EUCOPE
European Confederation of Pharmaceutical Entrepreneurs AISBL

EUCOPE

OMP Working Group Meeting

Brussels, 15 May 2019

I. Welcome / Introduction / Competition Law Compliance Policy / Meeting Agenda & Objectives

Chairs

Competition Law Compliance Policy

EUCOPE brings together representatives innovative companies to discuss common issues, challenges and trends affecting the pharmaceutical industry. This activity can be perfectly legitimate. However, certain competition law risks may arise in relation to EUCOPE's activities.

EUCOPE's European Union ("EU") compliance policy ("Policy") explains these competition law risks and aims to ensure compliance by all members and EUCOPE staff with the rules applicable in the EU. EUCOPE itself and its members are subject to these rules when engaging in any EUCOPE related activities. Any anticompetitive behavior adopted by a member can result in serious financial, criminal and/or disciplinary penalties, as well as other harm (e.g., reputational harm) for EUCOPE, represented companies and for meeting participants personally.

Competition Law Compliance Policy

There are certain matters which **should not** be discussed with competitors before, during or after any such meetings. These include:

- Territorial restrictions, allocation of customers, restrictions on types of services, or any other kind of market division;
- Prices, price changes, conditions of sale (including payment terms and guarantees), price differentials, discounts;
- Current market conditions and issues, including industry pricing policies or patterns, price levels; capacity (including planned or anticipated changes regarding those matters), except where limited to the discussion of historical or public information;

[cont'd]

Competition Law Compliance Policy

- Individual costs, cost accounting formulas, methods of calculating costs;
- Individual company figures on market shares, sources of supply, capacity;
- Information as to future plans of individual companies concerning technology, capacity, marketing or sales; and
- Matters relating to individual suppliers or customers.

Attention: these rules equally apply to informal discussions before, after, or during each meeting. If any sensitive information is discussed or disseminated, insist that the discussion be terminated immediately and make sure that your objection is recorded in the minutes. If necessary, leave the meeting and immediately inform EUCOPE's General Counsel.

Agenda (1/4)

I. Welcome / Introduction / Competition Law Compliance Policy / Meeting agenda and objectives

Chairs

II. Community Advisory Boards (CABs)

- Presentation of the CAB concept
- Feedback and lessons learned on a company experience
- Presentation of EUCOPE's draft position
- Group discussion

Rob Camp, EURORDIS
Flaminia Macchia, Vertex
Dr. Andreas Reimann & Philipp Gallwitz, Admedicum

Agenda (2/4)

III. Increased collaboration in rare disease Research and Development

- EUCOPE's position on European Reference Networks
- Update on the ERNs' response on ERN-industry interactions

Secretariat

- Presentation of recommendations for a path for Research & Industry to collaborate in Rare Disease data collection

George Reynolds, RareUrn

IV. EMA discussion paper on the use of patient registries for regulatory purposes

- Presentation of EUCOPE's comments

Maren von Fritschen, EUCOPE

Agenda (3/4)

V. National updates

- An update on the German Parliament discussions on the Draft Law for More Safety in the Supply of Medicinal Products (GSAV)

Alexander Natz, EUCOPE

- An update on compounding and compulsory licensing in the Netherlands and EUCOPE's activities

Andrea Corazza, FTI Consulting

VI. EUCOPE Study on the OMP Regulation

- Project objectives, timelines (refresher)
- Presentation of the initial findings
- Next steps

Martina Garau & Mikel Berdud, OHE

Agenda (4/4)

VII. European Commission conference on medicines for rare diseases and children - 17 June, Brussels

- Presentation of the event background, agenda and objectives
- Preparation of EUCOPE's participation

Chairs

VIII. A.O.B / Meeting conclusion

Chairs

I. Introduction

Secretariat

EUCOPE Survey

Members' footprint in the EU

Targeted audience: members that research and develop innovative therapies (80 companies + national associations):

Objectives:

- Mapping Members' EU presence, R&D in therapeutic areas and economic footprint.
- Aggregating data to evidence EUCOPE's messages in its advocacy efforts.

Additional information:

- Deadline: 25 May.
- Questions can be skipped if you do not wish to respond.
- Anonymised survey. Raw data provided kept confidential and available to Secretariat only.

II. Community Advisory Boards (CABs)

Rob Camp, EURORDIS
Flaminia Macchia, Vertex
Dr. Andreas Reimann &
Philipp Galwitz, Admedicum

Community Advisory Boards

Setting the agenda with patients

Rob Camp, EURORDIS

Contents

History

Historical Examples

Historical Accomplishments

Two current examples

Clinical Trials Charter

Memorandum of Understanding

Eurordis CABs today and tomorrow


STOP AIDS
DROP THE DEBT

ECAB

The European Community Advisory Board – ECAB was created in 1997. At the time, **patient advisory boards only existed on an ad-hoc basis and were convened by the pharmaceutical companies**, a major limitation that ECAB successfully overcame by putting forward *an innovative model* for the patient community to provide meaningful, independent, and valued input in HIV treatment and prevention research.

ECAB is a high-level scientific platform that brings together **expert patients and treatment advocates, scientific researchers, the pharmaceutical industry and international institutions** to address **key science and policy issues** related to HIV and its main co-infections, like hepatitis C or tuberculosis.

Results with 1 sponsor

- MEAT (multi-experimental agents trial)
- GRACE (Gender and Race)

  more reflective of the epidemic, now standard
- Entry criteria

  Drug users; high ALTs/ASTs
- Informed Consent

  More comprehensible
- 5 drugs approved in 9 years (HIV, HCV, TB)

  More on the way (microbicide, long-lasting (30- or 60-day) injections)

Treatment Activism-Advocacy

Community with representation in government, the pharmaceutical industry & research institutions

Importance of **treatment education and mentoring**

Understanding (barriers to) **treatment development** and the regulatory process

Development of **relationships w/ other stakeholders** - companies, regulators, investigators, larger community

Continuing **education and trainings**

Strategy development-*pro-action instead of reaction*

Community Participation in Research?

The mission for community involvement is to provide meaningful and broad input into the scientific efforts, operations, and activities of the research (network, company, sponsor).

e-Tuberous Sclerosis Complex

2010 – 2014 worked with Novartis on 3 trials of **everolimus**

Everyone signed the Clinical Charter and the MoU

Helped patient community consolidate (by-laws, statutes of European Fed)

worked on a patient registry

clear follow-up notes for next steps, etc

patient reporting

Nothing happened. Novartis didn't heed advice for trials, never recruited

Patients still willing to negotiate (at least 5 other companies…)

Cystic Fibrosis Europe

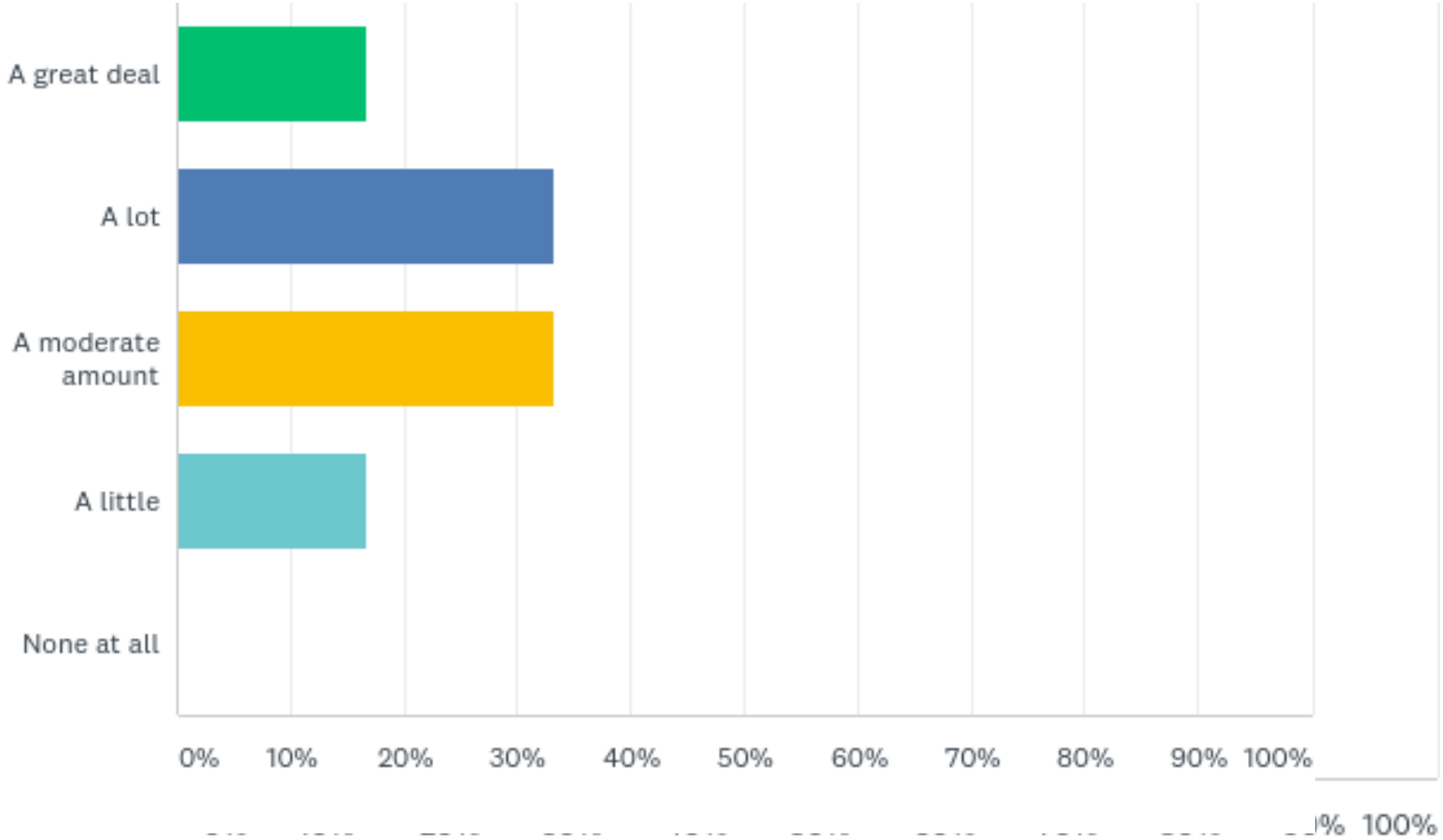
Set up process less than 3 years ago.

- Five CAB meetings
  - Includes preparatory & training meetings

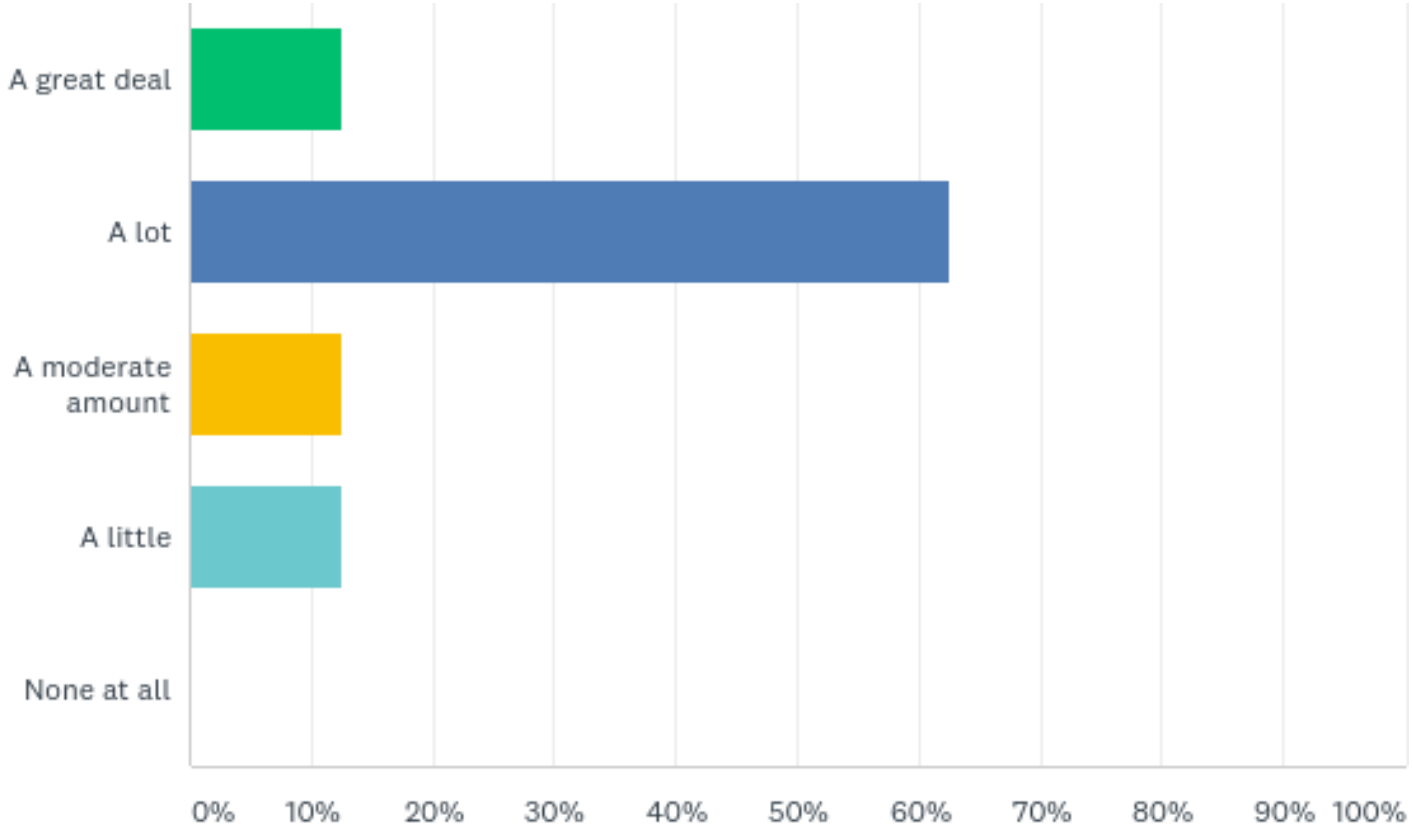
Success due to:

- Strong administrative core
- Active participation of members
  - Willingness to learn & advance

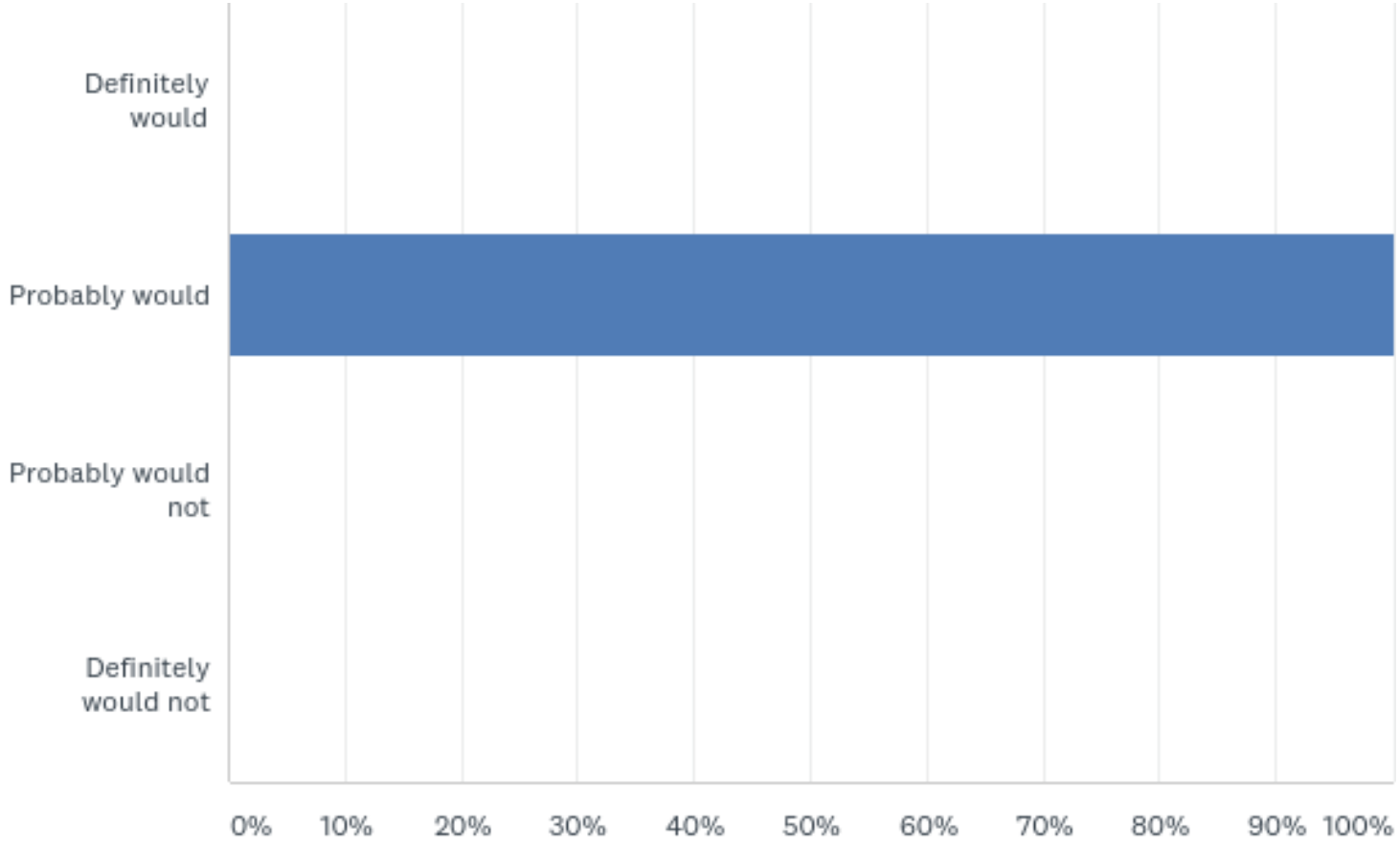
Have you identified distinct patient-relevant outcomes?



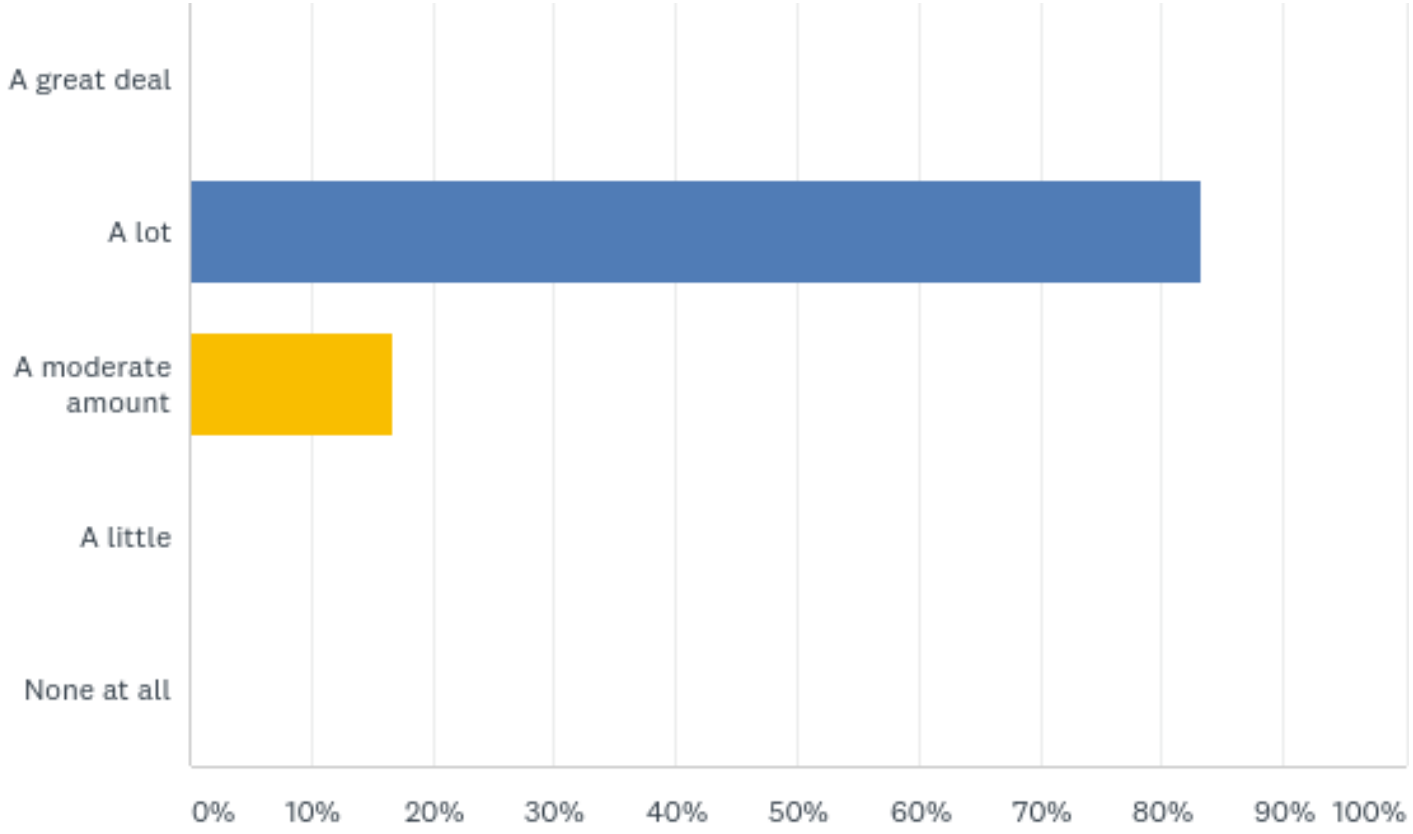
Will you be able to improve clinical programs that are more aligned with patient needs?



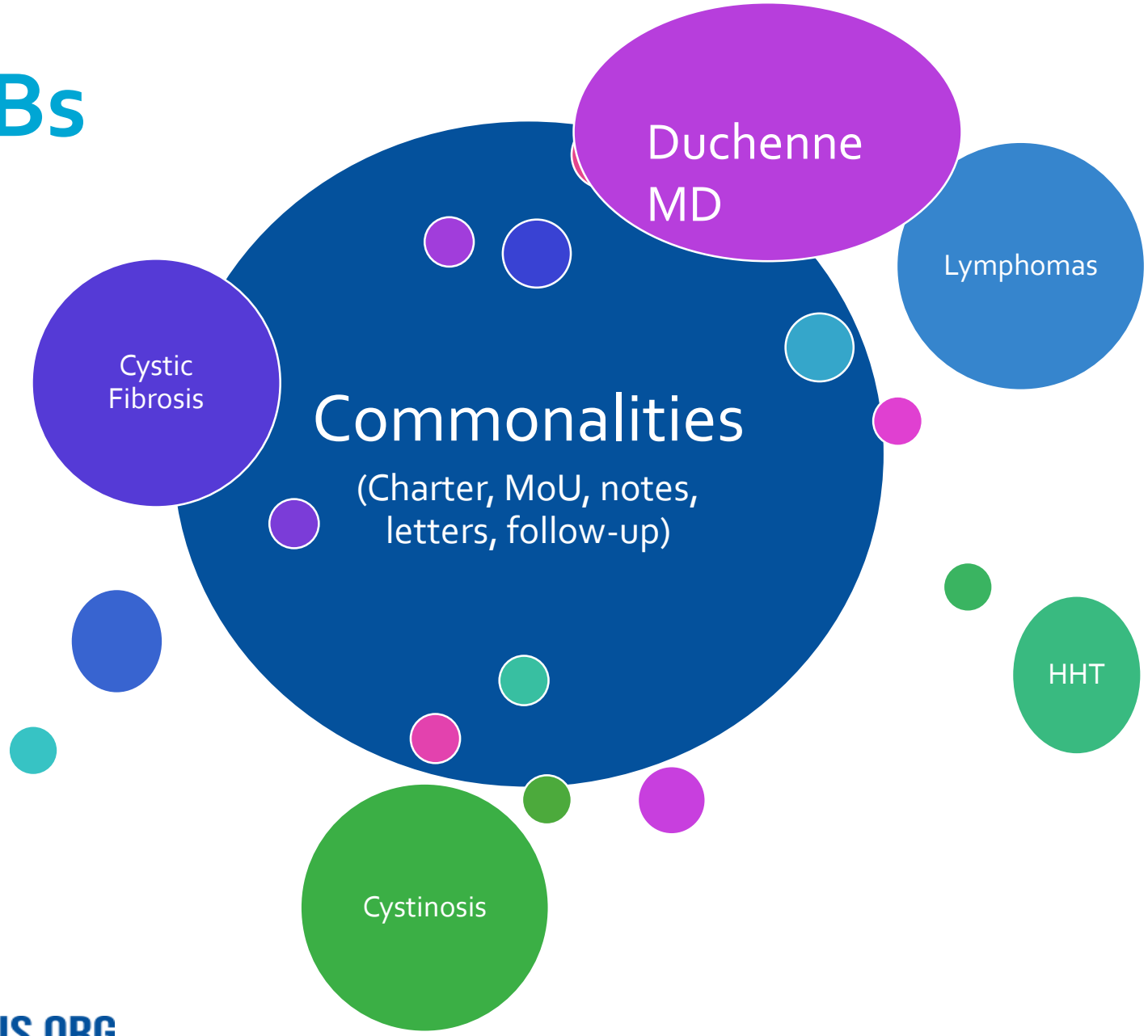
Will these CAB meetings help you demonstrate the value of the product to the regulators?



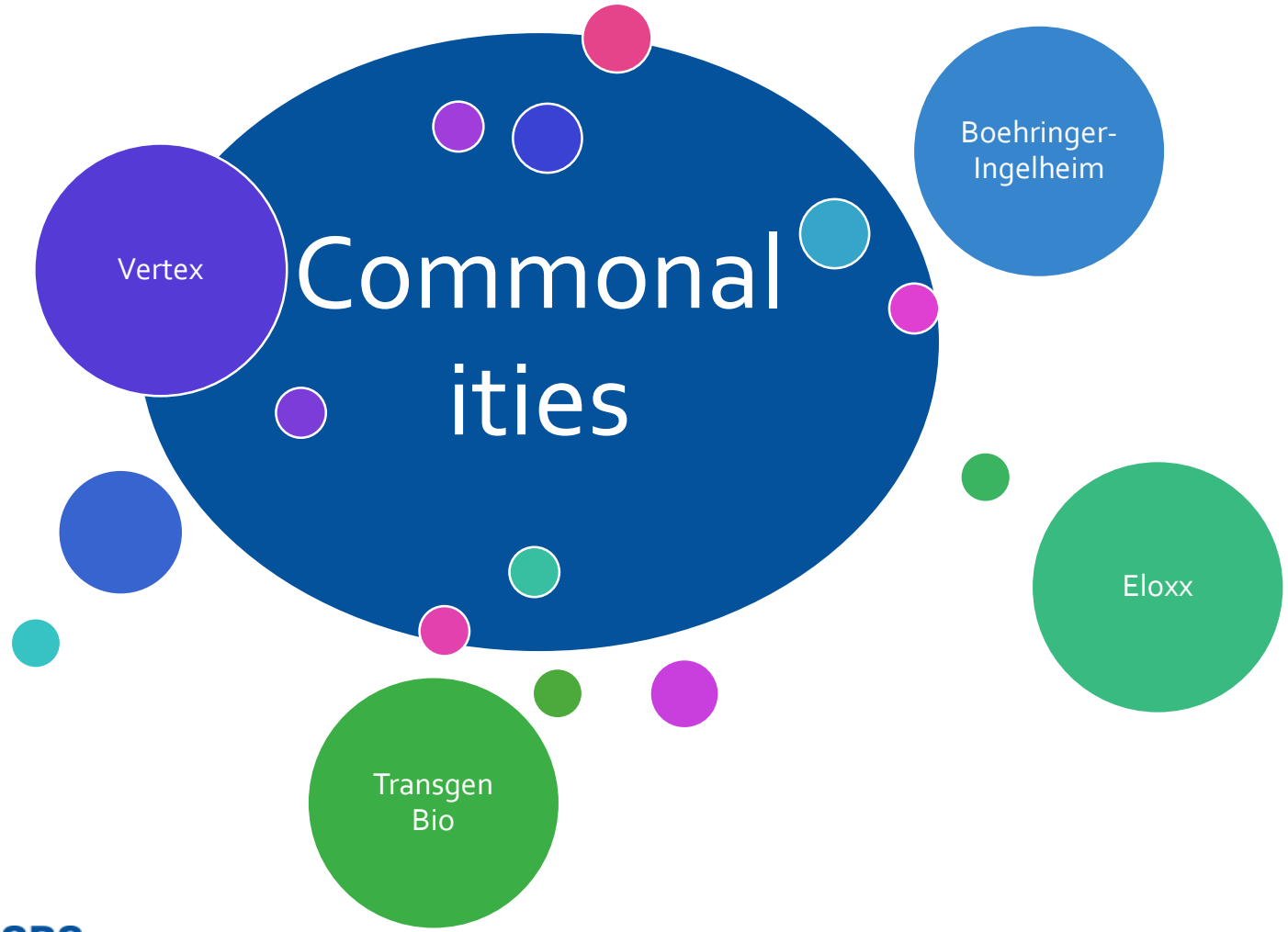
Has this meeting helped you identify previously unknown or unmet patient needs/preferences?



CABs

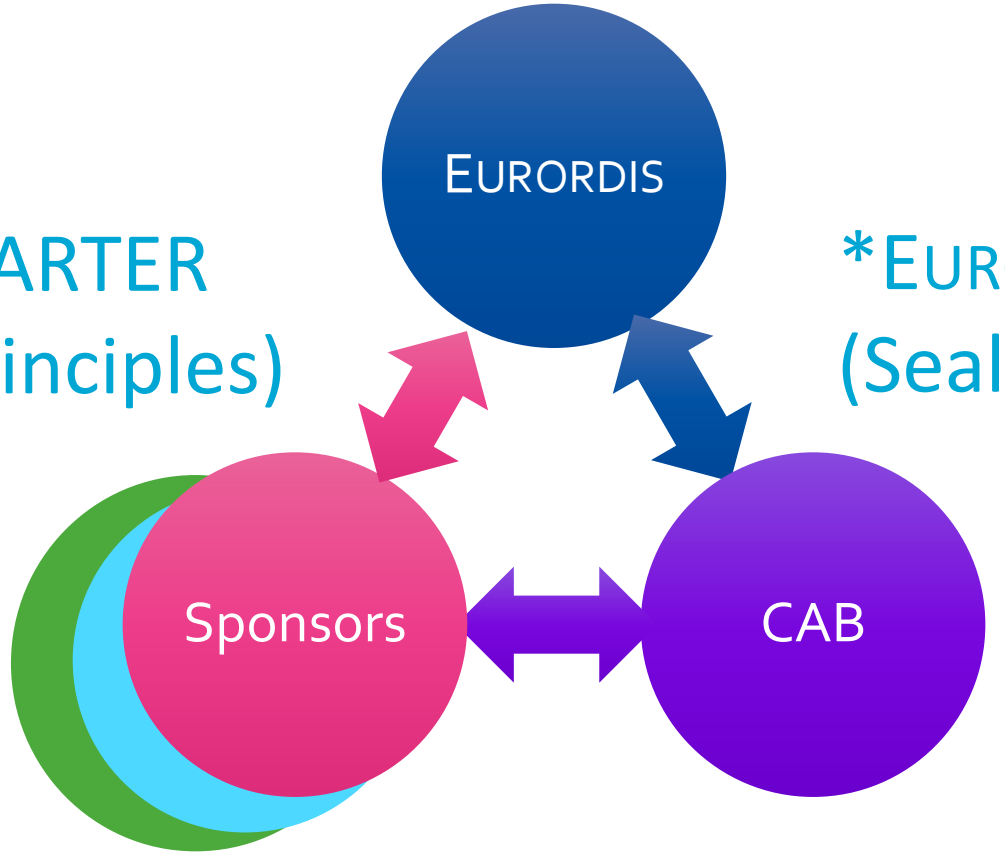

Duchenne MD
Lymphomas
Cystic Fibrosis
Commonalities
(Charter, MoU, notes, letters, follow-up)
HHT
Cystinosis

CABs


Commonalities
Vertex
Boehringer-Ingelheim
Eloxx
Transgen Bio

2019 EUROCAB Programme

The CHARTER
(CAB principles)



*EURORDIS CAB status
(Seal, check list)

Agree to an MoU

EURORDIS CHARTER FOR COLLABORATION IN CLINICAL STUDIES IN RARE DISEASES

EURORDIS, the European Organisation for Rare Diseases, represents more than 800 rare disease organisations from 69 countries including all EU Member States, and has emerged as the voice of approximately 30 million patients affected by rare diseases in the European Union. EURORDIS has contributed to the elaboration of the European Regulation on Orphan Drugs and has held seats on the Committee of Orphan Medicinal Products (COMP) at the EMA since its creation in 2000.

EURORDIS launched a process with a number of organisations involved in clinical studies, initially within the Alliance Maladies Rares. This process highlighted the pressing need to define a common framework for collaboration between patients' organisations and sponsors of clinical studies.

This Charter aims at responding to the expectations shared by both patients and sponsors: the rapid

Principles

- This Charter is an expression of mutual intentions and aspirations
- The Charter is not legally binding
- The collaboration is based on respect and is not tokenistic
- The CAB is recognized as an independent body and is not structurally dependent on the sponsor
- The work and the structure is transparent

Principles

- Agendas are cooperatively designed
- The dialogue is meaningful and of high quality
- Collaboration between the sponsors and the CAB is timely, where input can make a difference
- Confidentiality is respected by both sides
- The collaboration is based on trust
- All interactions are considered non-promotional

4 “pull-out” boxes

This Charter constitutes an expression of mutual intentions and aspirations and does not constitute a legally-binding agreement between the parties

While this Charter is not legally binding, the value of signing this Charter is a demonstration of the firm intention to collaborate with patients in the research and development arena, respecting the principles of this Charter

No commercially-sensitive data is to be made public without the prior consent of the sponsor

These face-to-face meetings and all interactions that accompany them (including webinars, teleconferences, emails, phone calls, etc) are not promotional and should not be considered as such.

MEMO OF UNDERSTANDING

- A/ Initiators of the research project
- B/ Protocol design
- C/ Implementation of the study
- D/ Conduct of the Research Study
- E/ Analysis and Dissemination of results
- F/ Financial aspects and commitments

MoU Commitments…

- Collaboration in Systemic Sclerosis and nintedanib

  - FESCA/SSC will announce the study in its Newsletter, on its website, with reference to this MoU
  - FESCA/SSC will support the participants (members or not of FESCA/SSC) during the study
  - FESCA/SSC will contribute to the lay dissemination of the results of the study even in case of negative results

  - Future/ need a Mentor/Admin, they want to make agenda, call meetings, they can find 11 people, want to get in at an earlier stage (than Ph III), how to negotiate better

Duchenne Community Advisory Board

Reviewing clinical trial protocols giving the point of view of patient community

Promoting best practices, procedures and ethics

Promoting universal access to fair, sustainable, affordable drugs

Promoting **research developments that improve the quality of life** for people living with the disease

Expected outcomes

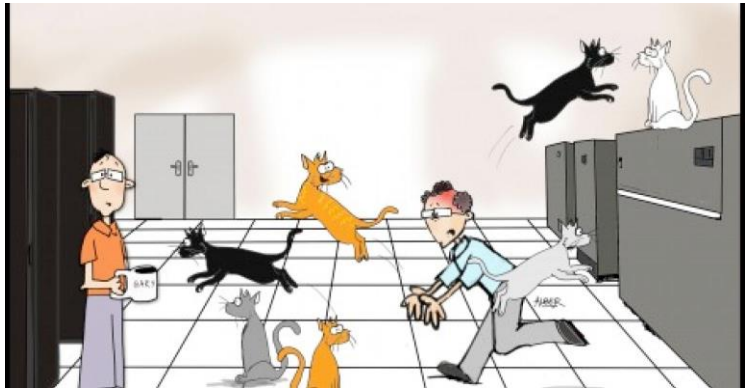
- Trial quality will improve
- Patient interest in research will grow
- Chances of a positive outcome of the trial/development due to
  - Better design, smarter comparator, patient-friendly practical aspects
  - Patients are retained due to better info flow, better follow-up of SEs
- Regulators and HTA can make better and faster decisions on QoL aspects, reimbursement

EUROCABs gives consistent substance to term

- By proposing a real meaning in research that brings the patient into a collaborative relationship with industry
- It is different from ad boards by its being patient-driven - you can get the maximum out of the same group of self-motivated patients over time
- Patient-driven vs company driven
  - Patients manage questions and discussions. It is also not a one-time event but continuous

Co-production

- Can be circuitous and unpredictable, but ultimately more worthwhile
- The flexibility that enables the networking and discoveries also makes planning firm schedules and deliverables tough.
- Inherently chaotic but ultimately will benefit real people



Evaluation

- Together with Athena Uni. (PARADIGM)
- First discussion with DMD CAB 30 November 2018 and how to define metrics
- Table of possible topics discussed yes/no if yes, main contribution:
  - Target population
  - Study feasibility, practical
  - Consent letter
  - Endpoints, including PRO
  - Comparators
  - Quality of Life
  - Standard of Care
  - Compassionate use
  - Pricing, market strategy

Thank you for your attention.

Rob and François

CABs

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EURORDIS.ORG

Cystic Fibrosis CAB

A company perspective

Flaminia Macchia, Vertex

The CF CAB : history

- CFE initiative to talk in a structured and transparent manner with industry; it began as a “pilot” with Vertex because Vrtx is currently the only company with CFTR modulators on the market;
- Important to know that CFE is meeting also with other companies active in CF;
- First Brainstorming meeting between Vertex and CFE, its members selected by CFE, and EURORDIS experts on setting-up CABs in Rare Diseases;
- “Unchartered territory” for Vrtx and CFE, we decided to learn and improve together along the way - rather than waiting to have the “perfect” CAB;
- Important moment to start this sort of open dialogue without any further delay;
- CFE has developed several documents to define the cooperation;
- 25th October it will be the 4th meeting of the CF CAB with a part dedicated to lessons learned and areas for improvement;
- Two operational persons, one at CFE and one at Vertex.

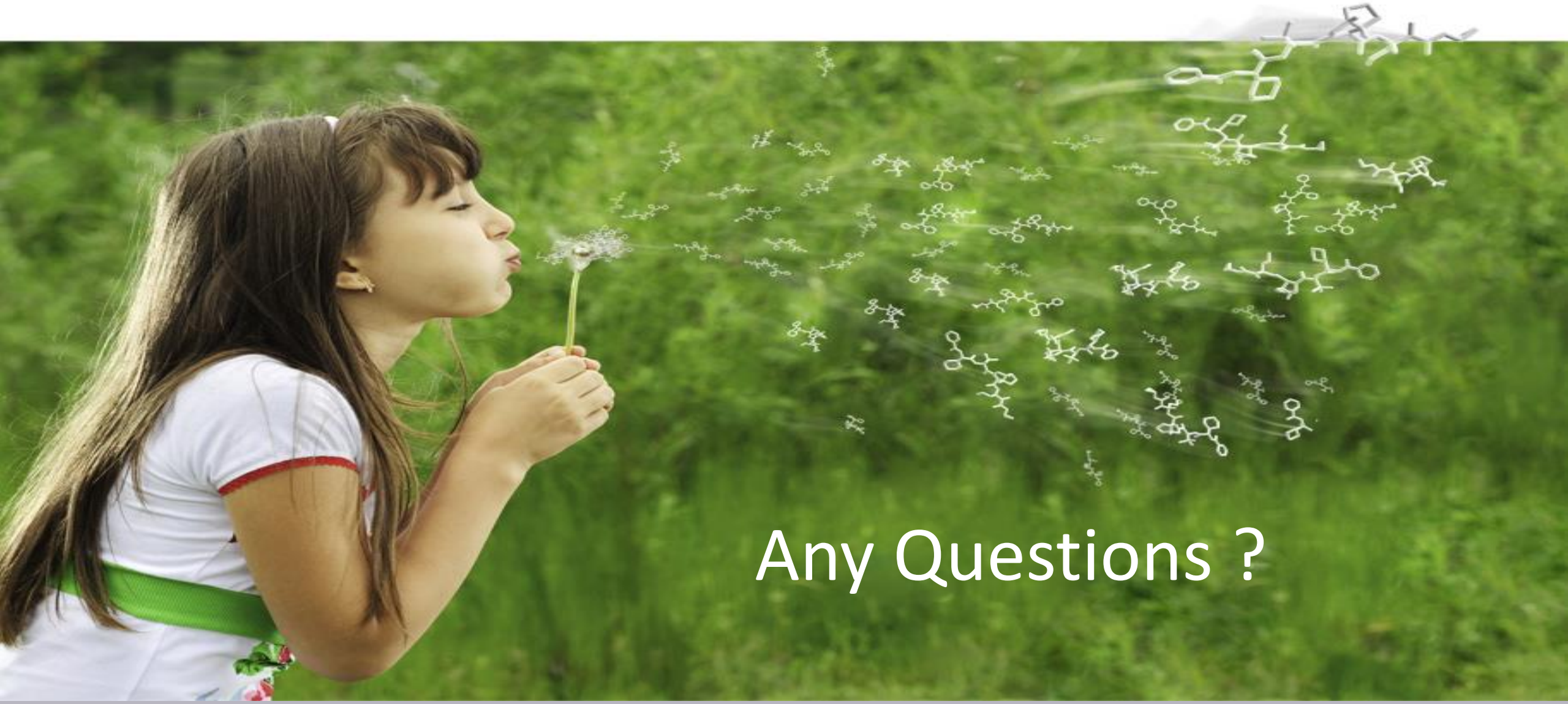
Benefits of the CAB dialogue

From the Company's perspective:

- Opportunity to get the patients' perspective informing the clinical development process and the post-approval data generation plan
- Opportunity to get feedback on Vrtx Pipeline and if/how the portfolio meets the needs of patients;
- Opportunity to exchange on (sometimes complicated) situations and get - at times tough - questions → opportunity to respond;
- Establish a two-ways dialogue and build trust;
- Get expert advice on endpoints, PROMs, QoL;
- Get a reality check of what patients/families need and expect and think;
- Get in put towards a more patient-focused development process of Vertex medicines;

Key Success Factors

- Real commitment and Support from the Leadership;
- Trust internally and externally;
- Motivation and “stubbornness” from the two operational persons : never give up;
- Development of - and agreement on - good boundaries for the collaboration (key documents);
- “Mentorship” and moderation (EURORDIS);
- Selection by the EU umbrella (CFE) of motivated participants, with different skills and background, as well as representativeness of disease heterogeneity;
- Expertise being recognized and valued;



CABs
EUCOPE's initial views

Dr. Andreas Reimann, Admedicum

Why a position paper on CABs?

Intentions

- EUCOPE members welcome the EURORDIS CABs initiative
- Fully supportive of involvement of patients in the R&D process
- Good patient engagement practices and impact measurement are key
- Concerns mainly regarding practical feasibility and agility
- Members heard from some patient organizations about similar concerns
- Goals of Position Paper:
    - Express the strong support of EUCOPE members
    - Comment on the expected benefits of CABs for patients and industry
    - Identify and discuss major concerns regarding downsides and challenges
    - Outline conceptual approaches for solution and propose collaboration

Major Benefits and Chances

For Patients and Industry

- Sufficient evidence out there of high value of continuous patient engagement starting early in the R&D process
  - Translating the principle of “patients first” into practice
  - Improved collaboration between patients and industry leading to overall better and more efficient drug and final product development as well as patient access.
- Clear guidance on how to do it right still lacking
- Possible major benefits of EURORDIS CABs entail input and impact on (non-exhaustive):
  - Efficient non-redundant discussion of **pre-competitive subjects**
  - Best understanding of **actual patient need** (pre-competitive) for **design of research** program before investment (confidential)
  - Chance to facilitate higher **mutual data transparency** and data sharing
  - Regulatory and HTA **patient-relevant evidence** generation in and outside of RCT
  - Efficient and patient-friendly CT **recruitment and retention**
  - **Patient access** related subjects

Some perceived challenges

Feedback from EUCOPE members

Agility:

- High burden for patients
- Capacity issue at EURORDIS:
- Involvement of EMA and EUnetHTA if not EURORDIS run?
- Timing: Operational Matching Challenges
- EU vs. US and global: only a few sites in Europe?

Mutual Trust and Acceptance:

- “Questions and discussions run by patients”: Agenda must be worked out jointly.
- How to deal with the diversity of the players: one size fits all really possible?
- Measuring impact: Does it move the needle at EMA and national HTA

Organizational challenges:

- Early patient engagement vs. current status
- Strict conflict of interest rules of CABs in rare diseases?
- Confidentiality and ownership of results (not confined to CABs)
- Country specific compliance requirements (not confined to CABs)

Proposal for Joint Solution Finding

Multi-stakeholder MoU

Work on a Memorandum of Understanding (MoU):

- EURORDIS, selected POs and EUCOPE members, others tbd
- Flexible additional ways of CABs
- Collaboration framework/checklists/accreditation:
  - Identify and jointly communicate on evidence for value
  - Definition of most relevant agile CAB-like models
  - Consensus based CAB principles to apply to any model
  - Potential roles of EURORDIS and e.g. EUPATI fellows or others outside of EURORDIS-run CABs
  - Ensuring joint learning also from these models
  - Measures to be taken within industry to enhance early PE

ONWARDS TOGETHER

Thank you!

III. Increased collaboration in rare disease Research and Development

European Reference Networks

- EUCOPE's position
- Update on EC & Member States' activities

Secretariat

SUSTAINABILITY OF ERNS & INTERACTIONS WITH INDUSTRY

EUCOPE recommendations

1. Rationale for ERN-industry collaboration
2. Funding & sustainability of ERNs
3. Areas for ERN-industry collaboration

SUSTAINABILITY OF ERNS & INTERACTIONS WITH INDUSTRY

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EUCOPE recommendations

1. Rationale for ERN-industry collaboration

Challenges in the rare disease space:

- **Scarce & scattered** disease knowledge and expertise
- High level of **heterogeneity** of rare diseases
- **Diagnosis odyssey**

A fundamental partner throughout R&D / access pathway to rare disease treatments

- potential to stand as the **backbone for rare disease research and development**
- An essential role in **improving diagnosis, prevention and treatment** of rare diseases and healthcare delivery for patients

A tremendous source of knowledge:

- Access to a **pooled set of information** on a given condition
- Data collection, **RWE generation**

SUSTAINABILITY OF ERNS & INTERACTIONS WITH INDUSTRY

EUCOPE recommendations

2. Funding & sustainability of ERNs

Despite the benefits of EU funding schemes, need to **diversify funding** to ensure optimal functioning of ERNs to deliver.

- **Project funding** to support specific research-related activities, i.e. on registries, in a number of ERNs.
- **In kind support**, for certain specified activities, where industry's experience may become relevant (i.e. IT or data-sharing companies)
- **Public private partnerships**

Proposal to fund ERNs via **corporate social responsibility deemed inappropriate** (compliance issues).

SUSTAINABILITY OF ERNS & INTERACTIONS WITH INDUSTRY

EUCOPE recommendations

3. ERN-Industry collaboration

In favour of the establishment of a collaboration framework between ERNs & industry, in line with the *Nov 2016 principles*:

- Industry **not to be involved in governance** or operational activities in relation to **healthcare delivery**.
- Industry **to be involved in ERNs' work on research and availability of rare diseases medicines** (clinical trials, knowledge & expertise-sharing, RWE-generation & sharing).
  - Industry to be involved in ERN Coordinators Group on Research

Suggestion to adopt a **pilot-approach** to explore solutions and build trust.

Possible areas of research activities: clinical trials, evidence collection & sharing, registries.

SUSTAINABILITY OF ERNS & INTERACTIONS WITH INDUSTRY

Next steps

Board of MS Statement

Revision

Position on interactions with industry

Coordinators, MS (and their national experts) to discuss and decide

FederReg©: The path for Research & Industry to collaborate in Rare Disease data collection

George Reynolds, RareUrn

FederReg©: The path for Research & Industry to collaborate in Rare Disease data collection

RareUrn

George Reynolds: Managing Partner

Providing independent consulting in clinical data collection strategies for rare disease research

A subject matter expert in ERNs Registries and RWD in Europe

Delivering a proactive data collection roadmap to avoid Dead End Data.

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George Reynolds Background

- Over 30 years' experience in green field business development and partnering for software companies in the UKI, EMEA and US.
- Worked exclusively for the last 6 years in the rare disease space.
- Managed multiple complex registry programs including Cystic Fibrosis, Epidermolysis Bullosa and Haemophilia
- Managed Pharma partnerships with Vertex (Orkambi), Biogen (Spinraza) and Shire (Haemophilia).
- Since 2013 has run the rare disease registry division of VItro Software and OpenApp helping them become the main European IT players in the ERN and registry software markets.
- Responsible for submitting the winning tender to the European Commission for the €5M contract to deliver the CPMS platform for all 24 European Reference Networks.
  - This game changing system is currently being deployed in over 300 hospitals throughout Europe.
- Currently providing consulting on registry programs in Vasculitis, Pulmonary Fibrosis, Gauchers and Brittle Bone (OI) disease areas.

RareUrn

The 1st problem: Ad Hoc registries produce Dead End Data

To comply with US Sunshine Act and European ToV guidelines Pharma need distance from Patient Organizations

Pharma needs access to anonymised data to verify reports provided to regulators

National registries are developed by doctorate students & delivered as unsupported open source solution: "Professorware"

Pharmas tend to provide funding to patch up these registries when required

Standard registries will not meet EMA requirement for timely reporting of Adverse Events

Without sustainable funding, data is patchy with duplicate, missing & erroneous fields

When market authorization is obtained it is too late to get verifiable longitudinal clinical data to prove efficacy for HTAs

Payers will only agree to reimburse the optimized cohort of patients used to pass Phase III.

This severely restricts the potential market for your treatment

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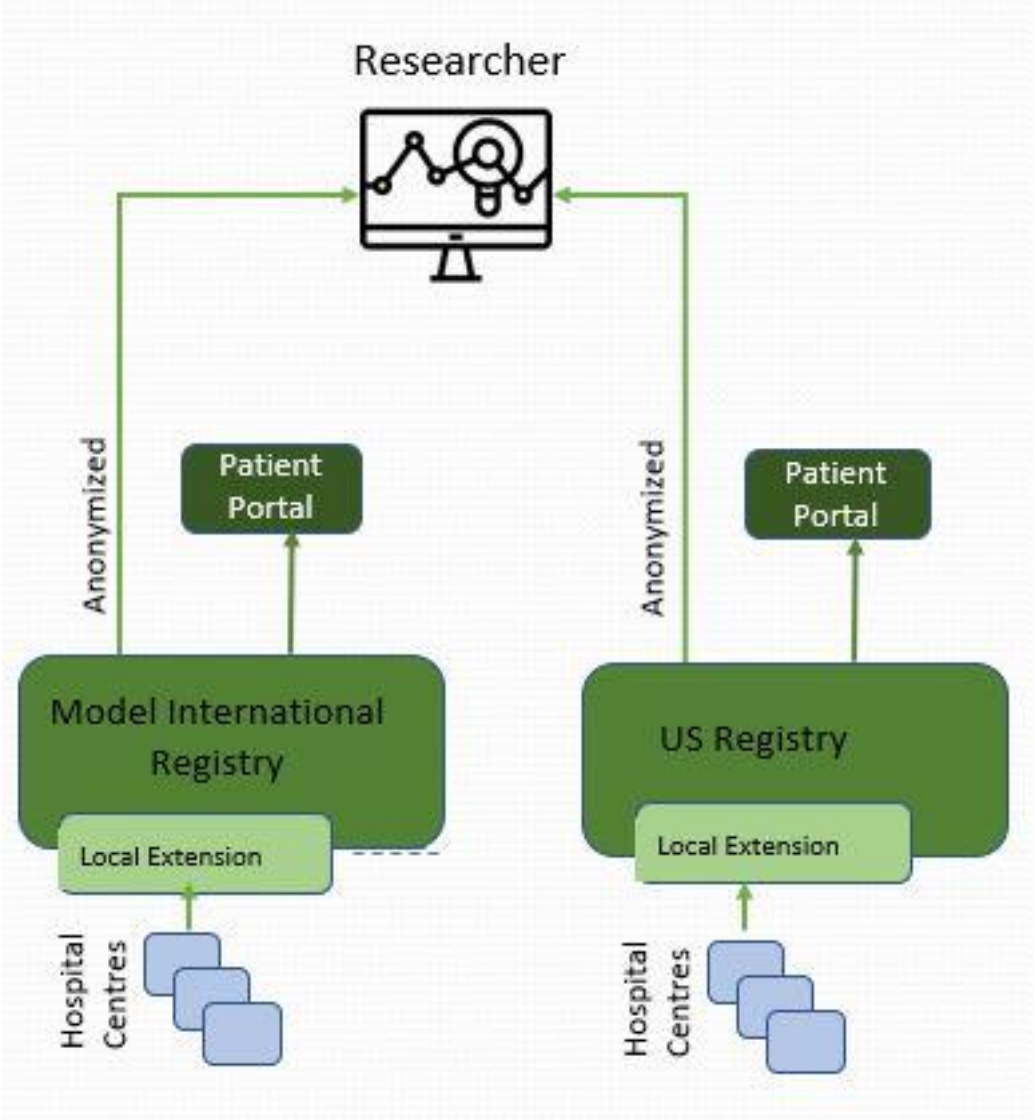
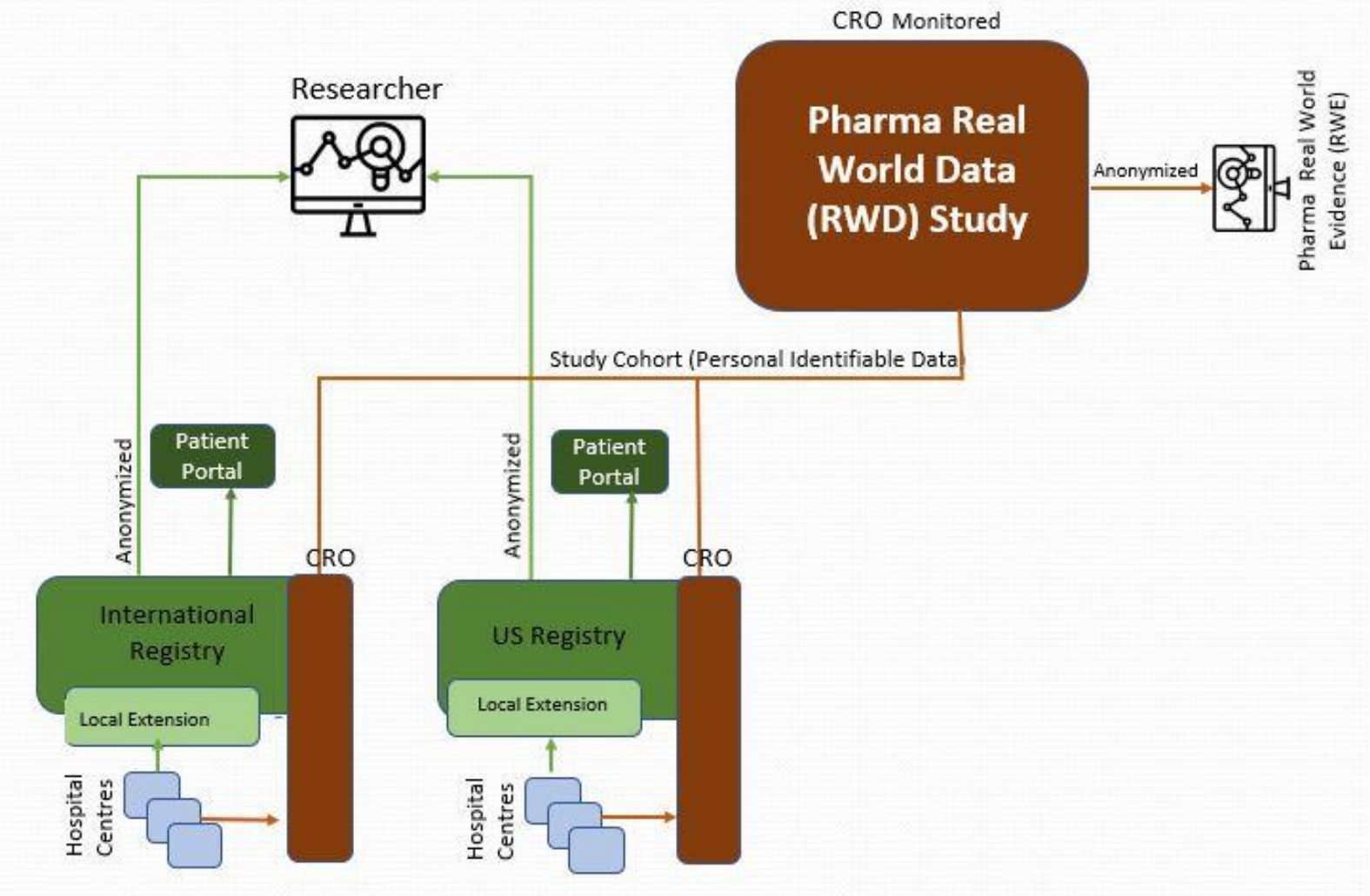
Solution: FederReg A platform that merges the data needs of Pharma, Patient Organizations and the Research Community

RareUrn

FederReg 1st phase: Model registries US and Europe



FederReg 2nd phase: Add the RWD study platform



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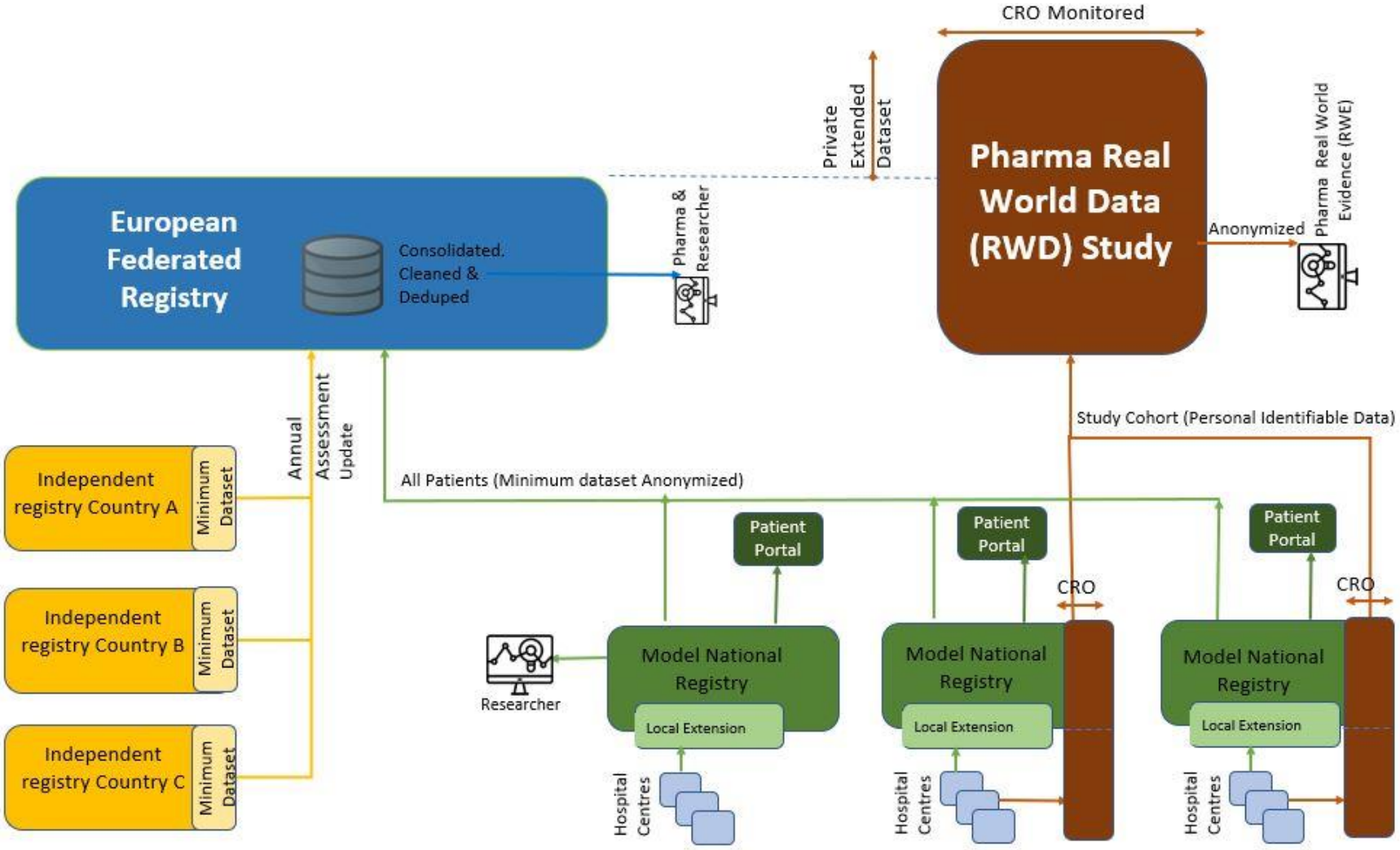
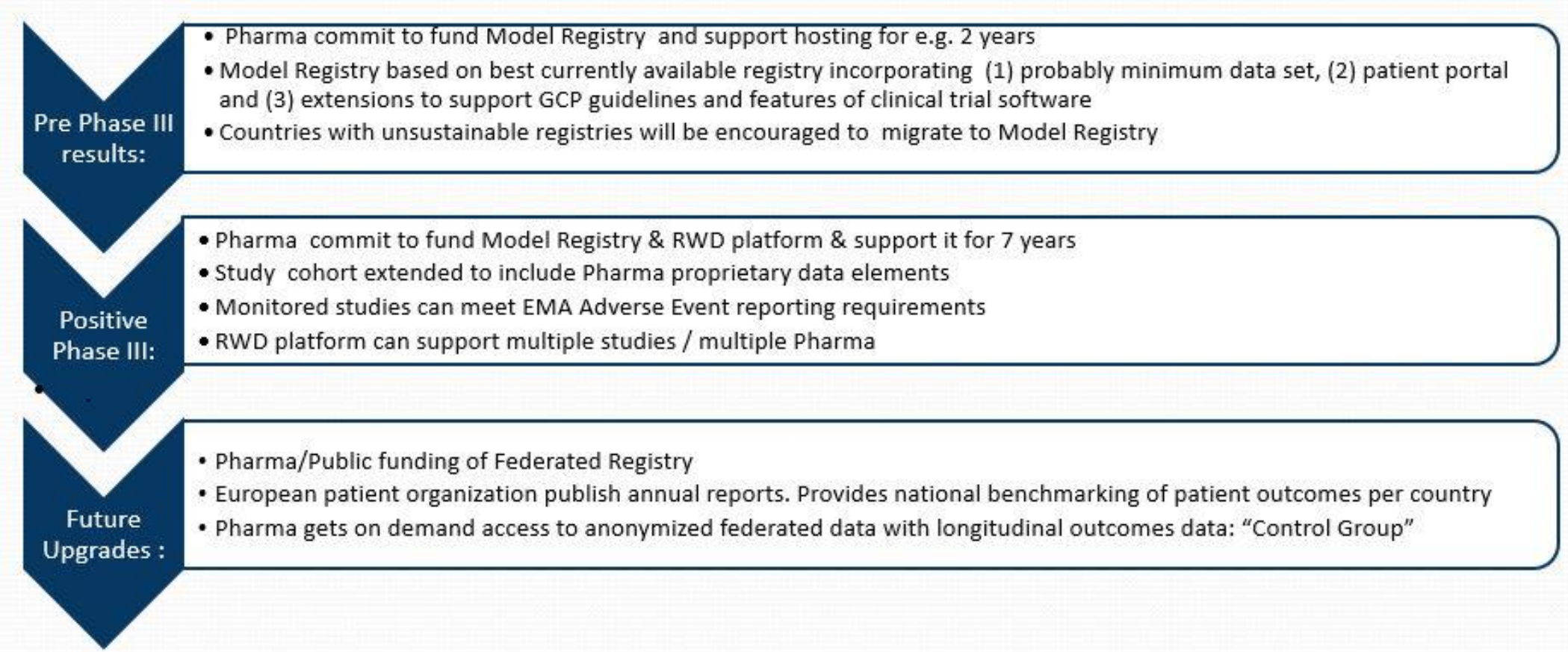
FederReg 3rd phase: A fully developed network registry



RareUrn

FederReg Roadmap outlines enhance commitment to stakeholders as candidate product passes clinical milestones



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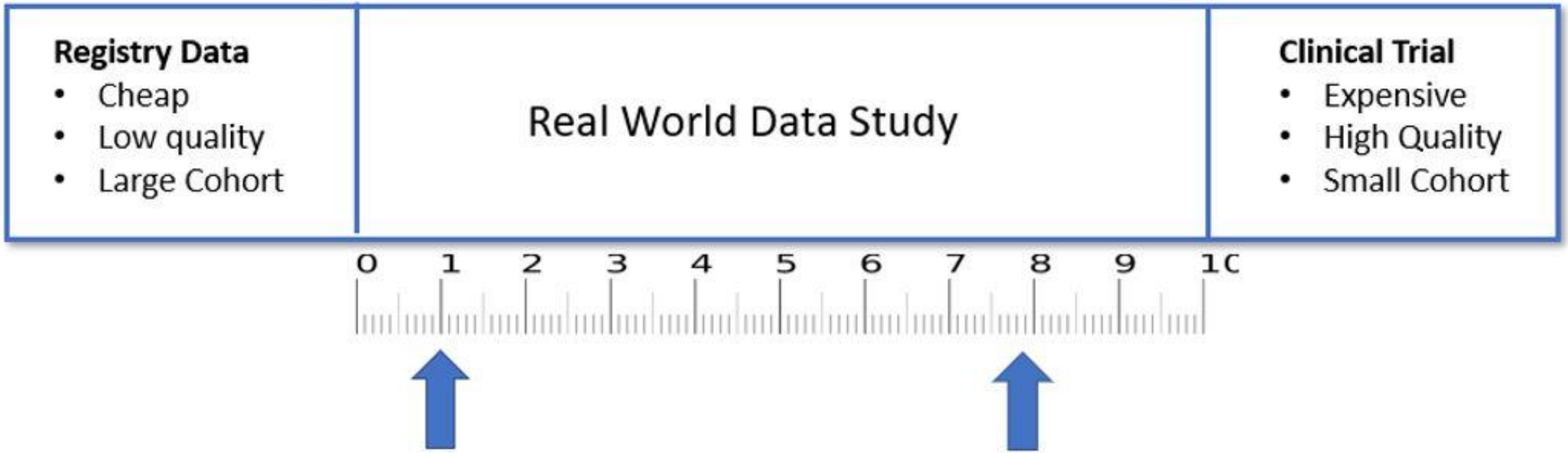
Advantages for Pharma

- Phased release of software platform: (1) National Registry, (2) RWD platform
- (3) European Federated Platform
- Pharma gets on demand access to anonymized federated data with longitudinal outcomes data: "Control Group"
- The Data Collection Roadmap outlines which 3rd party research funding proposals Pharma will support
- Pharma can run multiple RWD studies. Scaling as required between low cost unverifiable registry data to high cost verifiable Clinical Trial compatible observational studies
- Platform is available for pivotal studies for other Pharma who wish to invest in its future sustainability and upgrade path.
- Based on Real World Success: European Cystic Fibrosis Registry and Vertex cooperated successfully in developing dual platform for Orkambi study

RareUrn



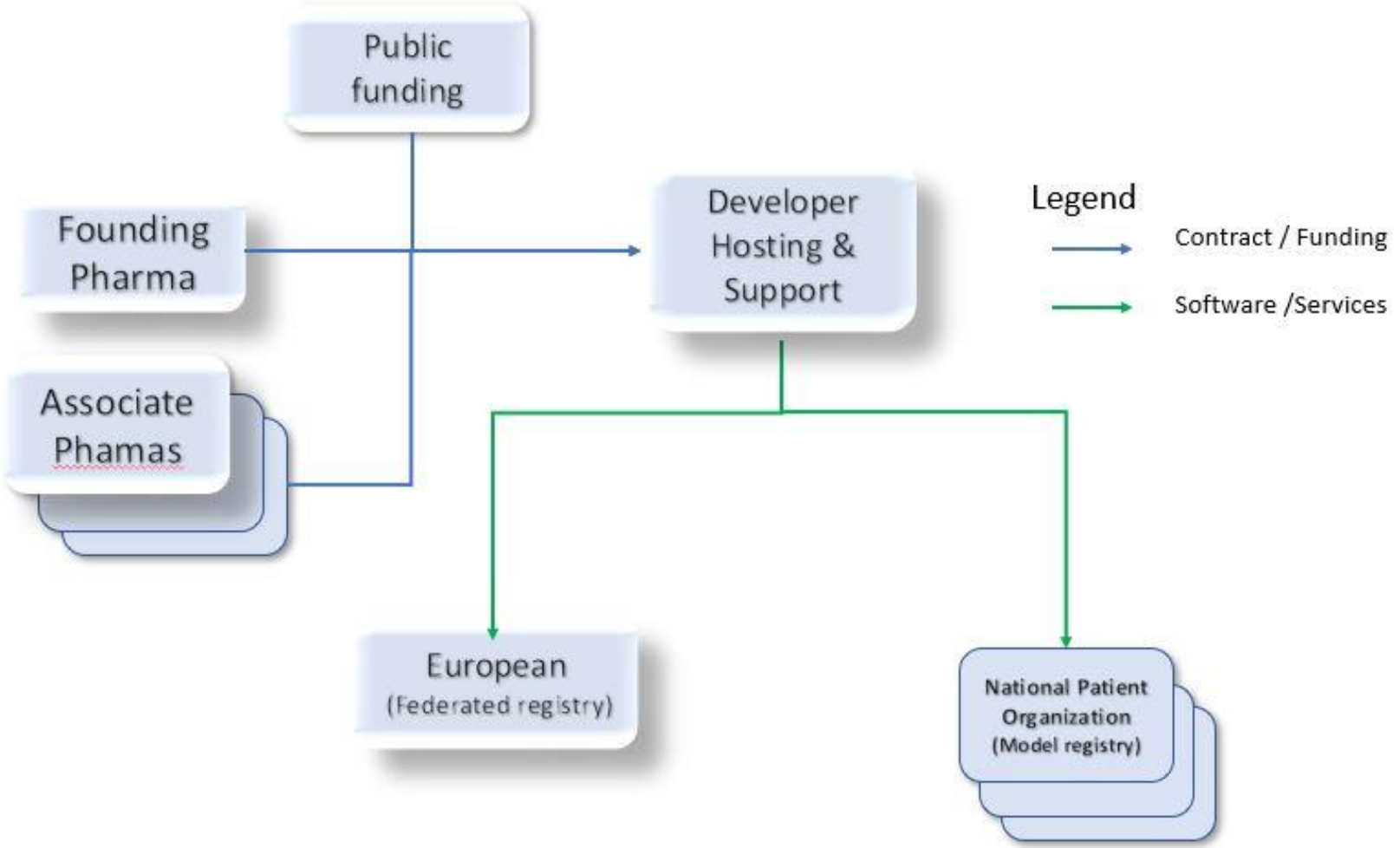
Flexible architecture will allow Pharma to set the cost/ data quality "dial" to make a study more like a registry or a clinical trial: as required

Advantages for Researchers & Patient Organizations

- Patient organizations receive a sustainable, state of the art registry for a minimal cost
- Pharma will not influence the scientific direction of the Model or Federated registry
- Supports existing sustainable registries & provides a platform for new registries that can be extended to support national data collection
- Loose Federated structure supports integrating data from registries at all stages in evolution
- The integrated patient portal will encourage patient and clinician enrolment and participation in data entry
- Patient organizations are not for profits. The 3rd party hosting company will make it easier for patient organizations to comply with GDPR
- The European wide registry provides significant deliverables to the patient organizations . Patients outcomes and standards of care can be compared across countries: Benchmarking

RareUrn

Funding Contracts & Services



RareUrn

Which Software Platform: Open Source / Proprietary

- No advantage or need for Pharma or development partner to use proprietary solution
- Open Source options
  - Redcap https://www.project-redcap.org/ ; https://www.redcapcloud.com/
  - https://www.openclinica.com/
  - Both have commercial solution built on top of opensource platforms
  - Both have large active user communities
  - Possible for national patient organizations to extend Model registry themselves whilst following the core approved dataset to integrate with RWD platform and Federated Registry
- Issues for development partner
  - Concern with response time & control. Pharma needs a responsive proactive development partner
  - Concern over conflicting goals and transient resources: "Professorware"....
  - Pharma needs full access to IP (source code) in case registry partner fails to deliver
  - Pharma needs to commit to stakeholders to host and support model registry for e.g. 3 years
  - Pharma needs to distance themselves from ownership of software or direct funding of patient organizations
  - By specifying the open source platform, Pharma can use multiple vendors

RareUrn

The other challenge: How Pharma can cooperate with ERNs:

- ERNs provide a list of validated centres of expertise
- ERN data architecture is similar to the architecture mandated by Clinical Trails (security, audit trail, encounter recording)
- **HOWEVER**
  - The Board of Member States will not allow funding by Pharma to avoid bias: The latest proposal is to make general contribution to a pool of funds....
  - ERNs are not legally incorporated

- Pharmas are regulated and need to contract with a legal entity
- Under the new European General Data Protection Regulation (GDPR), a Data Controller is any party who controls access to the Patient Data
- Data Controllers have significant responsibilities.
- As ERNs are not incorporated they cannot act as a Data Controller

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RareUrn

Pharmas and ERN: Common solutions to data collection problems

- ERNs have solved a lot of RWD problems:
  1. Defining centres of excellence
  2. Agreements on share data across borders
  3. Defining common datasets & interoperability standards
  4. Defining pseudonymisation and consent standards

- ERNs should be seen a catalyst : Link through ePAG
- Pharma are focused on their specific disease; not the general ERN
- An incorporated European Rare Disease Patient Organization is required to manage GDPR Data Controller responsibilities & consent
- Working in parallel with the ERN will simplify adopting future ERN policies on registries and research

RareUrn

IV. EMA discussion paper on the use of patient registries for regulatory purposes

Maren von Fritschen, EUCOPE

EMA patient registry initiative

Launched, September 2015 - set-up of a Cross-Committee Task Force

- Aims to facilitate use of disease registries by introducing and supporting a systematic approach to their contribution to the benefit-risk evaluation of medicines.
- Promote dialogue between regulators, companies and registry holders to understand barriers and opportunities of using disease registries.

- Pilot phase, 2016: Stakeholder feedback for greater utilisation of **disease registries**
- 28th October 2016 - Patient Registries workshop

Registries definition used by EMA

EMA: „*Registries are organised systems that use observational methods to collect*

- ***uniform data on a population***
- *defined by a **particular disease**, condition, exposure,*
- *and that is followed **over time**.“*

Strom, Pharmacoepidemiology, 2006: *„Registries are a systematic collection of*

- ***defined events** of product exposures*
- *in a **defined patient population***
- *for a **defined period of time“***

Registries – EMA activities

- EMA initiative for patient registries since **Sept 2015** aiming at a strategy on registries and a pilot phase to test whether this strategy better supports MAAs/MAHs to meet regulators' (and potentially other stakeholders') needs for data and information.
- Cross-Committee **Task Force on registries** established in late 2014

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 May 2017
EMA/180341/2017
Inspections, Human Medicines, Pharmacovigilance and Committees Division

Patient Registry Initiative- Strategy and Mandate of the Cross-Committee Task Force
EMA Initiative

EMA Patient Registries Workshop, Oct 28 2017

- Identify the challenges in collaboration
- Understand the technical challenges presented by disparate datasets
- Identify concrete solutions to better facilitate cooperation, avoid duplication and facilitate timely collection of relevant data.

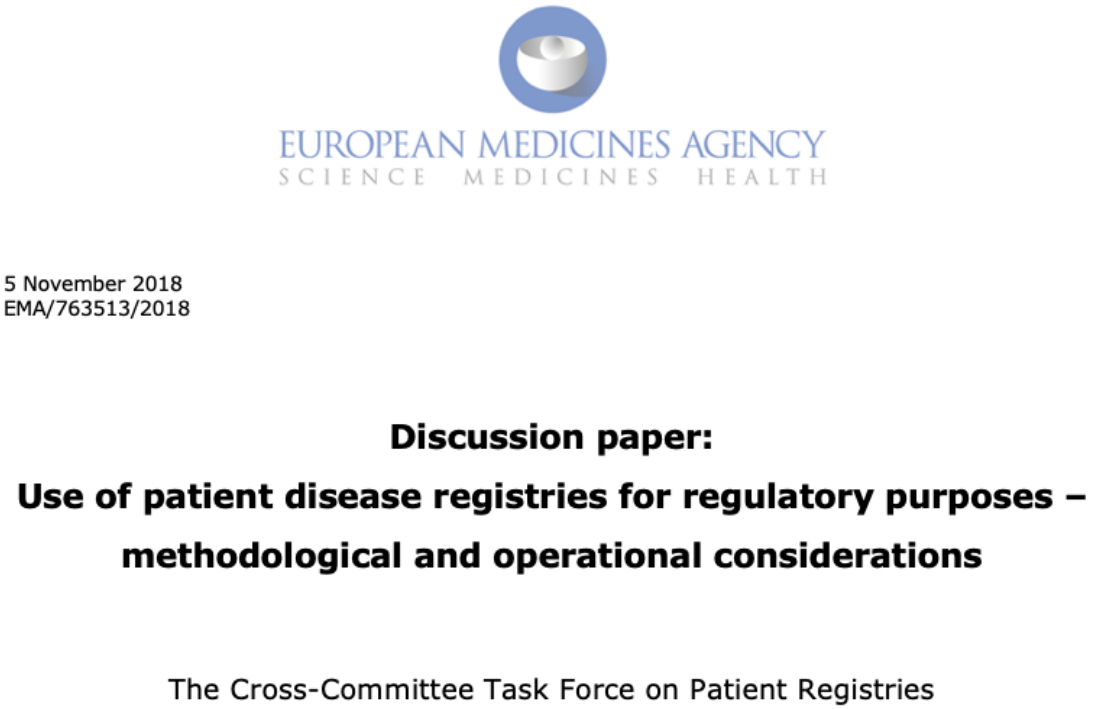
EMA patient registry initiative – current status

Specific workshops

- June 2017: Cystic fibrosis registries
- July 2017: Multiple sclerosis registries
- Febr 2018: Registries for CAR T cell therapies
- June 2018: Haemophilia (Factor VIII) registries

EMA discussion paper

Use of patient disease registries for regulatory purposes


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 November 2018
EMA/763513/2018

Discussion paper:

Use of patient disease registries for regulatory purposes – methodological and operational considerations

The Cross-Committee Task Force on Patient Registries

- On 8 November 2018 the cross-committee task force published a discussion paper on **methodological and operational considerations** in the use of patient disease registries for regulatory purposes
- **Comments by 30 June 2019**
- EMA will finalise document by the end of 2019

EMA paper on patient disease registries

EUCOPE contributors: Alexion, Biomarin, Covington, Orphazyme, Ultragenyx

General comments:

- Specific considerations for rare disease
- Global alignment with other jurisdiction (e.g. US Agency for Healthcare Research and Quality, AHRQ),
- Consider other initiatives (e.g. EUnetHTA WP5B, national HTA bodies, WHO; medical devices
- Consistency with CTR (registry studies)
- Recognize the value of product registries
- Harmonized standards (ISO-IDMP / SPOR)
- Broaden “Informed consent” / GDPR

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 March 2019

Submission of comments on EMA’s Discussion paper on the use of patient disease registries for regulatory purposes – methodological and operational considerations

Comments from:

Name of organisation or individual
European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) Rue Marie de Bourgogne 58 1000 Brussels Belgium

V. National updates

An update on the German Parliament discussions on the Draft Law for More Safety in the Supply of Medicinal Products (GSAV)

Alexander Natz, EUCOPE

Compounding and compulsory licensing in the Netherlands and EUCOPE's activities

Andrea Corazza, FTI Consulting

Dutch context

- NL has been driving discussion on price and access to medicines since their EU Presidency (IP review, BeNeLuxA, etc.)
- Led by sustainability concern and distrust in industry driven by individual cases (most recently Laediant)
- Polarization of the public debate – highly emotional / political

NL government objectives

- Affordability of medicines
- Financial sustainability of healthcare system
- Access to innovative medicines

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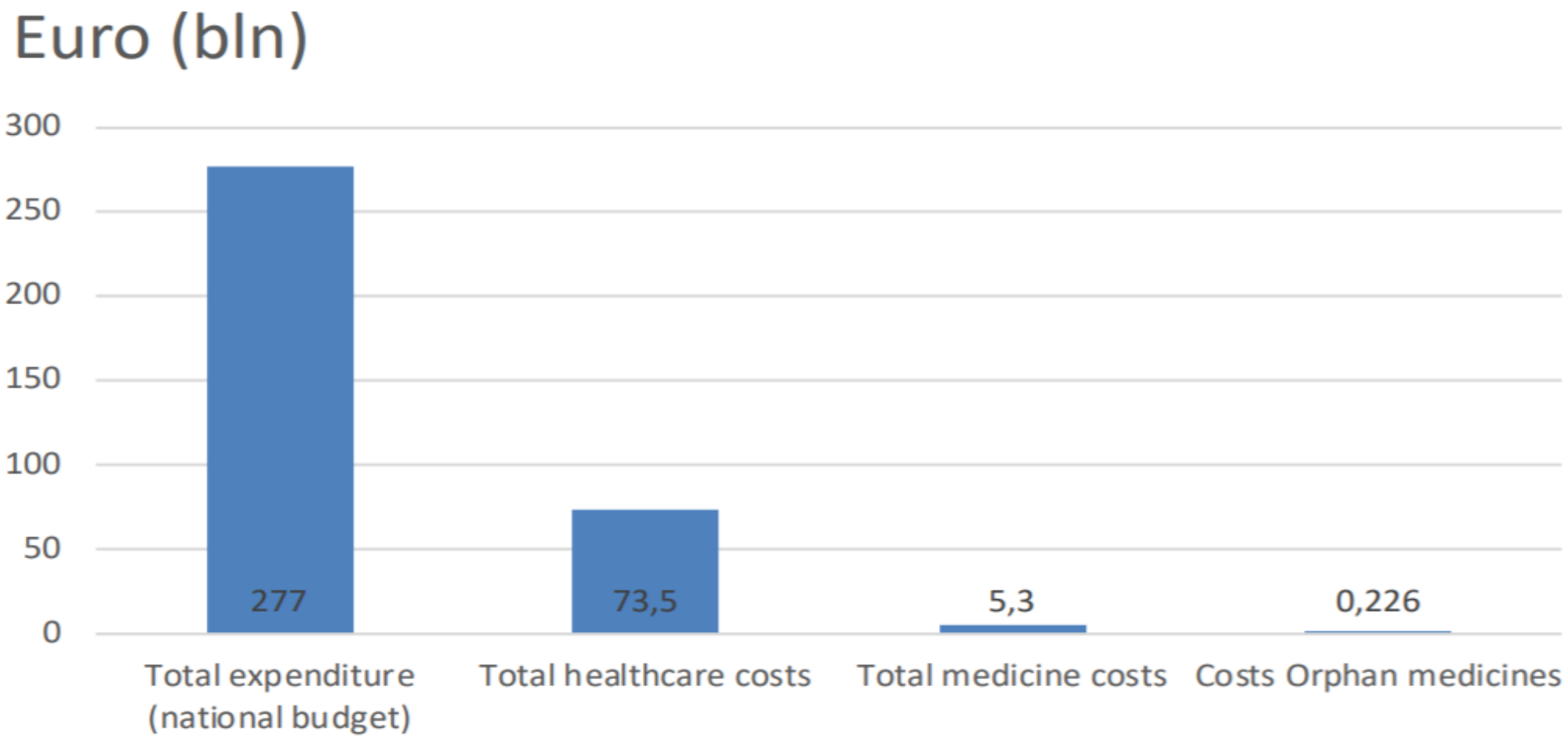
A real concern?



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Mixed targets of Dutch actions

Pricing & Reimbursement

- Transparency of R&D cost
- Comparison with unlicensed alternatives

Research & Development / IP

- Compulsory license threat
- IP review at EU level "***Why should a manufacturer have a monopoly for 10 years if there are no high investment costs?***"

Regulatory

- Use of compounded products instead of licensed ones
- Jeopardising of the EU regulatory system

Recent developments on compounding

- 19/11/2018 - IGJ Decision (Health inspectorate) about **OMP compounding to be considered small scale**, and thus compliant (Laediant's CDCA case) – this was openly supported by Minister Bruins
- 18/12/2018 - New KNMP (Dutch pharmacist association) guideline: **allowing for compounding high costs products** (before only if available products weren't satisfactory for patients)
- 19/12/2018 - NZa (Dutch Healthcare Authority) confirms **reimbursement for compounded products** even if authorised alternatives are available (from 1/01/2019)
- 20/12/2018 - Minister Bruins saying **compounding is an alternative to licensed product even if there is no excessive pricing**
- 1/02/2019 - Entry into force of "pharmacist exemption" to patent law which allows pharmacies to prepare patented drugs (**Dutch Patent Act exception**)
- 7/02/2019 - **Parliamentary debate** in the Netherlands on framework for compounding
- 8/04/2019 - **Letter of Minister Bruins to the Dutch Parliament** on compounding

Compounding is allowed and reimbursed small and large scale in disregard of any authorised product being available in the market

- *De facto*, **new regulatory framework in the NL** until the court will step in and block these decisions

Letter to the Dutch Parliament

"*The use of authorized medicinal products remains the starting point. Obviously, against a reasonable and acceptable price. If a financial arrangement has been concluded with me, in my view, there is a acceptable price of that particle medicinal product*."

Guidelines provided on "small scale":

- Dispensing to several to approx. 50 unique patients per month with long-term use of the medicinal product;
- Dispensing to approx. 150 pts per months with short-term use.

Is there a risk for orphan products? what's the total patient population? In each pharmacy? How long is long-term use? Is there a limit?

Patent exemption (art 53 DPA)

- Patent exclusive right does not extend to acts which serve pharmacists exemption.
- Introduced on 1 Feb 2019 but old law from 1980.
- Similar exemption exist in other EU countries, inc. FR, DE and UK.
- Clearly favour Narrow scope (explanatory statement):
  - *“exemption intended for the preparation of medicines for direct use for individual patients and on medical prescription in pharmacies”.*
  - *“the preparation of larger quantities of medicines for more patients, as is the case in hospital pharmacies, is not permitted. “*

Risks of economic compounding

- Compounding vs Authorised Medicines:
  - No **clinical trial** (not demonstrated their efficacy or safety profile);
  - Quality of the **active ingredient** (pharmacist is not obliged to disclose the source);
  - Not subject to **GMP** requirements (stability and quality of the product);
  - Not subject to **pharmacovigilance** practice in contrast to commercial drugs;
  - Act of compounding increases the **risk of contamination**.

- These practices are:
  - Threatening the European regulatory framework;
  - Endangering European patients' health and safety;
  - Disincentivising medical innovation in areas of great patient need;
  - Affecting the business of pharmaceutical companies.

Compulsory licensing

- Minister Bruins considers compulsory licensing cold be "*used as a means of pressure to get the prices of medicines down*" (December 2017).
  - Special committee investigating whether he can give other manufacturers the right to have a substance copied in the future if a pharmaceutical company refuses to reduce price.

- Art 57 Dutch Patent Act provides for the Minister of Economy the power to issue CL:
  - In the public interest
  - First investigate if patentee is willing to license
  - Reasonable conditions
  - Negotiate a reasonable compensation
  - No obligation to supply when there is a compulsory license

EUCOPE WG on Unlicensed Medicines

Who we are?

- The group was created in 2016 to tackle economic off-label and compounding.
- Coordinated by the EUCOPE Secretariat with the support of FTI Consulting.
- All funding for this Working Group is provided through additional members' financial contributions from the group's members.
- Members include: Biogen, Novartis, CTRS, Santhera, Oprhan Europe, and any interested EUCOPE member.

On compounding:

- EUCOPE **position paper** in June 2016 and a policy paper in November 2017.
- Educating stakeholders through a number of **meetings and a roundtable** in Brussels.
- Commissioned to Springer Medical a **report on patient safety issues** associated with the use of compounded medicines as alternatives to approved pharmaceutical products in Europe.
- Support to **individual members' responses** to compounding affecting their products.
- More to be done at national level to protect the regulatory framework…

VI. EUCOPE Study on the EU OMP Regulation

Martina Garau & Mikel Berdud, OHE

EUCOPE
European Confederation of Pharmaceutical Entrepreneurs AISBL

A Study on the Regulation of Orphan Medicinal Products in Europe

Presentation for the EUCOPE Members Board

15 May 2019

Outline

1. Introduction: background and objectives
2. The financial challenge of developing OMPs
3. The value of OMPs
4. Competition between OMPs for “rare indications”
5. Timelines and next steps

Outline

1. **Introduction: background and objectives**
2. The financial challenge of developing OMPs
3. The value of OMPs
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Introduction

Background

- The European Commission (EC) recently commissioned a study (to Technopolis) to assess the effectiveness of the OMP Regulation, with the view to publish a report in Q3 2019.
- EUCOPE has identified several aspects and perspectives which potentially will not be addressed in the EC's study and has commissioned OHE to explore them independently
- The aim is to communicate and show all complementary results and evidence to ensure the EC and policy makers take them into account in view of any policy review.

Introduction

Objectives

1. **Conduct a comprehensive analysis of the OMP regulation in the EU**:
   i. The financial challenge of developing OMPs
   ii. The (actual) value of OMPs for patients and society
   iii. Competition in OMPs markets.
2. Results should allow EUCOPE to **build convincing arguments and policy asks to**:
   i. Address any concern the EC may have
   ii. Maintain and improve the current OMP Regulation
3. **Influential and collaborative study**: our study should complement results of the study commissioned by the EC and provide additional evidence-based insights that help shaping the possible review of the OMP Regulation

Outline

1. Introduction: background and objectives
2. **The financial challenge of developing OMPs**
3. The value of OMPs
4. Competition between OMPs for “rare indications”
5. Timelines and next steps

The financial challenge of developing OMPs

Objectives and expected messages

- **The ‘financial challenge’ analysis aims to show that the development of an OMP is a more risky and financially challenging investment than the development of a medicine for a common disease**
- In addition to proving our baseline hypothesis **we also aim** to show that:
  - If characteristics of OMP developer are not properly addressed when analysing profitability misleading conclusions may be drawn for the policy design
  - Financial success of developing OMPs needs to take into account the pre-license development part of the OMPs life-cycle in addition to the post-license part
- **"Expected" messages:**
  - OMP focused companies’ financial performance and success is subject to higher level of risk and it is highly sensitive to changes in OMP regulation
  - Changes in OMP regulations based on analyses that do not take the inherent characteristics of OMP developers and rare diseases can undermine the delivery and access of innovative OMPs in the long term (dynamic inefficiency)

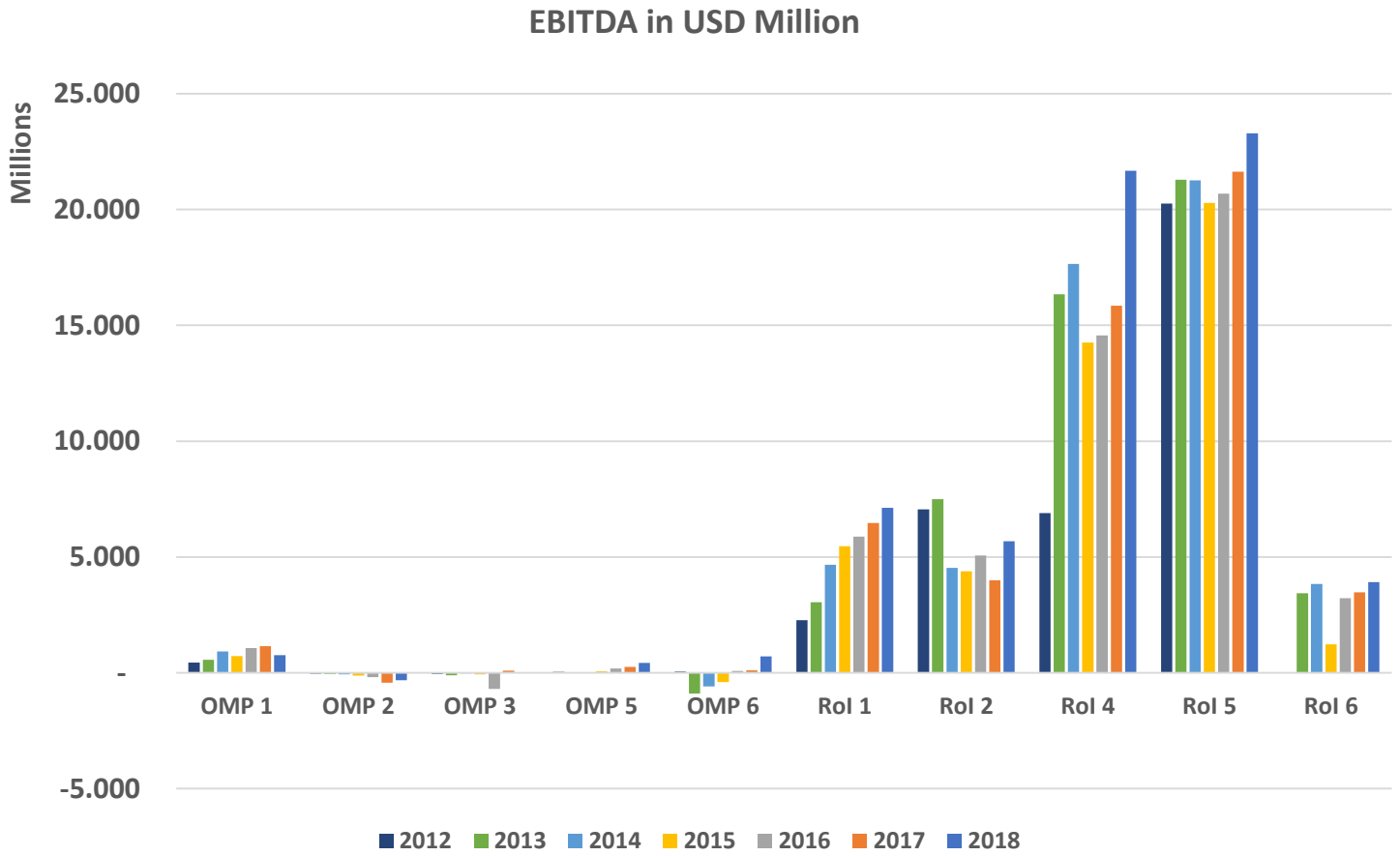
The financial challenge of developing OMPs

Methods and approach

1. **Create a data set** using the current European Commission list of medicines with orphan indication/designation and categorise OMP developers by size and portfolio
2. **Sampling:** select a sample of companies for a comparative analysis (6 OMP focused SMEs vs 6 rest of industry) and time period for the analysis (2012-2018)
3. Perform a **comparative analysis of companies' financial performances** and associated risks – data collected from annual financial reports and Morningstar®
4. Characterise **the business case for an OMP developer**: attrition rates, low target patient populations, size of companies, size of pipeline and product portfolios, expected economic return from investment.
5. Assessment of the **impact of changes in OMP regulation** (scenarios):
    a. Qualitative approach: we assess the impact for OMP developers in each scenario of regulation change using economic arguments - this have been complemented with the assessment of dynamic implications to the amount of innovation that may become accessible to patients in the future
    b. Quantification: we will calibrate each scenario in the NPV model to quantify impacts in terms of economic returns for companies specialised in developing OMPs

The financial challenge of developing OMPs

Some preliminary results

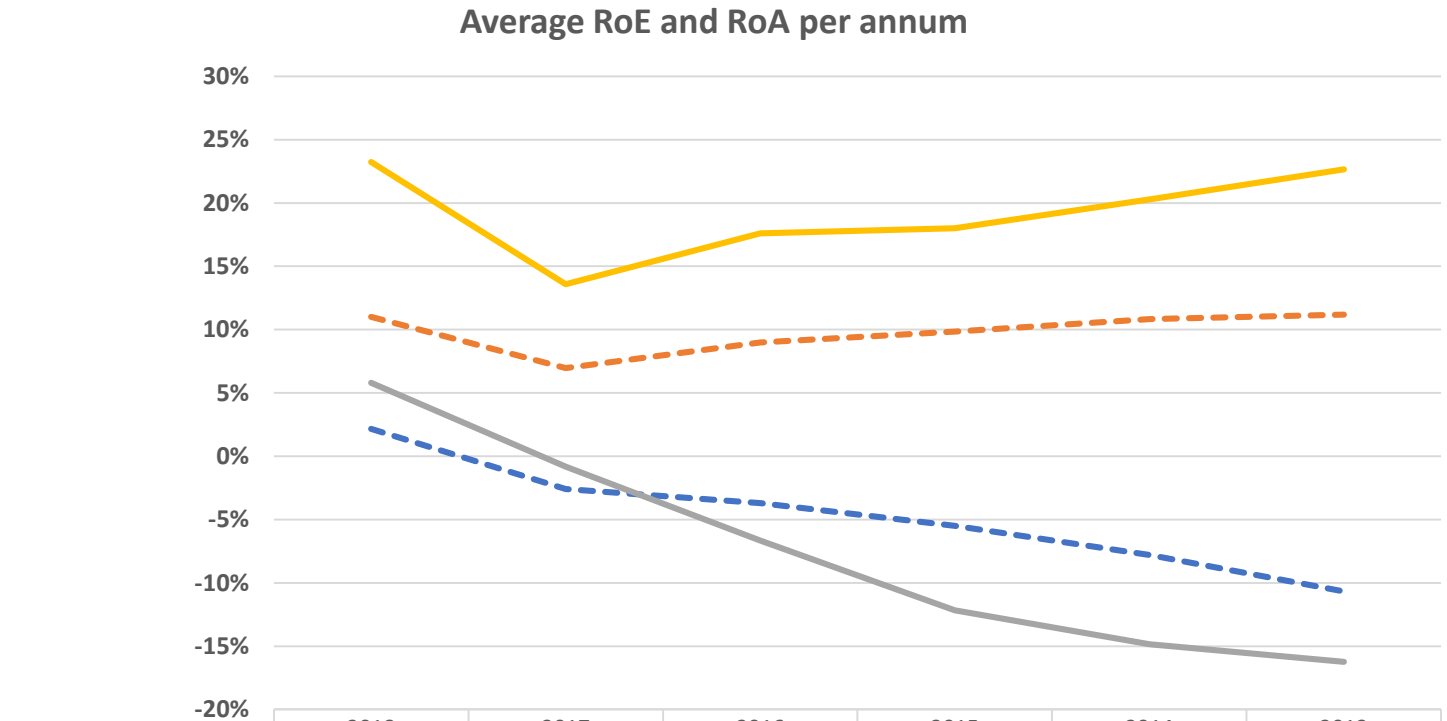


- The biggest difference to mention on EBITDA is that most of the OMP companies, show several years of losses – except OMP 2 all of them well established firms
- EBITDA is consistently positive for RoI companies showing excellent performances in general for all of them
- EBITDA analysis at company level shows that profitability of those companies focusing in OMP is lower, and more volatile, than RoI

Sources: Companies' financial statements, Morningstar®, OHE Consulting Ltd.

The financial challenge of developing OMPs

Some preliminary results



	2018	2017	2016	2015	2014	2013
RoA OMP average	2,16%	-2,58%	-3,71%	-5,49%	-7,81%	-10,68%
RoA RoI average	11,00%	6,96%	8,97%	9,84%	10,83%	11,18%
RoE OMP average	5,80%	-0,82%	-6,65%	-12,16%	-14,86%	-16,24%
RoE RoI average	23,23%	13,57%	17,60%	18,02%	20,28%	22,65%

Sources: Companies' financial statements, Morningstar®, OHE Consulting Ltd.

- Looking at average Return on Equity (RoE %) and Return on Assets (RoA %) we can conclude that:
  - for OMP arm both are mainly negative during the period of analysis (2013-2018), although increasing until positive results in 2018
  - Returns for RoI arm are in average quite stable and positive along all period of study

The financial challenge of developing OMPs

Some preliminary results

Estimation of expected future new product launches based on the pipeline

Arm	2026	2024	2022	2020	Total	Per year	Products already in the market
Average OMP-SME	2.3	0.9	2.3	0.2	5.6	0.8	8.0
Average RoI	1.8	2.9	12.2	5.1	22.0	3.1	44.5

Results of policy change impact analysis at company level

	Baseline 1	Baseline 2	Policy change 1		Policy change 2		Policy change 3		Policy change 4	
	Company 1	Company 2	2y reduction of exclusivity		5y reduction of exclusivity		Protocol assistance removal: 20% decrease of success rates		Policy changes 1 and 3 together	
			Company 1	Company 2	Company 1	Company 2	Company 1	Company 2	Company 1	Company 2
NPV	$17.9m	$75.1m	$8.9m	$50.8m	-$10.2m	$21.9m	-$34.9m	$22.3m	-$43.9m	$5.2m
Revenue Discounted	$225.3m	$426.4m	$197.5m	$373.8m	$138.8m	$262.7m	$225.3m	$426.4m	$197.5m	$373.8m

Source: OHE Consulting Ltd.

The financial challenge of developing OMPs

Discussion of preliminary results and concluding remarks

- Conclusions from financial performance indicators:
  - OMP focused companies show more financial risk, characterized by periods of income (loss) and return volatility
  - RoI arm companies' financial success is more stable and less risky
  - OMP companies require more R&D expenditure per unit of revenue, therefore the risk of failed investments is higher for them
- Conclusions from pipeline and product portfolios: OMP companies' ability to generate revenue in short- and long-run is low and more volatile because it relies on,
  - Low number of marketed products with small target patient populations (small demand sizes)
  - Small pipelines in highly specialised areas
- Conclusions from NPV policy change impact analysis shows that OMP companies financial performance is close to the profit/loss threshold: OMP developers' economic return is highly sensitive to changes in regulation
- Changes in legislation that potentially reduce industry's incentives to keep investing in rare diseases will potentially reduce the number of OMP companies and innovative medicines
- Other less specialized companies which are also currently investing in OMPs (e.g. larger firms with broader portfolio) will adapt to the new environment diverting investment from rare diseases to other more attractive areas

Outline

1. Introduction: background and objectives
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Value of OMPs

Objective

- The aim of the value part is to show that approved OMPs have generated value to:
    - patients (e.g. improving clinical outcomes)
    - their family and carers (e.g. reducing caregivers burden)
    - health care and social care systems (e.g. simplifying treatment pathway and reducing care costs), and
    - potentially led to scientific spillovers
- To show there is an increasing debate around the need for Value Frameworks (VF) capturing the full value of OMPs (as opposed to conventional HTA methods

Value of OMPs

Methods

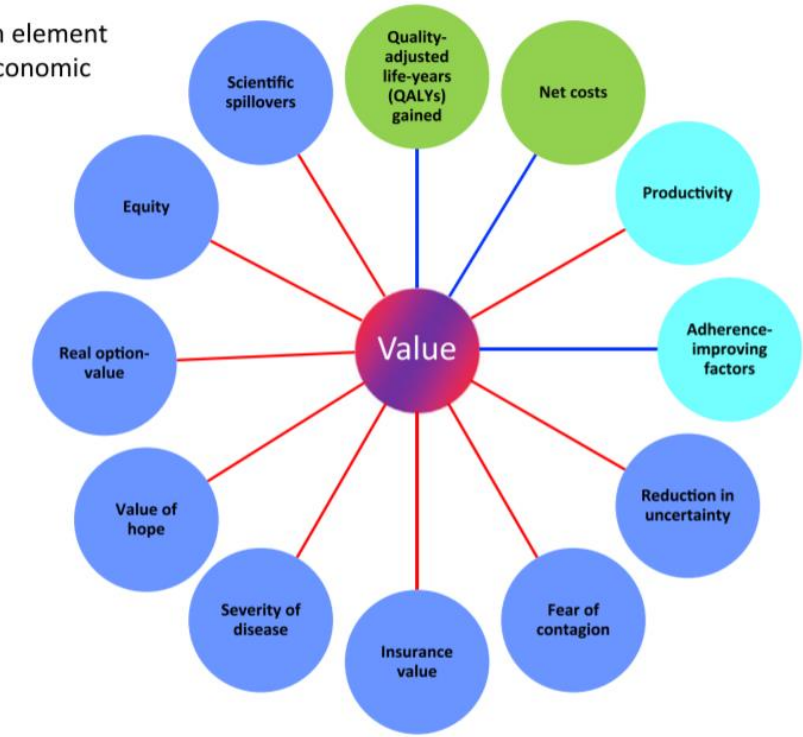
- The analysis is done by analysing the most recent VFs which include additional dimensions of value such as the value of hope and the value of cures
  - We emphasise the difference with standard HTA approaches

- The analysis might be followed by applying a tested, multi-attribute VF to two case study OMPs *(still under discussion)*

Value framework with expanded elements of value

- There are elements that warrant consideration in value assessments, some of which are not considered in the beforementioned HTA assessments
- Four of them—quality-adjusted life-years, net costs, productivity, and adherence-improving factors—are conventionally included or considered in value assessments
- Eight others would be more novel in economic assessments: reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity, and scientific spillovers
- Most of those eight are relevant to OMPs
- In addition, Jena and Lakdawalla (2017) stress the importance to consider impact on carers and families (non-financials), such as improvements in their well-being

Challenge: Map each element into an underlying economic framework for value assessment.



Source: Lakdawalla et al., 2018.

Value of OMPs

Preliminary conclusions

- Available VFs have the potential to show areas of value generated by new OMPs that current HTA approaches do not
  - e.g. severity of the condition and its impact on patients and their carers/families, equity

- However, there are methodological challenges in measuring some of those value elements (e.g. scientific spillovers) and evidence available on individual interventions is sometimes limited (particularly near launch)

- Future efforts should be focused on
  - encouraging HTA/P&R agencies to use multi-attribute value frameworks and decision-making aids to capture the full of OMPs in reimbursement decisions
  - developing "life-cycle value story" of consolidated OMPs to show the value delivered to patients, their families and society over time

Outline

1. Introduction: background and objectives
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3. The value of OMPs
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Market competition

Questions and methods

Questions addressed

- Is there evidence of the conditions for on-patent therapeutic competition?
- Are there orphan medicines facing generic competition?

Approaches to answer the questions

On-patent competition

- Using the current list of orphan designations identify indications addressed by more than one medicine
- Identified the time of market entry of each product and, therefore, the time span between first and subsequent entrants
- Calculated the percentage of the indications that are characterized by the on-patent competition as a share of the total number of indications

Generic competition

- Created the list of the products with withdrawn orphan designations (as a result of the expired market exclusivity).
- For each product from the list identified the number of generics biosimilars that have been licensed for the same indication
- Based on license data Identified the timing of entry of the generics/ biosimilars.

Market Competition

Key messages

On-patent competition

- 15 out of 110 orphan indications[a] (i.e. ~14%) are characterized by the on-patent therapeutic competition.
- The number of the on-patent players for each of these 15 indications varies between 2 and 4.
- Most of these 15 indications (around 55%) belong to the oncological therapeutic area with respiratory and metabolic areas having high representations (both around 18%).
- For 14 out of 15 indications the time before the entry of the second product does not exceed 5 years.

Generic competition

- We identified 42 products with the withdrawn orphan designation (as a result of the expired market exclusivity).
- 7 out of 42 (i.e. ~17%) products faced generic competition: oncology (3), metabolic (3) and respiratory (1).
- The number of generic entrants varies from 1 to 4 per indication.
- In some cases generics enter with the time lag exceeding two years.
- To date there are no instances of biosimilar competition.

[a] Orphan indication is the indication with at least one product with current orphan designation.

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Timelines and next steps

Timelines

- The three main parts of the study finalised by May 31
- Draft final report for comments and feedback by June 16
- Update to Members General Meeting and Board Meeting on June 25
- Final deliverables: report and executive summary by July 5

VII. European Commission conference on medicines for rare diseases and children

Chairs

EC conference on medicines for rare diseases & children

Programme (1)

MORNING

08:45 – 09:30	**Registration and welcome coffee**
09:30 – 09:35	**Opening of the day by the moderator**
09:35 – 09:55	**Keynote opening speeches** *Commissioner for Health and Food Safety – Vytenis Andriukaitis* *Member of European Parliament – Françoise Grossetête*
09:55 – 10:10	**Scene setter for medicines for children and rare diseases** *Head of DG SANTE Unit B5, Medicines: policy, authorisation and monitoring – Olga Solomon* *European Medicines Agency - to be confirmed*
10:10 – 12:20	**Break-out sessions** 1- Unmet medical need 2- Incentives 3- Medicines for children 4- From R&D to patients 5- Future developments
12:20 – 12:45	**Debrief from Break-out sessions**

AFTERNOON

14:00-16:00	**Open Space – Thinking Together: New Commission, New Ideas!**
16:00-16:45	**Conclusions from Open Space by the moderator**
16:45-17:00	**Closing speech and next steps** *Director-General of DG SANTE – Anne Bucher*

Moderator

Patrick Deboyser, Professor,
European College of Parma

Participatory Leadership Facilitators

> Dana Adriana Puia Morel

> Mariana Ghiţoi

EC conference on medicines for rare diseases & children

Programme (2)

Unmet Medical Need

1. Unmet Medical Need: does it mean the same thing to everyone? How to define and better address this need?
2. Orphan condition: how can we target more rare diseases?
3. Significant versus incremental benefit: how strictly should we follow the EU orphan legislation when applying this principle?

Incentives

1. Market exclusivity (ME): how successfully has this incentive supported innovation? Has there been any unintended impact for availability and patient access?
2. Reward for investment: how can we better guarantee that the reward is proportionate to the return on investment without knowing the cost of development?
3. Other incentives: what other actions could be considered for areas without treatment?

EC conference on medicines for rare diseases & children

Programme (3)

Medicines for children

1. How can we ensure the development of medicines for children without hampering research driven development of medicines for adults?
2. Why are there so few "paediatric only" medicines?
3. EU orphan and paediatric legislation and the wider context: how well do the two regulations interact, including with other national and European policies?

From R&D to patient

1. R&D: what are the main hurdles when developing orphan and paediatrics medicinal products?
2. Accessibility: how can public money for research be better invested in areas of unmet need? How can we make sure that medicines developed based on public funded research will reach patients across the EU?
3. Real World Data/Real World Evidence: how will it influence the development, authorisation and access to new medicines?

Future developments

1. What are the main scientific advances, which will influence future pharmaceutical product development? How will personalised medicines impact the landscape of orphan medicines and beyond?
2. What does the innovation pipeline tell us and can the EU orphan and paediatric legislation accommodate these developments in a data driven society?
3. How might scientific and technological developments affect the EU orphan and paediatric legislation?

X. A.O.B / Meeting conclusion

Chairs

Rare Diseases Research Challenges – an update

Secretariat

Rare 2030 – a participatory foresight study for policy-making in rare diseases

Ivana Cattaneo, Novartis

Thank you for your attention!