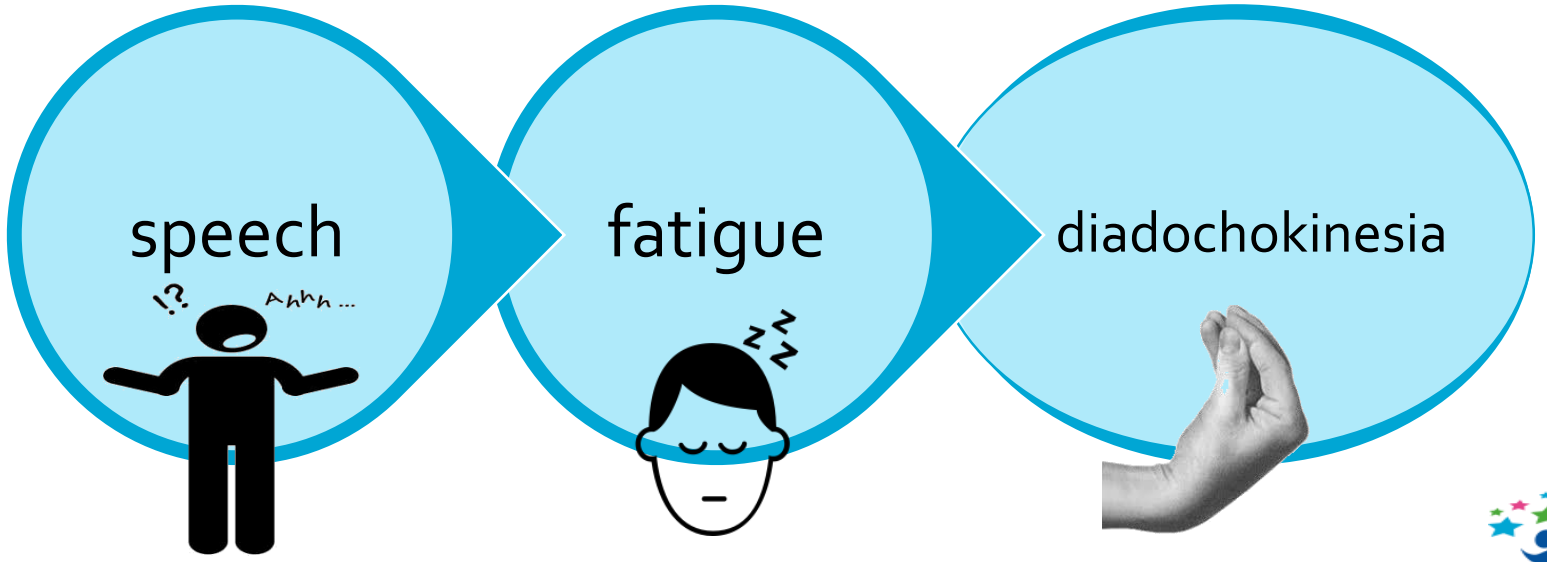
Friedreich Ataxia degeneration of nerve tissue in spinal cord, in particular sensory neurons due to reduced expression of the mitochondrial protein frataxin

A new product was tested: idebenone

- Primary Endpoint
  - level of the oxidative stress marker 8 - Hydroxy - 2' deoxyguanosine
  - a biomarker, not a surrogate
- Secondary endpoints:
  - movements control (standard scales for ataxia symptoms), impact on daily activities (using a questionnaire)
  - effect on heart function
- No endpoint was conclusive (results were not positive nor negative, impact of product on FA simply couldn't be evaluated)
  - Negative CHMP opinion

Yet, patients were reporting improvements

- 40% of patients treated in a compassionate use programme decided to continue taking the product after the rejection of the marketing authorisation
- They purchased it off-label, on line, paying out of pocket
- Placebo effect? Or real effect?
- They claimed some improvement for



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

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

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)

You need a pre-clinical scientific discussion with

- regulators and HTA experts (guidelines, scientific advice)
- clinicians
- patients: Community Advisory Board

Ideally

- There is a Community Advisory Board (CAB) for your disease community where you discuss these aspects with all researchers involved
- You're able to select Patient Relevant Outcomes
- This increases chances of a successful development

True stories – when there is a CAB

- Disease prevention trial (tuberculosis, public sponsor)
  - Inclusion in CT : Skin test to be applied (at hospital) and result to be read after 48h (at hospital)
  - Problem: few volunteers came back at 48h (only 40%) to read test → recruitment too slow
  - Advice given: send doctor or medical student to where the volunteers live and read the test there
  - Outcome: recruitment back to normal rate
- Discussion on "fair price" of a new medicine with private sponsor (pharma company)
  - Company realised the patients had no expertise to discuss economic aspects and fair pricing
  - Company proposed to adjourn the discussion on fair pricing
  - Company offered an educational grant to the CAB members for them to attend a training on fair pricing (LSE, UMIT…)
  - Discussions on fair pricing started again when CAB members were better informed

True story - CAB cases

- New product, phase II
- Maximum tolerated dose: highly active
- Same grade 3 or 4 safety profile than comparator
- Clinicians: all for maximum tolerated dose for phase III trials
- But loose stools in 20-40% treated participants (grade 2)
- C.A.B members: in favour of second best dose (loose stools in 8%)
- Company decided to test both doses in phase III
- MA: dose proposed by C.A.B members was authorised, as overall more effective (adherence+++)

Sales US$ 500 Mio higher than best scenario at year 2

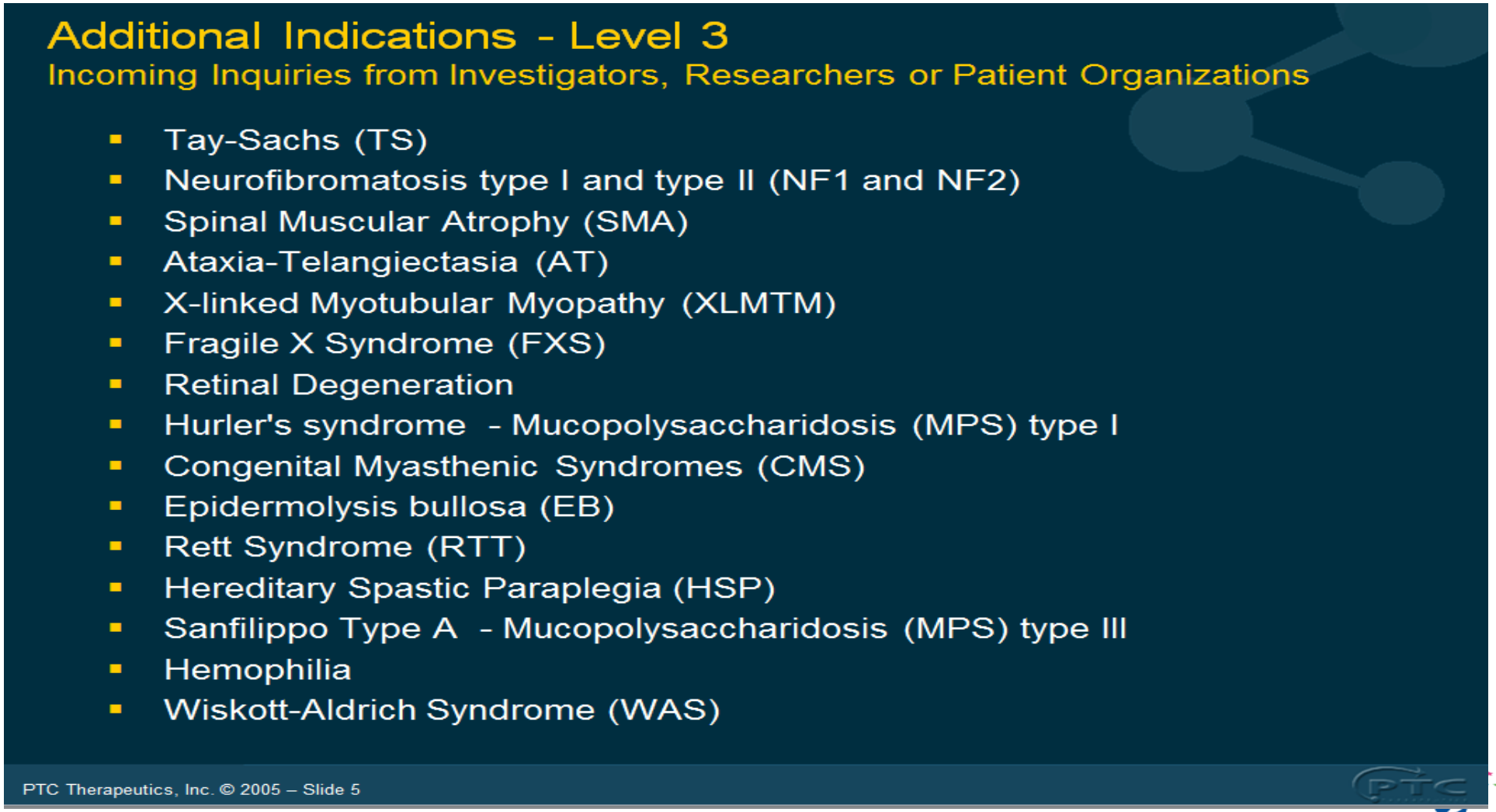
For each $ invested in this CAB meeting, the company gained US$ 10,000

Before the trial e.g. PTC Therapeutics

- PTC124, is a novel small-molecular agent designed to make ribosomes become less sensitive to, or possibly ignore premature stop codons
- PTC124 has been tested on healthy humans and humans carrying genetic disorders caused by nonsense mutations, such as some people with cystic fibrosis and Duchenne muscular dystrophy

Claudia Hirawat, PTC @ Eurordis Round Table of Companies
Keys for Ensuring Fruitful Collaborations Between Sponsors and Patient Organisations
Barcelona, November 21 2005

And many more candidates!



Problems

- PTC Therapeutics = small company
- Needed first a proof of concept in one/two disease to convince investors to invest for other eligible diseases

- How to decide which disease to start with?

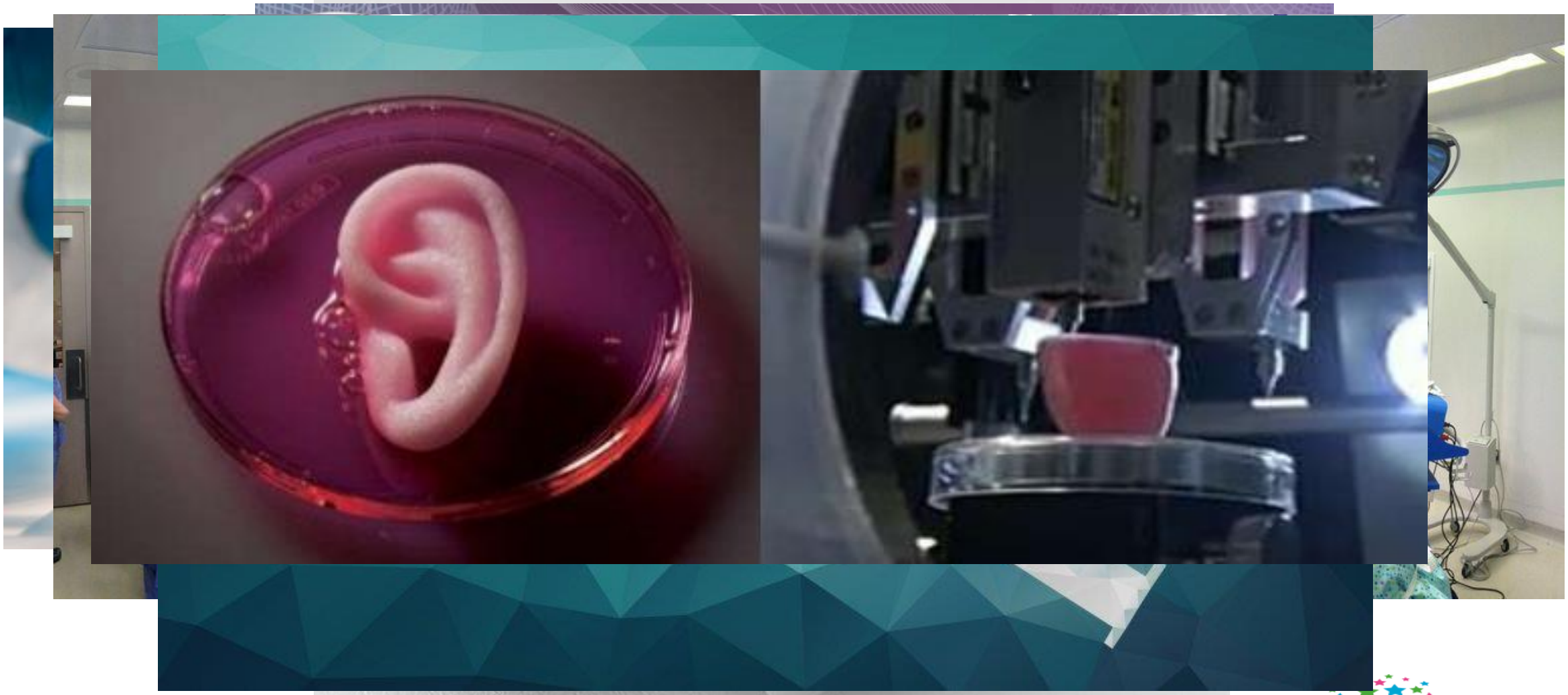
A community Advisory Board is

- A group of volunteer patients who offer their expertise to public or private sponsors of clinical research
  - Overall programme development
  - Or a single clinical trial
  - Other aspects beyond the research programme
- The same group of patients can advise several sponsors in their field
  - avoiding selection of patients' representatives by the sponsor
  - Agenda and secretariat driven by the patients

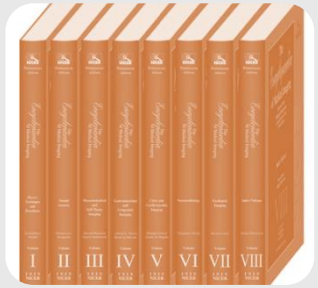
Fundamental raison d'être

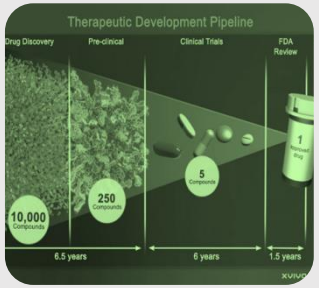
- Same way sponsors discuss with clinical investigators, they should also discuss with patients: patient investigators
- Only the content may change

For what? All health technologies



SCOPE: express your (unmet) needs





Trial protocol

All aspects, not just consent letter

Strategy trials

Collaboration with competitors

Compassionate use programme

Pipeline

drug development portfolio and plan

Reasonable pricing

World-wide Access

Patent availability to generics companies

And also Community Relations (DSMBs and at investigator meetings), marketing practices and publicity…

Commitment, training, organisation

2 – CAB in practice

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C.A.B. in practice: the "patient investigator"

- Same group of 10 - 20 trained patients (same disease or alike) committed to follow-up the research over the years
- When 20: 1 member, 1 alternate, same country
- Meet at regular intervals
- Mentor to help with the organisation, governance
- Confidentiality
- Rules to prevent insider trading
- Costs borne by company/sponsor
- Memorandum of Understanding (Scope, commitment…)
- Agendas are public (transparency)

Timeline - Example for a 2-day C.A.B

Friday

Arrival, information sharing, briefing

Training, according to needs: pharmacologist, trialist…

Saturday

Sponsor A

Lunch, with or without sponsor

Sponsor A or B

Departure

Alternatives

Anonymised and confidential consultancy (EATG)

- CAB members receive questions, protocols, documents from sponsor
- Ignoring the sponsor's name
- Respond in writing

Anonymised and response not confidential (Dravet ∑)

- CAB members receive questions, protocols, documents from sponsor
- Ignoring the sponsor's name
- Responses posted on a web page

Timeline - Example for a 3-4-day C.A.B or Cf-Europe?

Friday	Saturday	Sunday	Monday
Company A*	Training pharmacologist	Internal meeting debrief	Company B*
Lunch with company staff	Training epidemiologist	Social programme or departure	Lunch with company staff
Company A*			Letters, reports or departure

Working Principles (1)

tibotec

- Working Principles in place with ECAB & ATAC DDC:
  - Initial contact through Community Affairs
  - Yearly contracts with EATG for ECAB reviews, and with ATAC
  - ECAB/ATAC to appoint reviewers
  - Number of community reviewers from any organization limited to 5
  - Completion of review within 5 business days
  - Collation of comments in 1 feedback document, to which we respond
    - » Tibotec response on the protocol to occur within 14 days
    - » Tibotec response on the ICF to occur within 30 days
    - » Coordination of feedback through Professional/External Affairs

Working Principles (continued)

- Working Principles in place with ECAB & ATAC DDC:
  - Compensation at hourly rate for hours of active review
  - Payments are made directly to organization
  - Common understanding that with some consistency of reviewers, total time investment decreases
  - Prerogative to limit number of participants and/or total amount of time invested in any given review

More types of involvement

tibotec

- Advisory Boards:
  - Moment of reflection on appropriateness is in SOP
- Drug Safety Monitoring Boards (DSMB's)
- Investigator Meetings
- Investigator Webcasts
  - Informed on issues

Conclusion

tibotec

- Active patient involvement in Clinical Trials is possible and *positive for both parties*, if:
  - Long-Term relation is built to ensure trust and confidence;
  - Patient Community representation is organised;
  - Strong organisational structures exist (SOP's);
  - Patient literacy is ensured to optimise feedback;
    - » ECAB sponsored to attend London School of Economics
  - Mutual acceptation exists of limits to what can be achieved;
  - Strict confidentiality can be ensured.

What EURORDIS proposes to

Help you set your own Community Advisory Board

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EURORDIS services to members

RareConnect.org
A EURORDIS INITIATIVE

Centres of Expertise

Help Lines for Rare Diseases

CAB

Respite Services

Therapeutic Recreation Programmes

School Services

EURORDIS SUMMER SCHOOL

Rare Patients' Barometer Voices Survey
A EURORDIS INITIATIVE

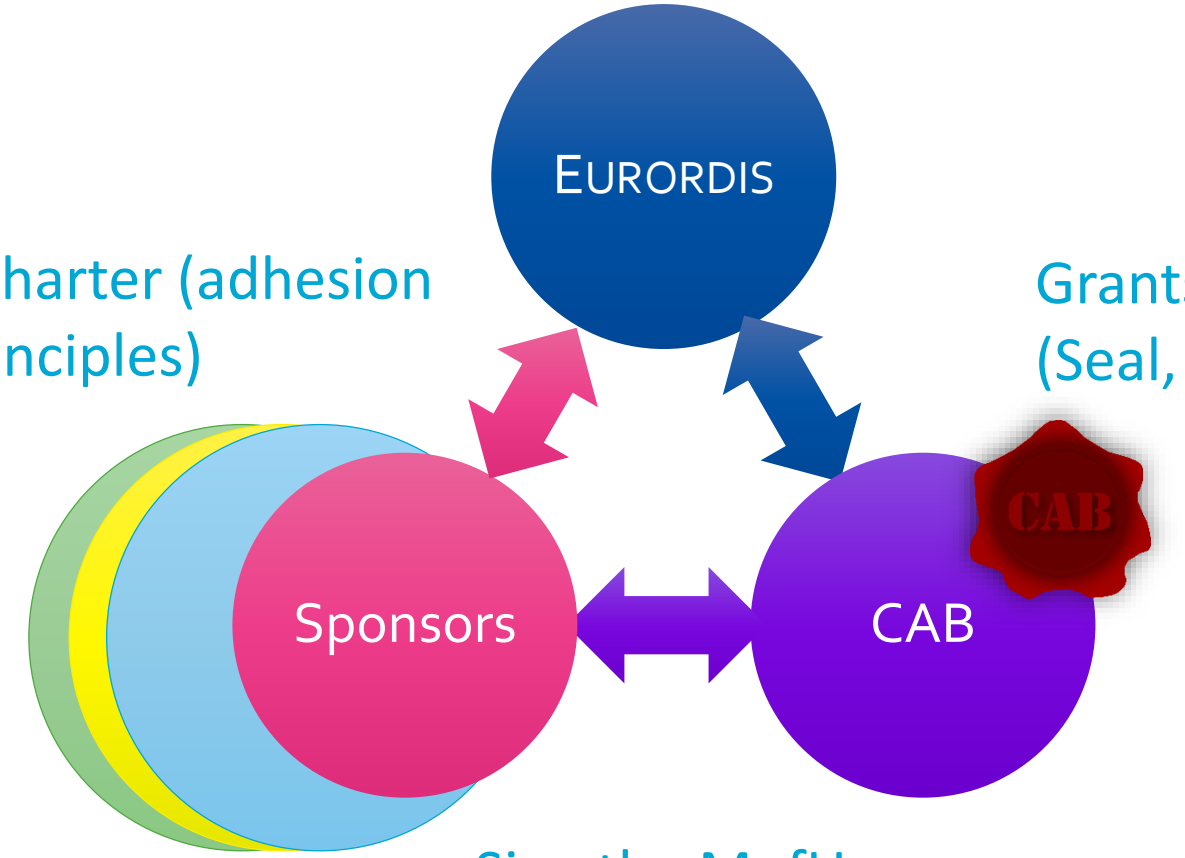
RARE!TOGETHER Knowledge Base
Capacity building for networds of Rare Disease patient organisation

A service to members

- Based on their needs and capacities
  - Guidelines and advice for all
  - Mentor for those who can't operate a CAB themselves from the beginning
  - Transient administration (expenses, logistics) for those who don't have the adequate structure yet
  - Other: fully autonomous, may ask for the EURORDIS CAB seal

- Advantages:
  1. Benefit from experienced advice on how to operate a CAB and to do it right - 21 years of experience
  2. Benefit from EURORDIS training programmes
  3. Benefit from EURORDIS credibility and strong governance
  4. Qualify for regulatory procedures (standard)
  5. Be aware of all initiatives along the products life-cycle where you can make a difference
     (CT authorisation, ethics committee, Early Dialogues, Scientific Advice, Protocol Assistance, Horizon Scanning, PRIME, MOCA, CHMP/Scientific Advisory Groups, scoping/HTA, Late dialogues, Pharmacovigilance, Variations…)
  6. Become more largely visible

In short: EURORDIS s a backup office for all CABS



EURORDIS programme for CABs

A Memo of U template — Signed between sponsor and CAB members

- Defines the scope and arrangements between the sponsor and the CAB

A Charter — Co-signed by each sponsor and EURORDIS

- Ensures the sponsor adheres to the principles

An EURORDIS CAB seal — Attributed by EURORDIS to the CABs

- Ensures the CAB satisfies the recommendations and guidelines as proposed by EURORDIS
- Check list

A Code of Practices — To be followed by CAB members – Form to declare interests (to be created)

- Defines the principles to be followed by patients' representatives when working with sponsors of clinical trials and developers of health technologies

A mentor programme — An experienced EURORDIS staff member or volunteer

- For CABs with no or little experience

An EMA qualification? — Discussion needed with EMA SAWP, PCWP, MB

- So that patient investigators are level 2 Conflict of Interest as clinical investigators

Standard Operating Proc. — SOP on how to run the CAB programme / guidelines for CABs

- 90% completed

C.A.B.s (28), situation and prospective July 2017

Signed Charter and/or a CAB

- Systemic Sclerosis ILD (12 companies)
- Tuberous Sclerosis (2 companies)
- Cystic fibrosis (20 companies)
- Spinal Muscular Atrophy

- = 4

- Discussions engaged
  - Liver Carcinoma (ILCA)
  - Batten Disease

- = 2

Signed Charter and no CAB (discussions)

- RD in the portfolio of CSL Behring, Chiesi, Johnson & Johnson, Sobi, Takeda, β-Innov
- (these companies expressed and confirmed their interest)

Waiting list (PRIME)

- Glioblastoma
- EBV lymphoma
- B-cell Lymphoblastic Leukaemia
- β-Thalassemia Major
- B-cell lymphoma
- Primary haemophagocytic lympho-histiocytosis
- Sickle Cell Disease
- Acid sphingomyelinase deficiency
- Haemophilia A
- Haemophilia B
- Progressive Familial Intrahepatic Cholestasis
- SMA type 1
- Synovial carcinoma
- Hepatic porphyria
- Primary Biliary Cholangitis

- = 15

Waiting list (HTA)

- Niemann-Pick
- Myasthenia Gravis
- Ovarian cancer
- Thyroid cancer
- Sanfilippo syndrome
- Haemophilia A
- Multiple Myeloma

- = 7

Issues identified in Bergen, 1997

- Dependency on pharmaceutical companies
- Operating procedures
  - Training, recruitment, representative character, …
- Outcomes, evaluation
- Attitudes of physicians
- Conflicts of Interest
  - financial, intellectual, participatory
- Long-term commitment
- Transparency, confidentiality, insider trading prevention

Issues (some)

- Attitudes of physicians involved in clinical trials
  - Sometimes difficult for clinicians to accept the concept of community involvement in the clinical trial
- Conflicts of Interest Policy
  - In particular at EMA / HTA
- Recruitment and replacement of members
- Procedures governing the relationship between the pharmaceutical company and the CAB (e.g. when a conflict arises)
- Training of CAB members and treatment advocates

- Guidelines to be validated with you
- A call to EURORDIS members to express interest
- Prioritisation, match making expressions of interest / opportunities
- Training, mentoring, evaluating, developing

How to create a Community Advisory Board (CAB)

Identify 10 to 20 patients from 5-10 countries

- Via clinicians
- Via online communities, social media
- Via sister organisations
- "Job description"
- Define disease stages
- Parents or carers
- All speak English
- Confidentiality form signed
- Insider Trading prevention material signed

Call for a meeting to discuss a trial

- Eurordis can provide a mentor
- 1st day: training Why you're here
- 2nd day: meeting with investigators
- Sign a Charter for collaboration
- Make agenda public
- Expenses paid by the trial sponsor
- Meeting can be linked to a scientific congress

Follow-up

2nd meeting (2 days)

- Patients can review the informed consent
- Make suggestions on how to improve the trial
- Suggestions are followed-up (CAB secretariat)
- More training (EUPATI…)

Typically 2 meetings a year. Can be more. Conference calls in between.
Training on regulatory and reimbursement process, clinical trials…

EURORDIS Charter for Clinical Trials

- A signed document between POs and the sponsor (MofU)
- That defines the scope of the collaboration
- EURORDIS acts as a mentor for the PO and accompanies the C.A.B

EURORDIS proposes to facilitate the implementation of the Charter

- For a given clinical trial and upon request, EURORDIS will help the sponsor identify European POs interested in collaborating
- EURORDIS may assist in the setting-up of the collaboration without interfering in the study itself
- EURORDIS helps ensuring the C.A.B operates according to evolving standards and policies (S.O.P)
- EURORDIS Summer School as a support to POs
- Additional documents regarding collaboration - glossary, examples of agreements of understanding are on Eurordis' website.

Conclusion
Expected outcomes: society will benefit, as

- Trials' quality will improve
- Patients' interest for clinical research will increase
- Chances of successful development will increase as
  - Trials become more attractive
    - Adequate design, agreed comparator, smart practical aspects…
  - Patients' retention increases
    - Proper information, follow-up of all unexpected events…
- Regulators / HTAs can make better decision
  - concerning diseases related quality of life, treatment reimbursement…

Patients' contribution

- Bring a diversity of opinion, of viewpoint, and experience
  - patient advocates often think outside the box of a purely "scientific approach"
- Have a vested interest in conduct and outcome of trials leading to meaningful therapeutic options
- Provide "ground level" input that is based on personal and community experience: a street sense
- Help FDA/EMA appreciate patient feelings about balancing efficacy and concern about risks, to help FDA/EMA make better risk/benefit decisions
- A value judgment overlay on top of measureable, empirical clinical trial evidence
- Patients add value to decision making

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Thank you for your attention.

Name

Job title

Tel: Phone number

Email address

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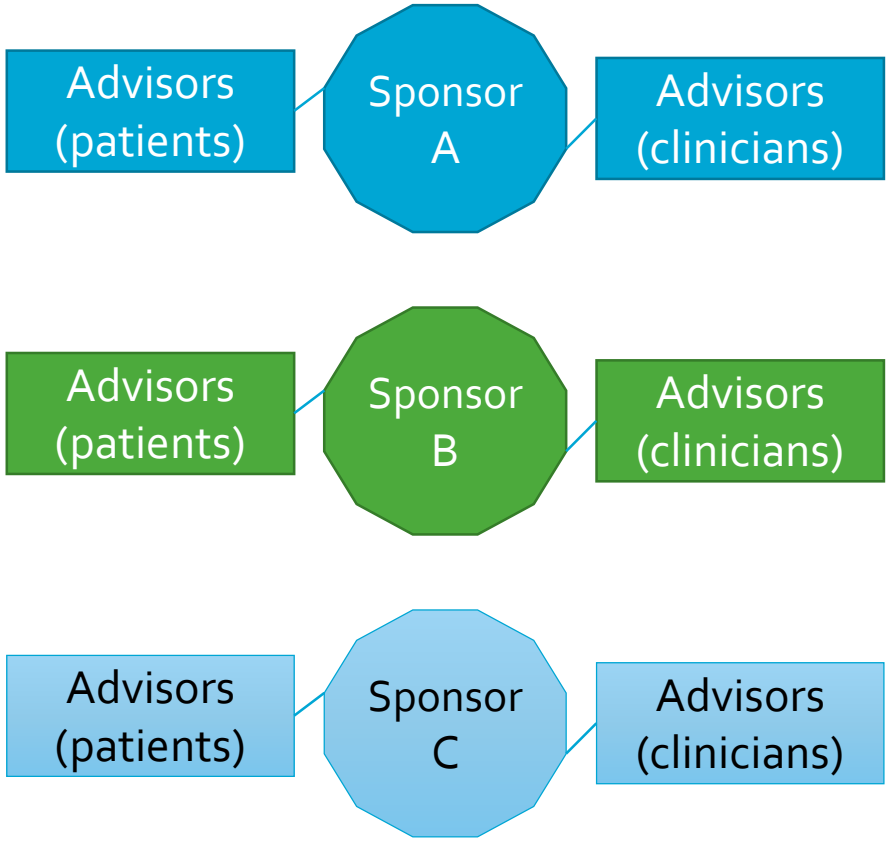
typically

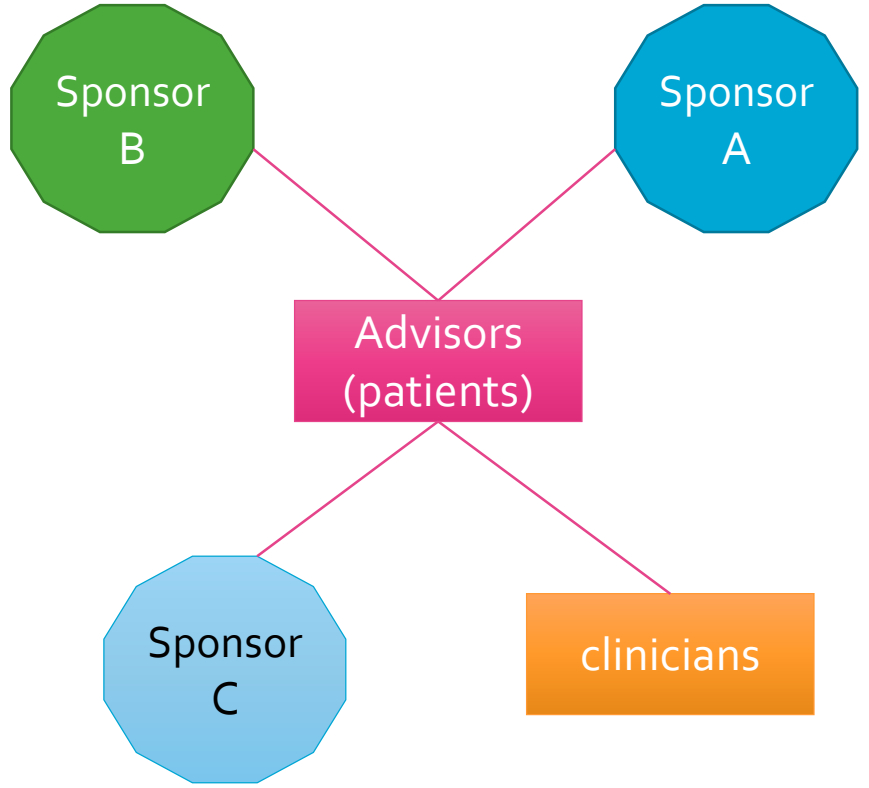
- Review clinical trial design at the planning stage
- Discuss inclusion criteria to reflect real life
- Review and simplify informed consent sheets
- Suggest trials that reflect patient and community needs
- Negotiate compassionate use
- Monitor access to all in the region. Advocate for fair, sustainable and affordable pricing

Same disease area, different sponsors

Sponsor dependant model



C.A.B model



How to obtain the opinion of patients in R&D?

Sponsor sets its own group of interlocutors among patients (piggyback model)

- Selection? Independence? Different groups / same disease?

Investigators and not the sponsor interact with patients (paternalistic model)

- Indirect discussion, no access to the decision maker

Patients set their own structure (Community Advisory Board model)

- Deontological standards needed, training. See Bergen Report 1997

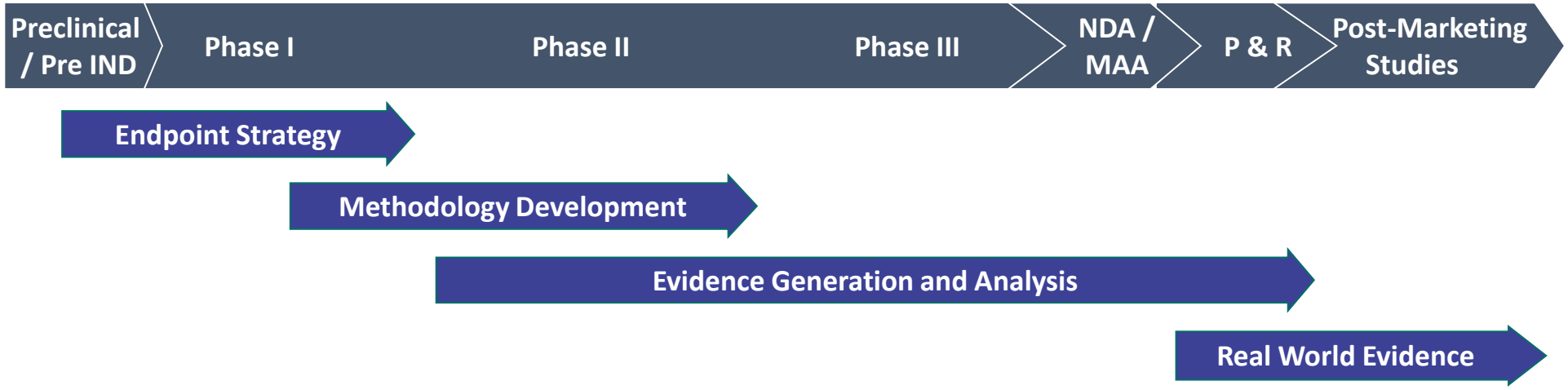
Now, how to involve regulators and HTA experts?

Main role: involve a patient community (disease, condition, indication) in clinical research

In particular:

- Understand the clinical development of the product
- Voice concerns regarding specific clinical studies, their development, implementation and outcomes
- Give assistance concerning issues related to the accrual and retention of trial participants
- Give means to address grievance issues
- Promote ethical research practices

When to consults with patients?



Explore patient needs
Prioritise hypotheses
Define strategy
Instrument selection
Scale distribution
COA databases

Cross-cultural development
Linguistic validation
Content validation
Psychometric validation
Clinical meaningfulness
Compassionate use

Study design
Protocol development
Mixed Methods
Analysis & modeling
Reporting & communication
Briefing documents
Regulatory meetings
Utilities
Reasonable price
Direct access to patients

Clinical practice tools
Observational studies
Registries
Patient satisfaction
Patient adherence
Personalised medicine
Risk sharing
Market entry agreement