Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

www.pei.de

Haemophilia Registries quantity versus quality

The current situation in Europe

Christine Keipert
Workshop on
Haemophilia Registries
July 1st, 2015

Topics

- From local to global: The current state of haemophilia registries
- What is publicly available of european national registries?
- What must be done to enhance the benefit of registries?

- Besides marketing authorization, there are more open questions in haemophilia care that must be addressed by clinical research

- Due to the very limited number of haemophilia patients, it is necessary to maximize the use of the limited amount of attainable data

- The inclusion and monitoring of patients in well-designed and well-managed registries may provide useful supporting information for evaluating the safety and efficacy of new therapeutic products

- Therefore, registries can potentially elucidate overarching issues, help to optimize treatment, and estimate the balance between the demand and supply of FVIII products.

- Does the growing number of haemophilia registries improve the knowledge of haemophilia and patient safety?

From local to global

The current state of registries

European registries and data collections

- Provide adequate care for every haemophilia patient in Europe
- Standardize the evaluation of safety, efficacy and quality
- Facilitate Research and Healthcare Development
- Ensure the availability of supply
- May help to prevent the migration of haemophilia patients searching for optimal healthcare

European registries and data collections

- PedNet registry to facilitate research and healthcare development in children with haemophilia
- EUHASS (European Haemophilia Safety Surveillance) to monitor the safety of treatment for people with inherited bleeding disorders throughout Europe
- ABIRISK (Anti-Biopharmaceutical Immunization: prediction and analysis of clinical relevance to minimize the RISK) to generate a comprehensive database concerning ADA formation in haemophilia and other diseases treated with biopharmaceuticals

Worldwide data collections: international databases and cohorts

- Certain parameters can only be studied in subgroup of patients like
  - PUPs
  - Patients with a specific genetic mutation

To gain significat results, larger patient cohorts are required. These cohorts can only be obtained using worldwide databases, meta –analyses and multinational and multicenter studies.

Worldwide data collections: international databases and cohorts

- The International Registry of Rare Bleeding Disorders was established in 2005 as an international registry to homogenously collect data.

- SIPPET (Survey of Inhibitors in Plasmaproduct Exposed Toddlers) was initiated in 2006 as an international, prospective, controlled, randomized, and openlabel clinical trial on inhibitor frequency in PUPs and minimally blood component-treated patients.

- GEHEP (Global Emerging Haemophilia Panel) is an international, multi-institutional consortium to advance haemophilia care. A global protocol was developed to facilitate the sharing of aggregated data among GEHEP members on the intra- and inter-institutional differences in patient populations, diagnosis, and treatment.

Industry-initiated data collections

- Clinical trials for marketing authorisation
- Postauthorization Safety and Efficacy Studies (PASS/PAES) to ensure consistency in the long-term outcomes between preauthorization clinical studies and routine use
- Product specific registries
- Patient diaries (!)

Patient diaries

- Pharmaceutical companies provide patient diaries for application documentation
- In Germany: Most of the companies agreed to harmonize their patient diaries starting in 2014
- Currently, analogue diaries are transformed into digital diaries that can be used as mobile applications (apps) on the patients‘ smart phone
- Hopefully, the harmonization of paper diaries will lead to harmonized digital diaries
- Digital diaries smooth the way of data sharing between patient and physician and, if equipped with a suiteable interface, with (national) registries
- May be useful for postauthorization studies, improving of products and for identifying marketing gaps

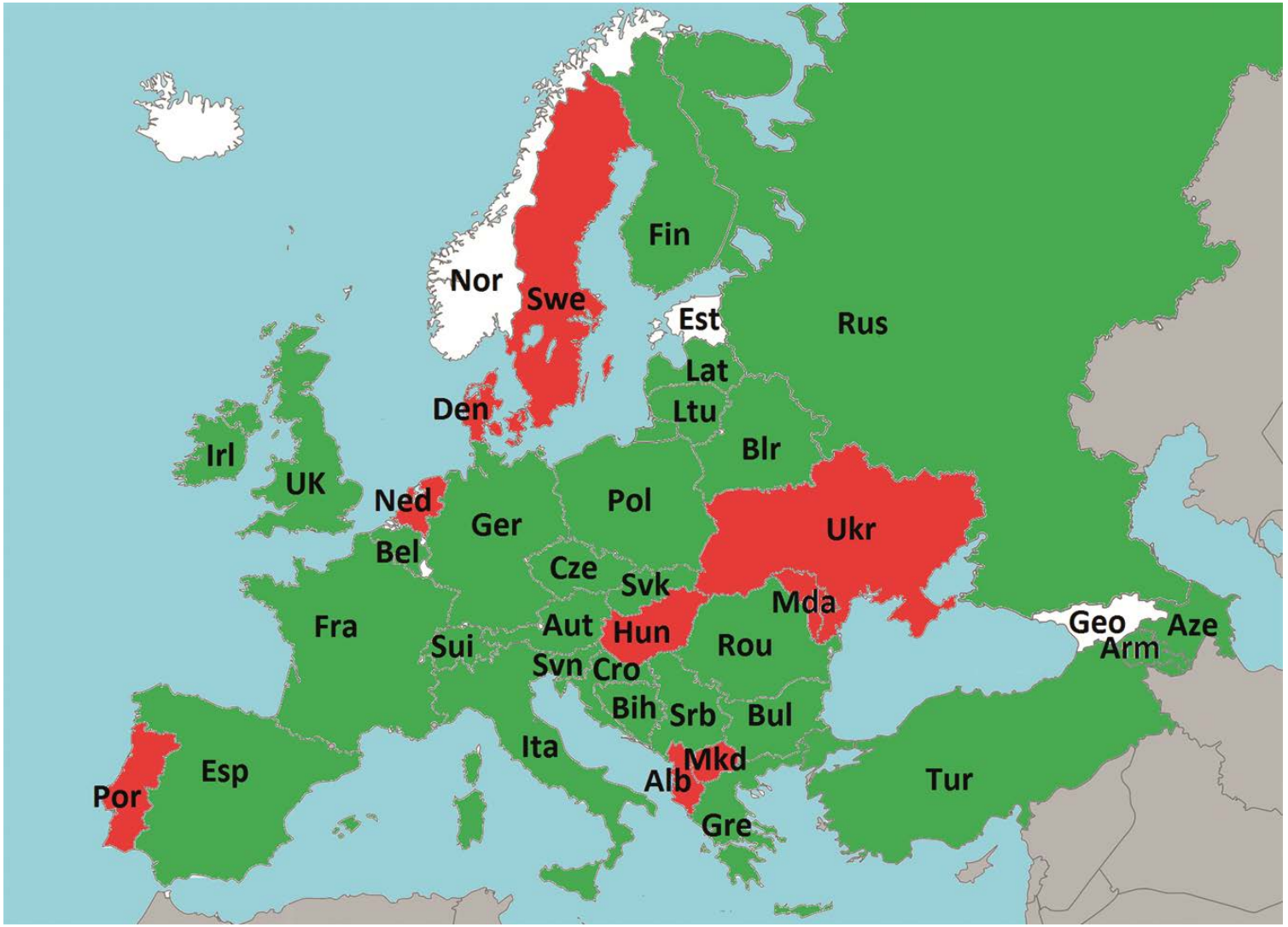
What is known about this registries and data collections?

- Which parameters will be observed
- Which patients will be included
- What is the number of enrolled patients
- What is the outcome of the registry
- How complete is the data
- When will an analysis be performed and will it be published

National Registries

- no pan-European structure for how to manage, design, or host such registries.
- located at the Ministry of Health or organized by academia or patient organizations.
- could be set up by different stakeholders at different time-points and focus on different aspects of the disease, so that some countries end up with several national registries with no or minor interoperability.

What do we know about national registries?



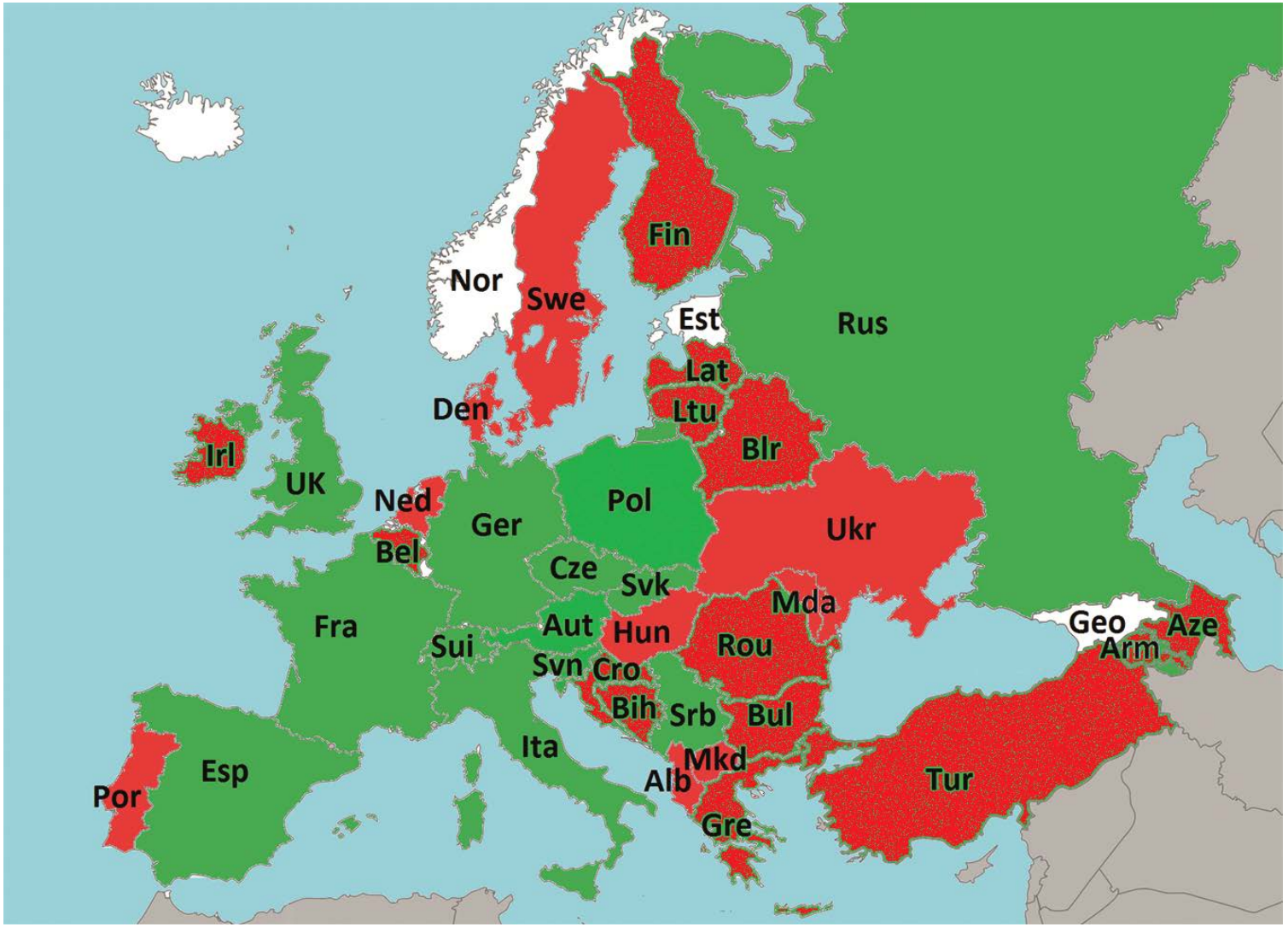
O'Mahony et al. (2013): Haemophilia care in Europe - a survey of 35 countries. Haemophilia 19(4):e239-47.
Map modified from the original map at Wikimedia commons, CC BY-SA 3.0, original file can be found at http://commons.wikimedia.org/wiki/File:Europa.svg.

Table 1. Overview of clinicians' assessment of haemophilia care in Central and Eastern Europe (CEE) countries.

Country	FVIII IU per capita (2012)	Central haemophilia organization (council etc.)	Functional national registry	Prophylaxis for children	Prophylaxis for adults	Immune Tolerance Treatment for children	Immune Tolerance Treatment for adults
Bulgaria	2.14	Unrecognized	Incomplete	Yes	No	No	No
Czech Republic	4.8	Yes	Yes	Yes	Yes	Yes	Yes
Estonia	3.9	No	No	Yes but not official standard	No	No	No
Hungary	8.43	Yes	Yes	Yes	Yes	Yes	Yes
Latvia	2	No	No	Yes but not official standard	No	No	No
Lithuania	5.3	No	No	Yes but not official standard	Yes in selected cases	Yes under special request and permission	Yes under special request and permission
Poland	4.76	Yes	Incomplete	Yes	No (foreseen for young adults <26 years)	Yes	Yes
Romania	0.69*	Yes	Incomplete	Yes	No	No	No
Slovakia	6.6	Yes	Yes	Yes	Yes	Yes	Yes

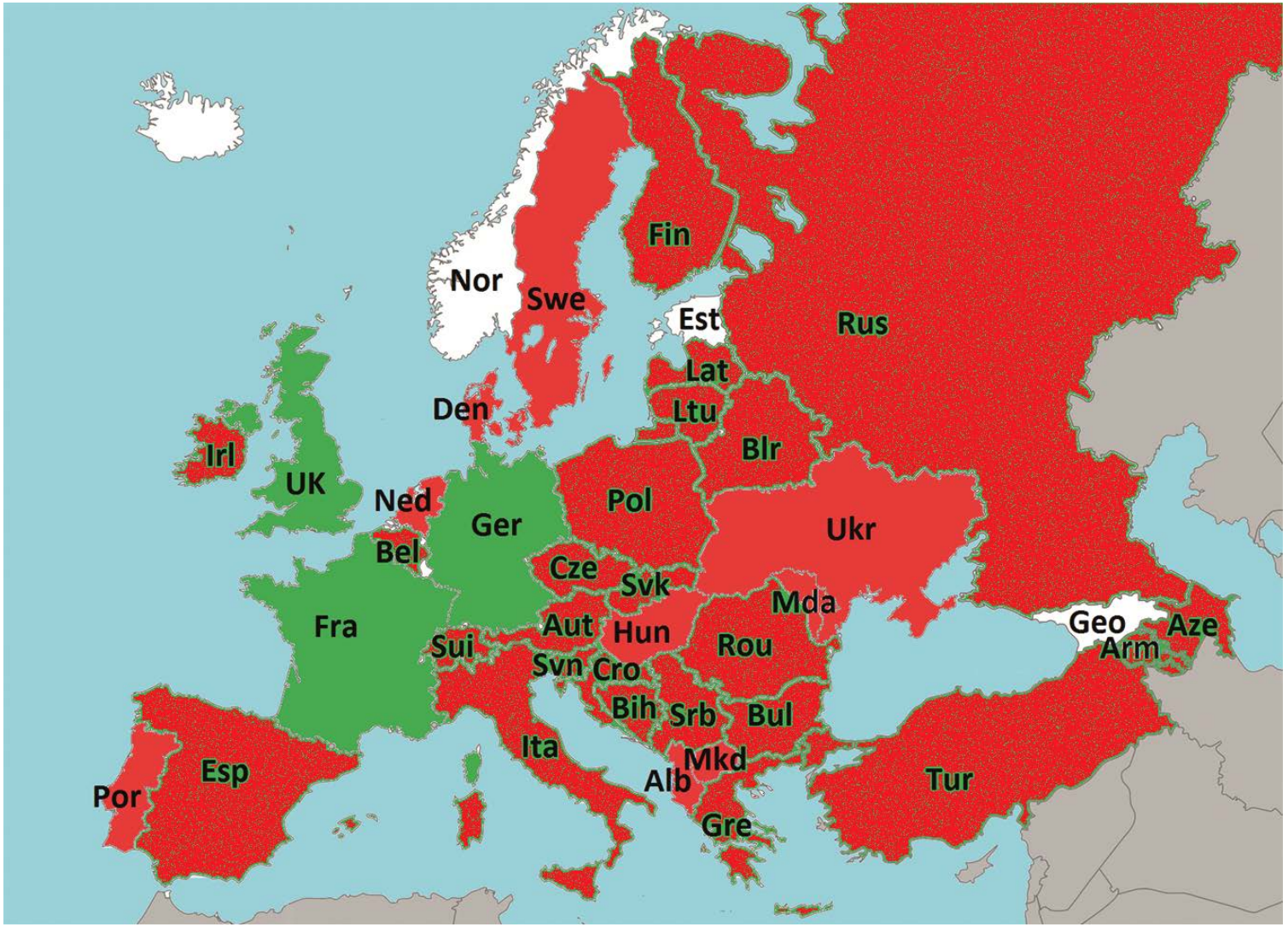
Data provided by the authors of this article. As the aim of this letter is to present the clinicians' perspective, the data above reflect personal experience of leading CEE haemophilia clinicians. No additional formal assessment has been carried out.
*Romania has seen an increase in factor VIII (FVIII) per capita to 1 in 2014.

What do we know about national registries?



Keipert et al., (2015): The growing number of hemophilia registries: Quantity vs. Quality. Clin Pharmacol Ther 97(5):492-501
Map modified from the original map at Wikimedia commons, CC BY-SA 3.0, original file can be found at http://commons.wikimedia.org/wiki/File:Europa.svg.

What do we know about national registries?



Map modified from the original map at Wikimedia commons, CC BY-SA 3.0, original file can be found at http://commons.wikimedia.org/wiki/File:Europa.svg.

National Registries

Why is transparency so important?

→ to obtain a meaningful overview and to facilitate the scientific evaluation of haemophilia treatment, the **sharing** and **pooling** of data, as well as **collaboration** with other countries, are critical and are only possible when all patients are registered with the same definitions and collected parameters.

Gouw et al.: **Factor VIII products and inhibitor development in severe hemophilia A**. N Engl J Med. 2013 Jan 17;368(3):231-9

“In conclusion, the use of recombinant factor VIII products in children with severe hemophilia A did not have a **significant effect** on the risk of inhibitor development, as compared with the use of plasma-derived products (…). An unexpected finding was that second-generation full-length recombinant products **were associated with** an increased risk of inhibitor development, as compared with third-generation products.”

Calvez et al.: **Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A**. Blood. 2014 Nov 27;124(23):3398-408

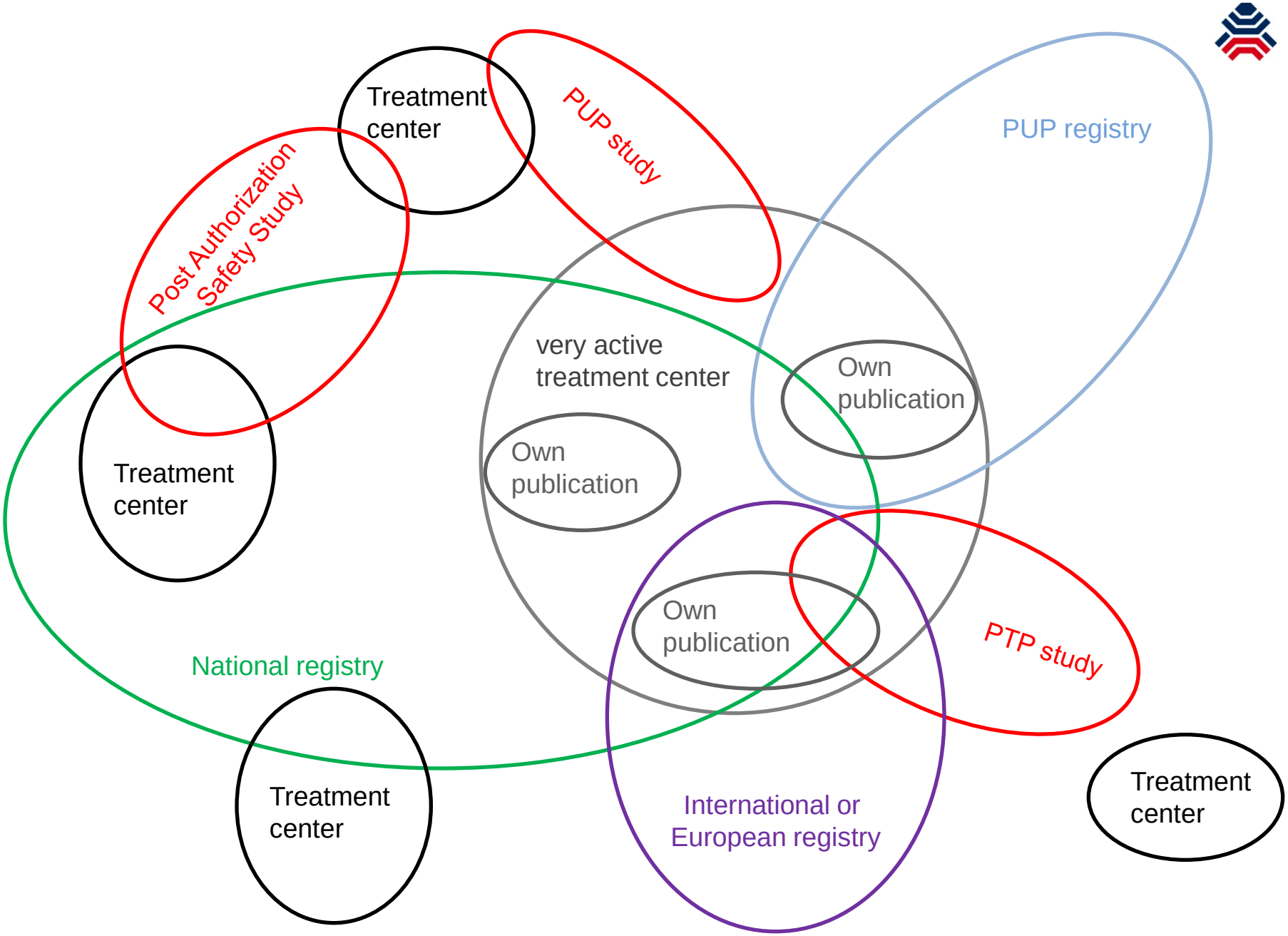
“After excluding 50 patients who participated in the RODIN study (…)”
“We observed a **significant association** between the rFVIII product received and the “all inhibitors” outcome.
“The consistency between our findings and those of the RODIN study **suggests (but does not prove)** that the observed association between rFVIII products and the risk of inhibitor development is causal.“

Collins et al.: **Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe hemophilia A, 2000-2011**. Blood. 2014 Nov 27;124(23):3389-97

“A French study has reported an increased incidence of any inhibitor with Kogenate Bayer/Helixate NexGen compared with Advate on univariate analysis, although the association was **not statistically significant** after adjustment for known risk factors for inhibitor formation”

“Despite any shortcomings of the RODIN, French, and UK studies, the similarity of the results for Kogenate Bayer/Helixate NexGen compared with Advate **makes findings more plausible**. In conclusion, although an increased incidence of inhibitor development in PUPs associated with Kogenate Bayer/Helixate NexGen **has not been definitively proven**(…)”

- Own patient registry in the treatment center
- Regional registries or locally collaborating treatment centers that populate a local registry
- National Registry
- European and trans-regional registries and data collections
- International data collections and registries
- Industry-initiated data collection


Treatment center
PUP study
PUP registry
Post Authorization Safety Study
very active treatment center
Own publication
Own publication
Treatment center
Own publication
PTP study
National registry
Treatment center
International or European registry
Treatment center

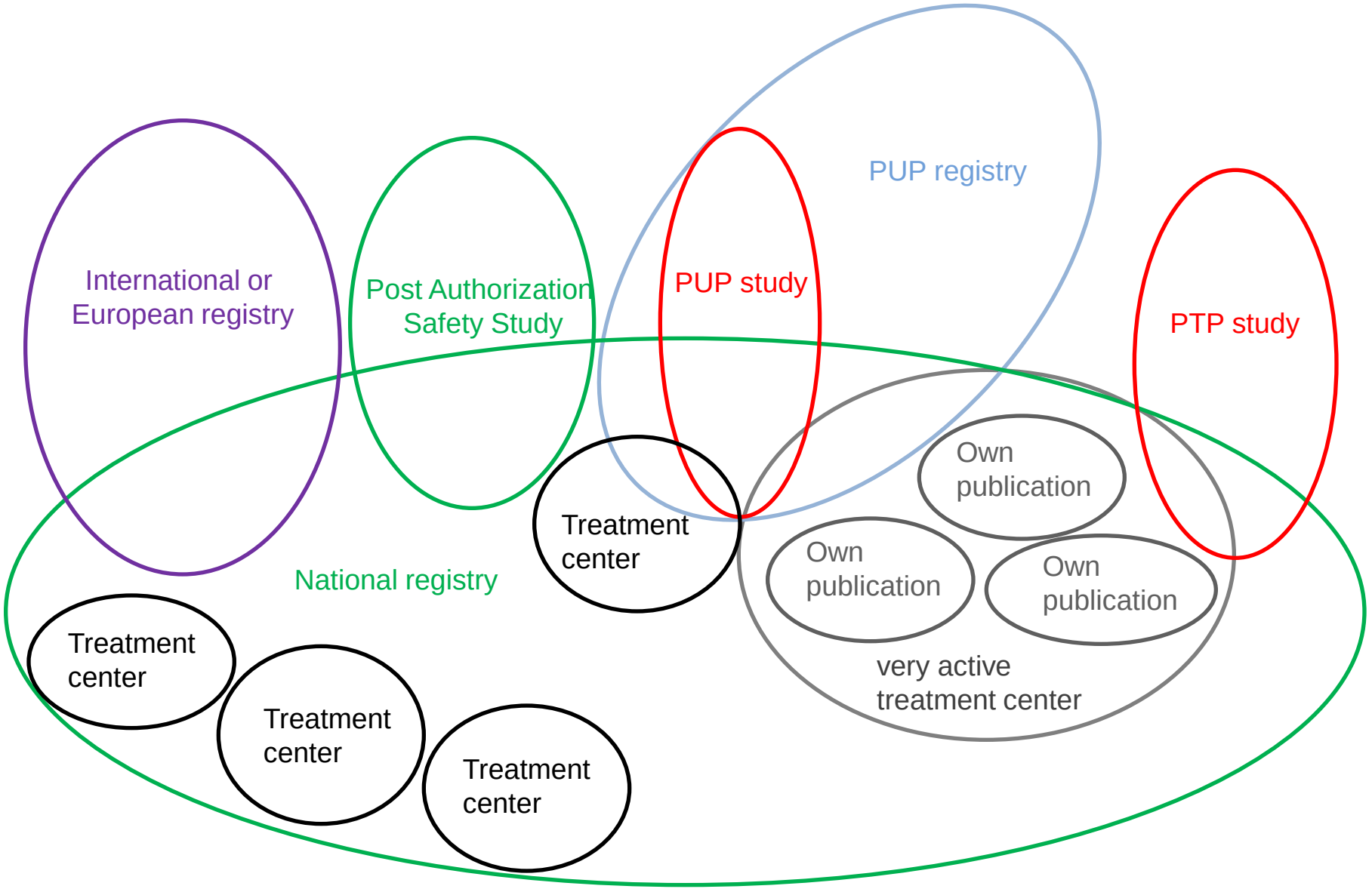
Does the current number of hemophilia registries improve patient safety and leads to a better research in the field of Haemophilia?

What is the consequence that some patients are registered in several registries and others in none?

Which bias is generated during the assessment of “standard treatment methods” if the involvement and visibility of treatment centers differs that much?

Does the growth of the number of registries come to the expense of the overall data quality?

What could or needs to be done to transform registries into a powerful clinical research tool?


International or
European registry
Post Authorization
Safety Study
PUP registry
PUP study
PTP study
Own
publication
Own
publication
Own
publication
very active
treatment center
Treatment
center
National registry
Treatment
center
Treatment
center
Treatment
center

What must be done to enhance the benefit of registries

- For…
  - …Patients
  - …Physicians
  - …National Competent Authorities
  - …Industry
  - …Health care providers

Transparency

Harmonization

Collaboration

Participation

Thank you
for your attention