BBS & EFSPI Seminar

The potential and challenges of registry use when generating evidence in small populations

Henriette Thole
Novartis Postgraduate in Quantitative Safety and Epidemiology
June 27, 2018
BBS & EFSPI Seminar: Small populations and level of evidence

NOVARTIS

Registries- a way to organize data

*"A registry is an organized system that uses observational methods to collect uniform data on specified exposures and outcomes over time, in a population defined by a particular disease, condition or exposure."**

NIS vs. registries: NIS are generally based on limited endpoints, have shorter duration and introduce specific tools for data collection**

Theoretically open-ended**, BUT in an EMA paper "PASS registries" with a minimum duration of 2 years were considered correctly classified***

- Disease registry: inclusion criteria is the condition
- Drug registry: inclusion criteria is the taken medication

* as per Annex I of the EMA Guideline on Good Pharmacovigilance Practices (GVP), 2012
** ENCePP Guide on Methodological Standards in Pharmacoepidemiology, 2010
*** Bouvy et.al 2017

Registries in small populations

NOVARTIS

Registry studies under industry considerations

Data origin

1. PDC: Primary Data Collection, data collected specifically for a study*
2. SUD: Secondary Use of Data, data already collected for another purpose, e.g. as part of electronic health records*

Registry origin

A. Existing registries: e.g. open-ended third party registries, often run by countries, patient associations, etc.

B. New registries: registries initiated newly as part of e.g. conditional market-access, risk-management-plan

* EMA, scientific guidance on PAES, 2016

Regulator view on registries

Overall

- Current use: post-marketing obligation
- Recognized challenges include harmonization/ interoperability, data quality, stakeholder alignment and data privacy
- Recommendations:
  - Joining established registries preferable over initiating new registries
  - Disease registries preferable over drug registries
  - Recognized potential for additional registry use (e.g. label extension, adaptive pathways, treatment sequencing)

Small populations

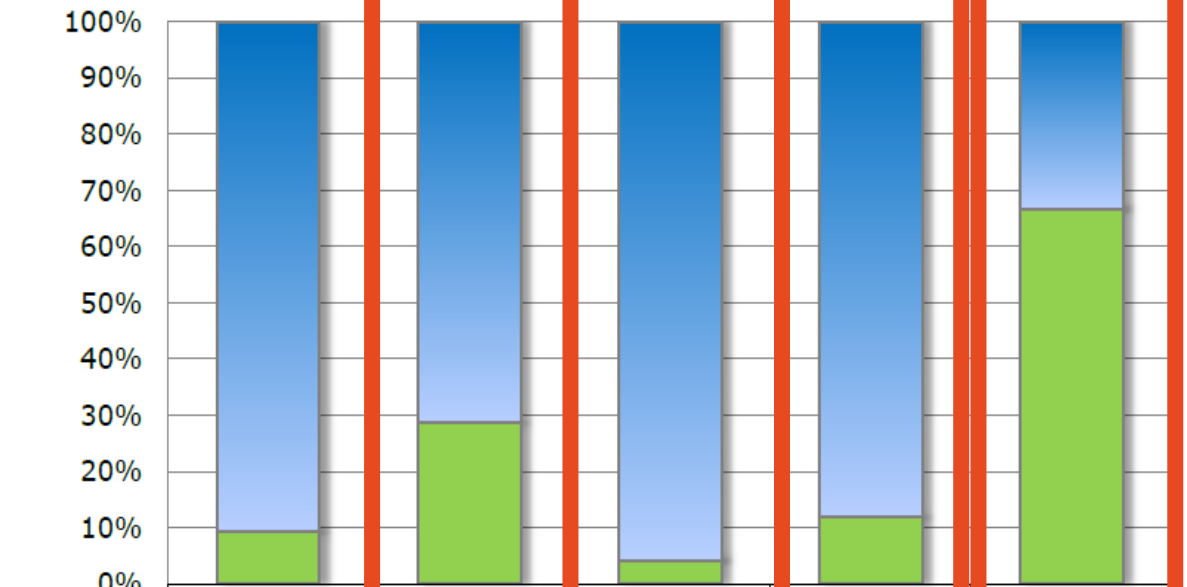
- Registry use is encouraged when RCTs are not feasible due to small patient populations
- Registries may provide more timely access to medications in rare diseases with high unmet medical needs
- Regulators primarily rely on high quality registries during regulatory decision-making processes

EMA Activities: Registry analysis 2005-2013

EUROPEAN MEDICINES AGENCY

Registry Analysis 2005-2013:

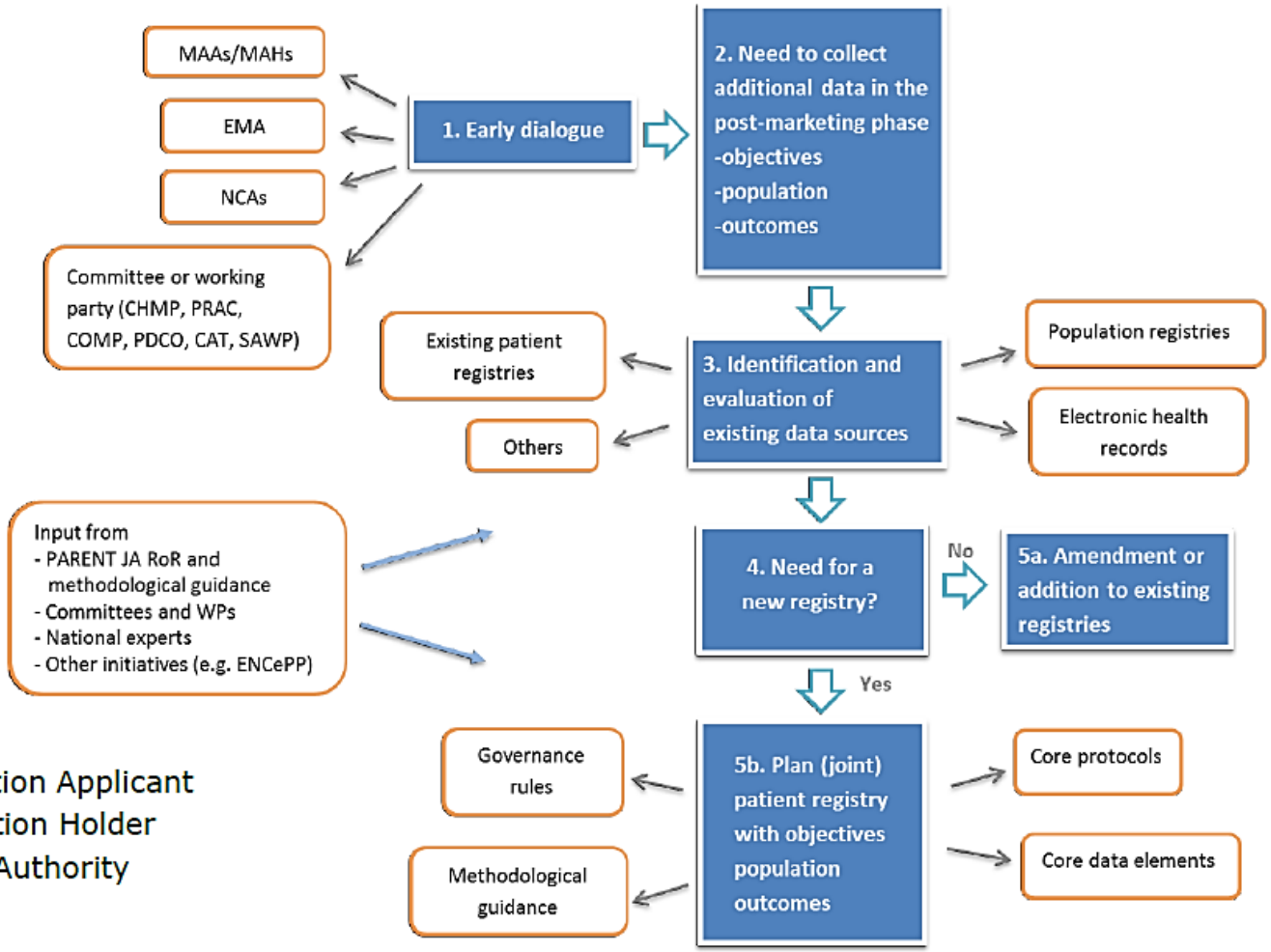
Determined number of registries imposed as an obligation at the time of authorisation from 2005-2013



	all (n=335)	orphan (n=70)	non-orphan (n=265)	conditional (n=17)	exceptional circumstances (n=21)
no registry	304	50	254	15	7
registies	31	20	11	2	14

Cave, A. EMA, What are the real-world evidence tools and how can they support decision making?, 2016

EMA Strategy on Registries



MAA = Marketing Authorisation Applicant
MAH = Marketing Authorisation Holder
NCA = National Competent Authority

Cave, A. EMA, What are the real-world evidence tools and how can they support decision making?, 2016

Implications for Pharmaceutical Industry

- (Disease) registry use is encouraged to demonstrate safety, efficacy and effectiveness in small populations
- Impossible for the pharmaceutical industry to build high quality registries for all rare diseases
  → basis for regulatory decision-making
- Pharma may rely on existing (third party) registries for this approach
  → registries usually not designed for clinical research
- Careful planning needed!

Novartis rare disease example 1

Novartis Example

- Oncology*
- Imposed PASS
- Pediatric population
- Long-term safety and survival
- 5 year observation period

What do you think?

- Drug vs. disease registry
- Existing vs. new registry
- PDC vs. SUD vs. both

Answer

- Drug registry
- New registry
- PDC

Why?

- Endpoint is survival
- No alternative treatment option
- No existing third party registry

* 70% of Novartis rare disease treatments are oncology drugs

Novartis rare disease example 2

Novartis Example

- Oncology
- Post-marketing obligation
- Effectiveness, efficacy, survival and compliance
- 2 year observation period

What do you think?

- Drug vs. disease registry
- Existing vs. new registry
- PDC vs. SUD vs. both

Answer

- Drug registry
- New registry
- Both SUD and PDC

Why?

- Very rare population
- Prospective and retrospective data analysis

Novartis rare disease example 3

Novartis Example

- Immunology and Dermatology
- Burden of disease, current standard of care, quality of life
- 1 year observation period

What do you think?

- Drug vs. disease registry
- Existing vs. new registry
- PDC vs. SUD vs. both

Answer

- Disease registry
- New registry BUT it will be integrated into another registry upon completion
- PDC

Why?

- Comparability of treatment options
- NVS Drug was not developed for this indication (95% off-label drug use in rare diseases*)

* Minghetti, P., Lanati, E. P., Godfrey, J., Solà-Morales, O., Wong, O., & Selletti, S. (2017). From Off-Label to Repurposed Drug in Non-Oncological Rare Diseases: Definition and State of the Art in Selected EU Countries. *Medicine Access@ Point of Care*, *1*(1), maapoc-0000016.

Novartis rare disease example 4

Novartis Example

- Oncology
- Pediatric and adult
- Comorbidity, treatment pathway, and resource use

What do you think?

- Drug vs. disease registry
- Existing vs. new registry
- PDC vs. SUD vs. both

Answer

- Disease registry
- Existing registries
- SUD

Why?

- Use of 3 existing national registries (Electronic Health Records, Prescription, Cause of Death)
- Conducted in Scandinavian registries (high data quality and density)

NOVARTIS

Recap- registry study planning in small populations

- There is no “right” or “wrong” design for registries
- Need for a case-by-case approach under clear consideration of (a) study objective (b) existing registry landscape
- Awareness of frequent issues in registry studies in small populations
- Good understanding of small population registries

Understanding rare disease registries

Objective upon initiation

- To connect affected patients, families, and clinicians
- To learn the natural history, evolution, risk, and outcomes of specific diseases
- To support research on genetic, molecular, and physiological basis of rare diseases
- To establish a patient base for evaluating drugs, medical devices, and orphan products

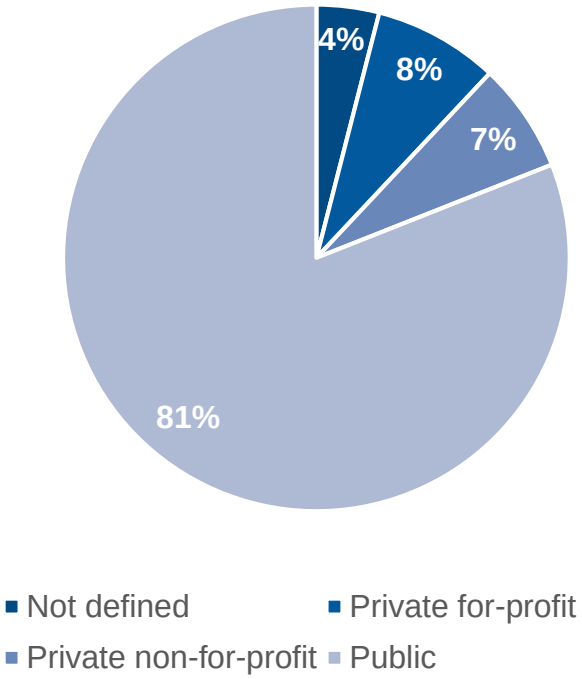
Stakeholders

- Patients and their families, patient advocacy groups (often multiple and umbrella groups)
- Clinicians and scientists
- Regulators (especially for conditional market-access or post-marketing commitments)
- Industry and payers

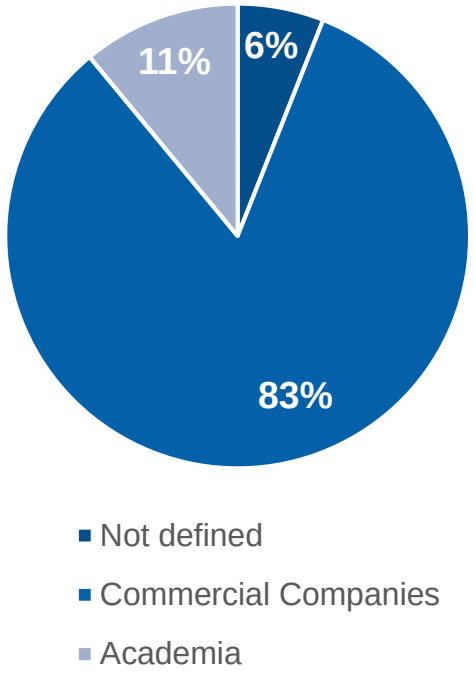
(Gliklich RE, Dreyer NA, Leavy MB, editors. Registries for Evaluating Patient Outcomes: A User's Guide [Internet]. 3rd edition. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr.)

Distribution of registries by affiliation

Registry affiliation



2010-2012 orphan-drug origins

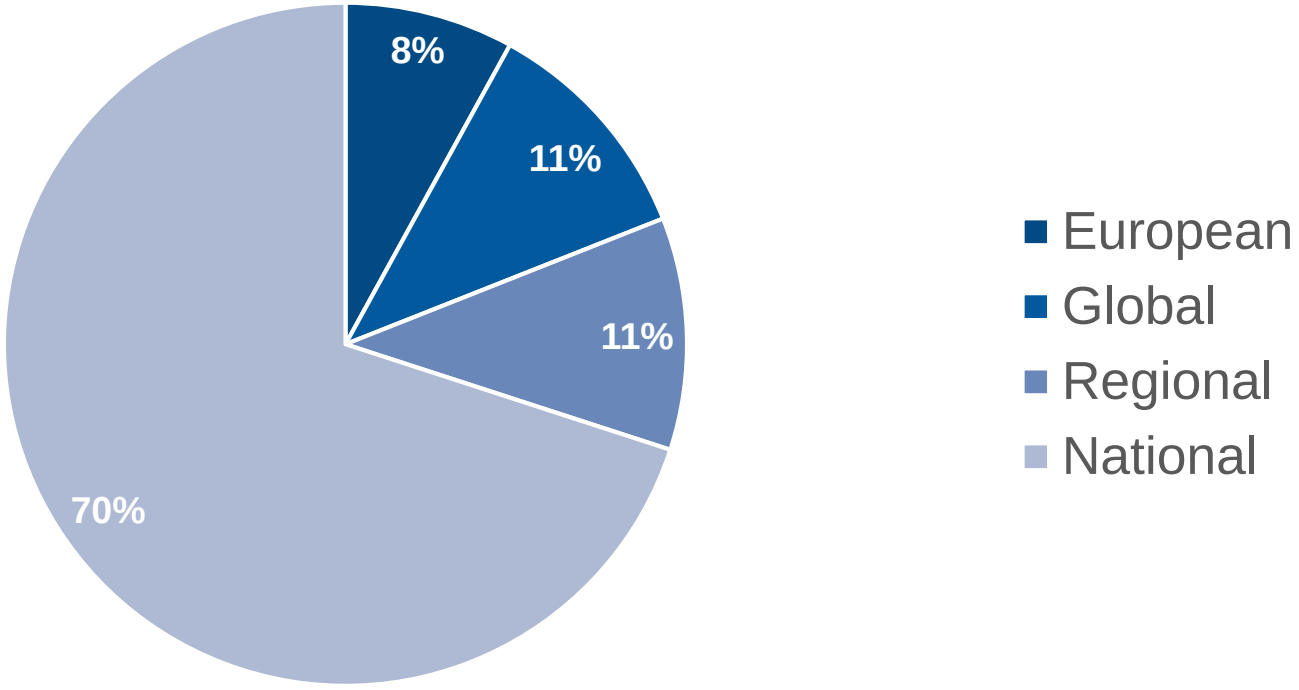


Orphanet report series- Rare disease registries in Europe, January 2016

Lincker, H. et al. Nature review drug discovery, 2014: 13:92-3

NOVARTIS

Geographical coverage of rare disease registries



Orphanet report series- Rare disease registries in Europe, January 2016

Issues prevalent to rare disease registries

Small population	Difficult to enroll patients, patients enrolled in multiple registries, competing for patients
Harmonization/ interoperability	• Differences in inclusion criteria, common data elements etc. • Lacking standard diagnostic procedures or treatments
Data quality	The more information included the higher the investigator burden, rates of discontinuation and challenges in data management
Stakeholder alignment and governance	Funding, patient recruitment, data ownership, registry agenda, collaborations, publications
Data privacy	Small populations make patients easier identifiable
Common disease with rare sub-population (e.g. breast cancer in men or pediatric Multiple Sclerosis)	• Existing registries often exclude rare sub-populations • Few specific patient registries, or patient associations for rare sub-population

Novartis rare disease example 1

Novartis Example

- Oncology, global pediatric PASS
- Long-term safety and survival
- New PDC drug registry

Problems

- Very low accrual
- Long observation period (5 years)
- Patient overlap with other NVS study

Addressing Problems

- Reduced planned enrolment by 50% (agreed with EMA)
- EMA allowed retrospective diagnosis and data
- 2 amendments

Protective measures

- Higher enrolment by use of patient association as enrolment platform
- Annual status report to EMA with continuous dialogue
- Early dialogue with the EMA during planning of the registry study

NOVARTIS

Novartis rare disease example 2

Novartis Example

- Oncology, local post-marketing obligation
- Effectiveness, efficacy, survival and compliance
- New SUD and PDC drug registry

Problems

- Very low accrual
- Local registry
- Many patients were excluded due to prior participation in clinical trials

Addressing Problems

- Reduced planned enrolment by 50%
- Extended enrolment period and study duration
- Increased number of sites
- 5 amendments

Protective measures

- Early recognition of problematic enrolment
- Potential problems and corrective actions discussed during initial planning phase
- Dialogue and negotiations with Health Authority possible

NOVARTIS

Novartis rare disease example 3

Novartis Example

- Immunology and Dermatology
- Burden of disease, current standard of care, quality of life
- New local PDC disease registry

Problems

- Very low accrual
- Local registry
- Patient overlap with 2 other studies
- No additional sites opened

Addressing Problems

- Reduced planned enrolment (by 2/3)
- Widened inclusion criteria after discussion with local health authority
- 1 major amendments

Protective measures

- Continuous dialogue with local Health Authority during planning and maintenance
- Early recognition of problems
- Opportunity for one major amendment addressing all problems

NOVARTIS

Novartis rare disease example 4

Novartis Example

- Oncology, pediatric and adult
- Comorbidity, treatment pathway and resource use
- Existing local patient registry SUD

Limitations

- Limited number of variables
- No information about drug efficacy, effectiveness or safety possible in these registries

Advantages

- Clear information about population size
- No need for amendments
- Short duration

Protective measures

- Access to all, patient Electronic Health Records, Prescription and Cause of Death registries, since launch of drug
- Renown quality of Scandinavian national registries

NOVARTIS

Recap- risk and issue mitigation in small populations registry studies

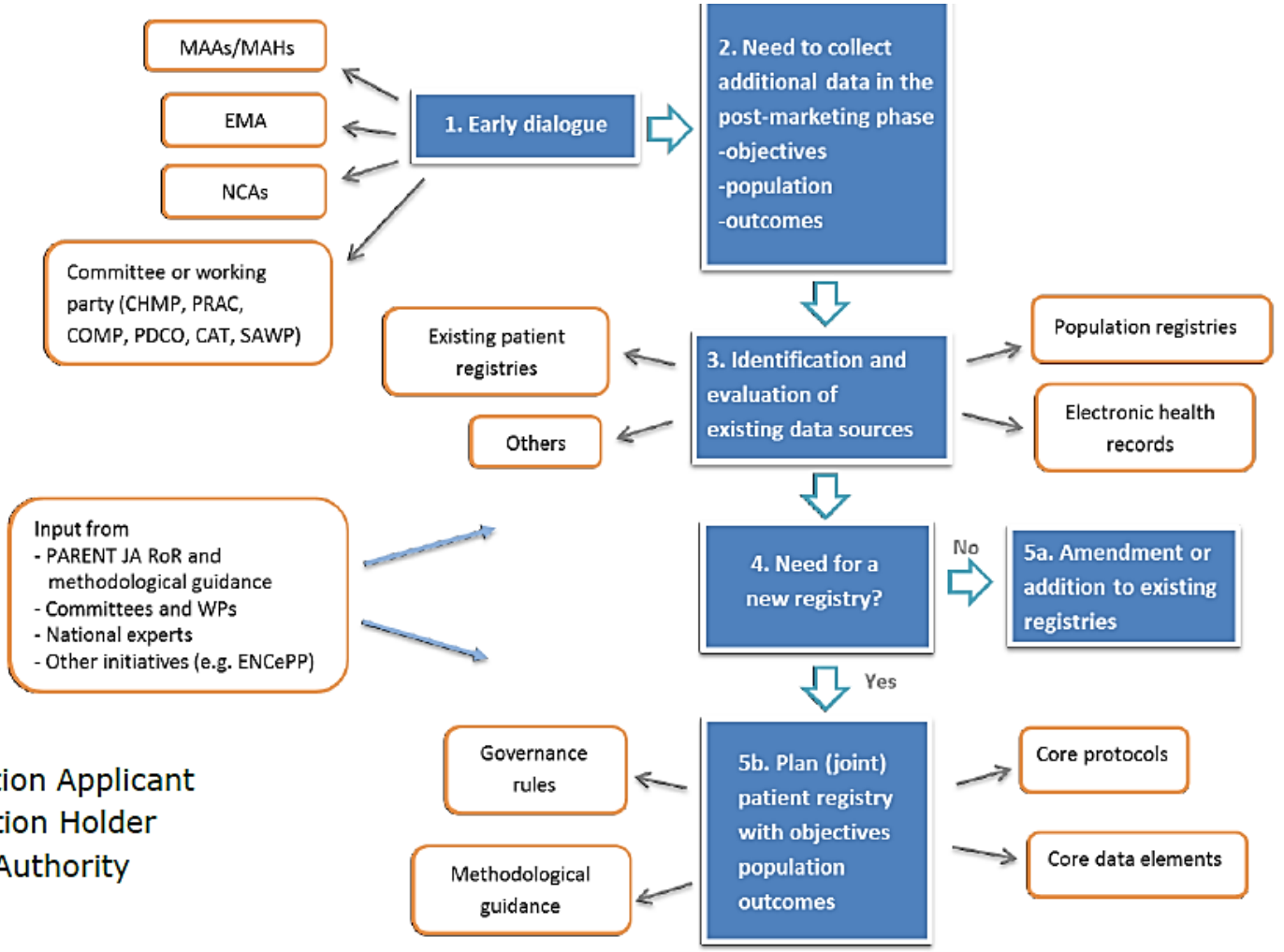
Risk mitigation for PDC in small population registries

- Continuous and early dialogue with Health Authorities
- Close work with Patient Associations (planning and recruitment)
- Consideration of problems and drafted corrective actions when planning
- Early recognition of problems
- Allowing retrospective diagnosis and data

Risk mitigation for SUD in small population registries

- Use of SUD preferable when possible to avoid enrolment issues
- Use of registries with proven high data quality and density
- Problematic interoperability of registries: ensure diagnostic criteria and tools are aligned between registries

Step-by-step approach when planning a registry study in small populations



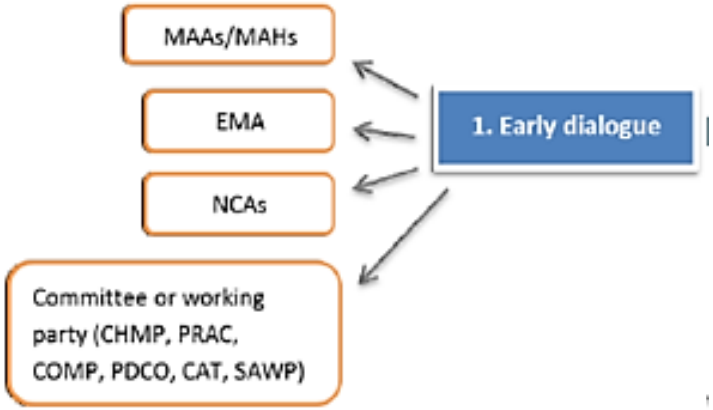
MAA = Marketing Authorisation Applicant
MAH = Marketing Authorisation Holder
NCA = National Competent Authority

What are the real-world evidence tools and how can they support decision making?, Dr Alison Cave-EMA, 2016

NOVARTIS

1. Early dialogue with Health Authorities

- Early dialogue
- EMA-EUnetHTA parallel consultation
- Adaptive Pathways
  - Medicines Adaptive Pathways to Patients (**MAPP**),
  - Commission Expert Group on Safe and Timely Access to Medicines for Patients (**STAMP**),
  - EMA pilot
  - Accelerated Development of Appropriate Patients Therapies, a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes (**AdaptSmart**)
- Priority Medicines (**PRIME**)



Step 2 and 3

2. Objective and population

- Would a SUD registry study be possible?
- Could information be generated through alternatives e.g. ARGUS data, MarketScan analysis?

3. Existing registries

- Can there be a SUD in an existing registry?
- Can a PDC in an existing registry be initiated?
  - Existing registries (e.g. RD-connect registry finder, PARENT-JA RoR, etc.)
  - Patient associations (e.g. EURODIS)

4. Need for a new registry or PDC in existing registry?

- If there are existing registries:
  - Assessment of collected variables, data quality and data density (e.g. EMA qualification opinions on registries)
  - Protocol amendment possibilities
  - Existing registry population and their use as baseline or historical control

- If there are no existing registries:
  - Plans from patient associations

5. Sustainable new registry

- Focus on harmonization/ interoperability
  - Common data elements (e.g. EPIRARE)
  - Diagnostic criteria (additional rare disease codes will be available in ICD-11, due 2018)
  - Alignment with other (national) rare disease registries
  - EMA Registry Initiative
  - Cross Border Patient Registries Initiative- Joint Action (PARENT-JA)
- Ensure clear data governance and alignment between ALL Stakeholders
- Completeness of data: need to have vs. nice-to-have variables

HTA bodies and registries

Traditionally, HTAs depended on RCTs and literature reviews

- Little information for economic and coverage decisions
- Use of RWE as a basis for HTA evaluation: what happens when treatment is made available to the public?*
- Registries provide the best basis for RWE in HTA evaluation**

* Dang, A., & Angle, V. S. (2015). Utilizing patient registries as health technology assessment (HTA) tool. *Systematic Reviews in Pharmacy*, *6*(1), 5.)

** Kennedy, L., & Craig, A. M. (2004). Global Registries for Measuring Pharmacoeconomic and Quality-of-Life Outcomes. *Pharmacoeconomics*, *22*(9), 551-568.)

HTA bodies and rare disease registries

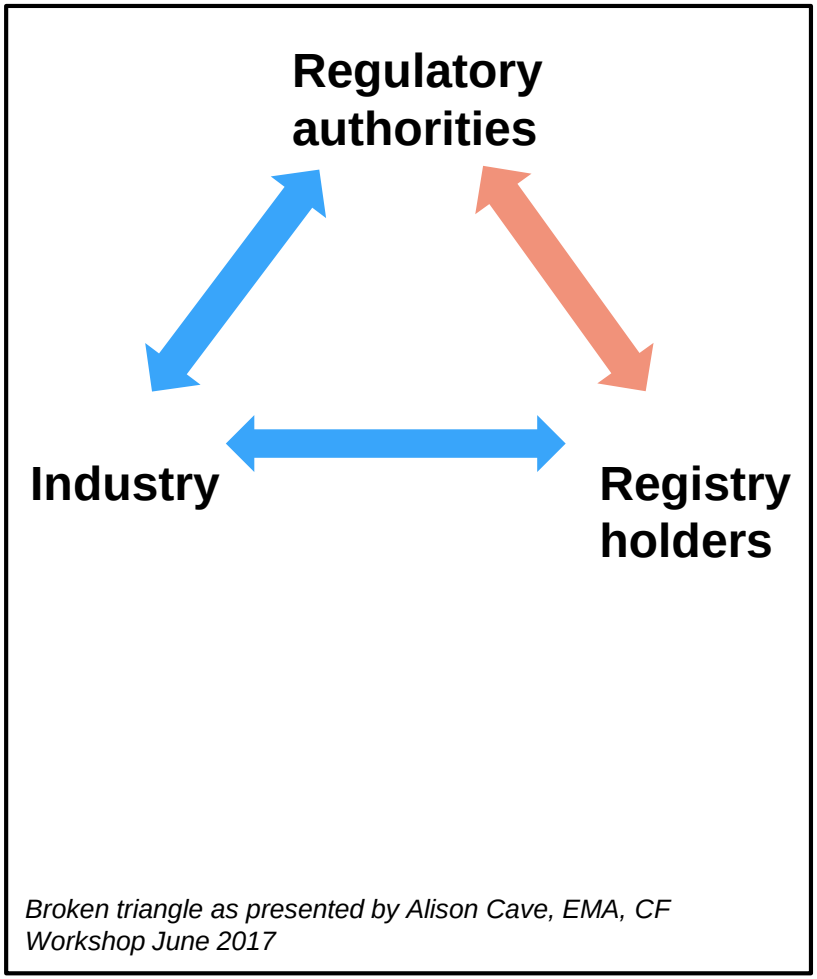
Rare disease registries should include:

- Costs of disease (medical products, hospitalization, burden of disease)
- Orphan-drug use appropriateness
- (relative) Effectiveness
- Added value
- Clinical pathways
- Outcomes of treatments, including interventions
- Types and severity of side effects of treatments
- Services used

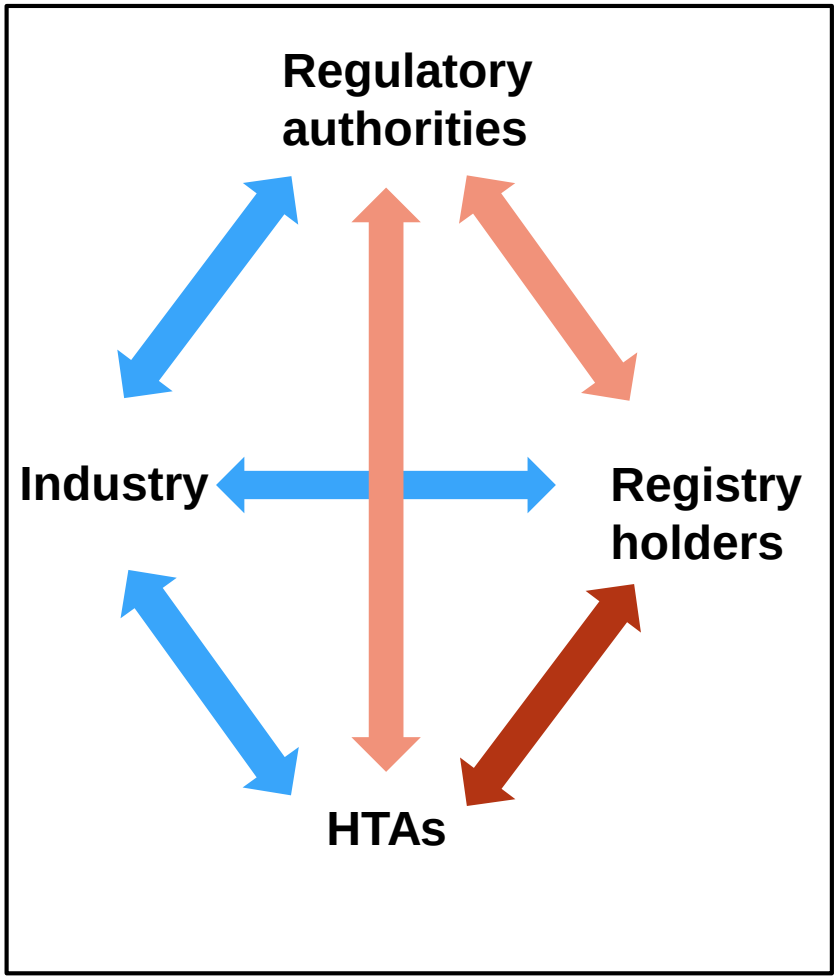
(Vittozzi, L., Gainotti, S., Mollo, E., Donati, C., & Taruscio, D. (2013). A model for the European platform for rare disease registries. *Public Health Genomics*, *16*(6), 299-304.)

NOVARTIS

Issues in registry data use for HTA decision-making



Broken triangle as presented by Alison Cave, EMA, CF Workshop June 2017



NOVARTIS

Issues in registry data use for HTA decision-making

Objective upon registry initiation

- Few registries are designed with HTA as an objective, particularly not in rare diseases (see slide 13)

Alignment between different HTA bodies

- Acceptance of RWE and registry data differ between countries with different guidelines on evidence generation*
- EUnetHTA-JA 3 WP 5B PLEG, Registry guidelines expected in 2019**

Alignment between HTA bodies and Health Authorities

- EMA-EUnetHTA parallel consultation: how to generate optimal and robust evidence that satisfies the needs of the respective decision-makers***

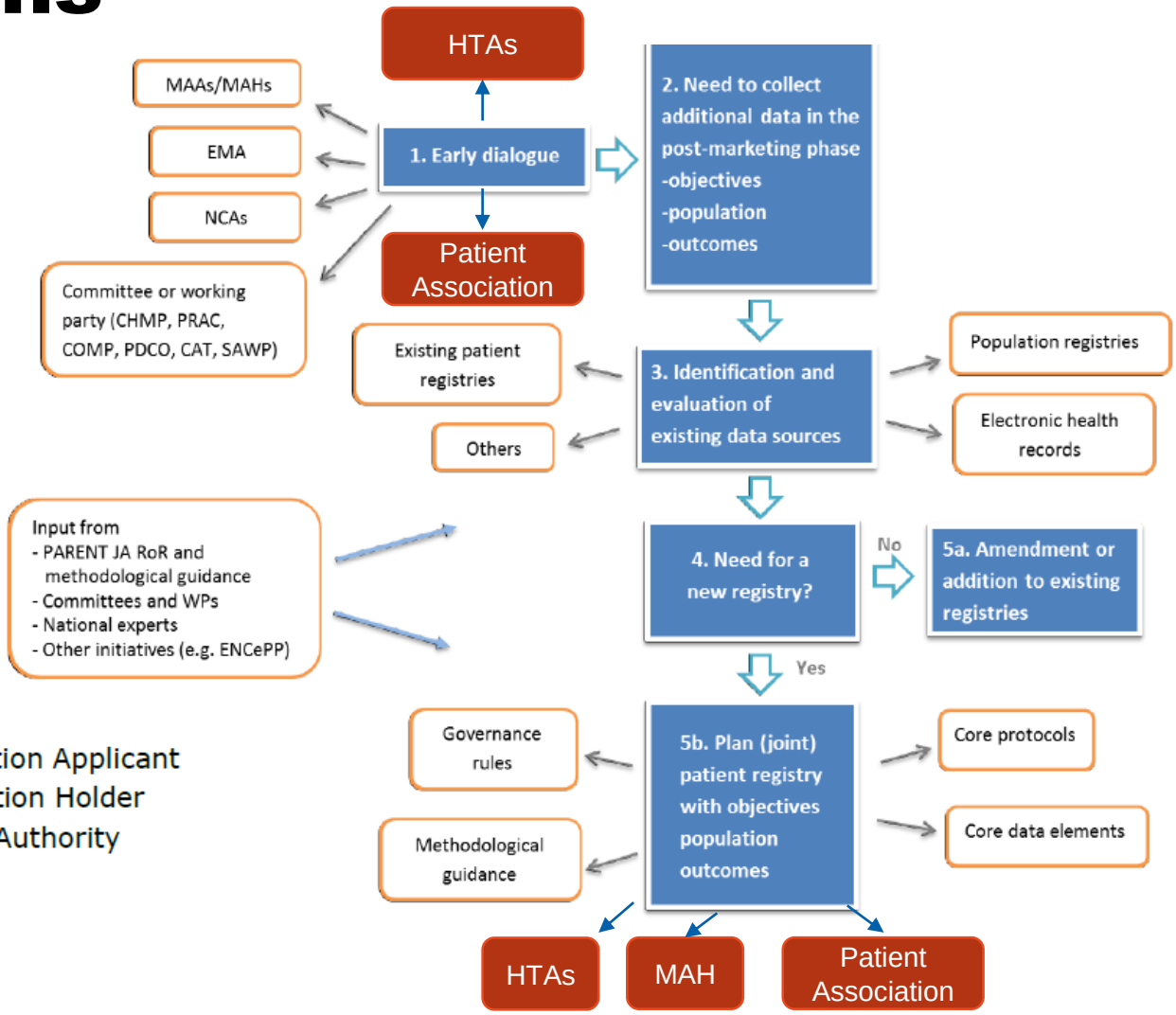
* Makady, A., ten Ham, R., de Boer, A., Hillege, H., Klungel, O., & Goettsch, W. (2017). Policies for use of real-world data in health technology assessment (HTA): a comparative study of six HTA agencies. *Value in Health*, *20*(4), 520-532.)

** EUnetHTA Assembly Forum, May 2018)

*** EMA, EUneHTA. Guidance for Parallel Consultation, 2017

NOVARTIS

Planning a registry study in small populations



MAA = Marketing Authorisation Applicant
MAH = Marketing Authorisation Holder
NCA = National Competent Authority

Adapted from: What are the real-world evidence tools and how can they support decision making?, Dr Alison Cave-EMA, 2016

NOVARTIS

Thank you

NOVARTIS

Literature

- Bouvy, J. C., Blake, K., Slattery, J., De Bruin, M. L., Arlett, P., & Kurz, X. (2017). Registries in European post-marketing surveillance: a retrospective analysis of centrally approved products, 2005–2013. *Pharmacoepidemiology and drug safety*, *26*(12), 1442-1450.
- Cave, A. (2016). What are the real-world evidence tools and how can they support decision making. *EMA-EuropaBio Info Day*
- Dang, A., & Angle, V. S. (2015). Utilizing patient registries as health technology assessment (HTA) tool. *Systematic Reviews in Pharmacy*, *6*(1), 5.
- ENCePP Guide on Methodological Standards in Pharmacoepidemiology, 2010
- EMA, scientific guidance on PAES, 2016
- EMA, Cystic Fibrosis Workshop, 2017
- European Medicines Agency -European network for Health Technology Assessment. (2017, June 30). *EMA, EUnetHTA.* Retrieved from Guidance for Parallel Consultation: http://www.eunethta.eu/sites/default/files/Guidance%20on%20Parallel%20Consultation.pdf
- EURODIS. Mapping out the similarities and differences between rare cancers and rare diseases; 2015. Available from: http://www.eurordis.org/sites/default/files/rare-cancers-2015-2016.pdf.
- Gliklich RE, Dreyer NA, Leavy MB, editors. Registries for Evaluating Patient Outcomes: A User's Guide [Internet]. 3rd edition. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr.)
- Kennedy, L., & Craig, A. M. (2004). Global Registries for Measuring Pharmacoeconomic and Quality-of-Life Outcomes. *Pharmacoeconomics*, *22*(9), 551-568.
- Lincker, H. et al. Nature review drug discovery, 2014: 13:92-3
- Makady, A., ten Ham, R., de Boer, A., Hillege, H., Klungel, O., & Goettsch, W. (2017). Policies for use of real-world data in health technology assessment (HTA): a comparative study of six HTA agencies. *Value in Health*, *20*(4), 520-532.
- Minghetti, P., Lanati, E. P., Godfrey, J., Solà-Morales, O., Wong, O., & Selletti, S. (2017). From Off-Label to Repurposed Drug in Non-Oncological Rare Diseases: Definition and State of the Art in Selected EU Countries. *Medicine Access@ Point of Care*, *1*(1), maapoc-0000016
- Vittozzi, L., Gainotti, S., Mollo, E., Donati, C., & Taruscio, D. (2013). A model for the European platform for rare disease registries. *Public Health Genomics*, *16*(6), 299-304.

Used Rare Disease examples

- All Novartis examples are considered orphan/ ultra-orphan indication according to:

https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_decreasing_prevalence_or_cases.pdf

NOVARTIS

Contact points

Technical projects on rare diseases registration e.g.

- The Health Programme is supporting the **EPIRARE** (European Platform for Rare Disease Registries) Project, in order to build consensus and synergies to address regulatory, ethical and technical issues associated with the set up and management of registries for Rare Diseases patients in the EU and to contribute to prepare a platform for the registration of rare disease patients in Europe and to ensure the quality and best use of the registered data,

- The aim of the **PARENT Joint Action** (Cross Border PAtient REgistries iNiTiative), under the Health Programme, is to support MS in developing comparable and coherent patient registries in fields where this need has been identified (e.g. chronic diseases, rare diseases, medical technology), and to support MS states in the provision of objective, reliable, timely, transparent, comparable and transferable information on the relative efficacy and effectiveness of health technologies.

- The FP7 Project **RD-CONNECT** (An integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research)will provide an integrated, user-friendly RD-Connect platform, built on efficient informatics concepts already implemented in international research infrastructures for large-scale data management, will provide access to federated databases/patient registries, biobank catalogues, harmonised -omics profiles and cutting-edge bioinformatics tools for data analysis

- Objectives of **IRDiRC** (International Rare Diseases Research Consortium)in the field of rare diseases registration, in a transatlantic basis, are in the direction of a meta-registries or registry of registries as suggested by the agency for Healthcare Research and Quality (AHRQ USA). A registry of registries should prove to be very helpful to the public who are seeking an appropriate patient registry for patient participation.

- The **EUCERD** (European Union Committe of Experts on Rare Diseases) adopted on 5th June 2013 the following recommendation: EUCERD Core Recommendations on Rare Disease patient registration and data collection

Extracted from European Commission: Supporting rare diseases registries and providing a European Platform for rare diseases registration
https://ec.europa.eu/health/rare_diseases/policy/registries_en