# ISTH and EAHAD perspective on Haemophilia Registries

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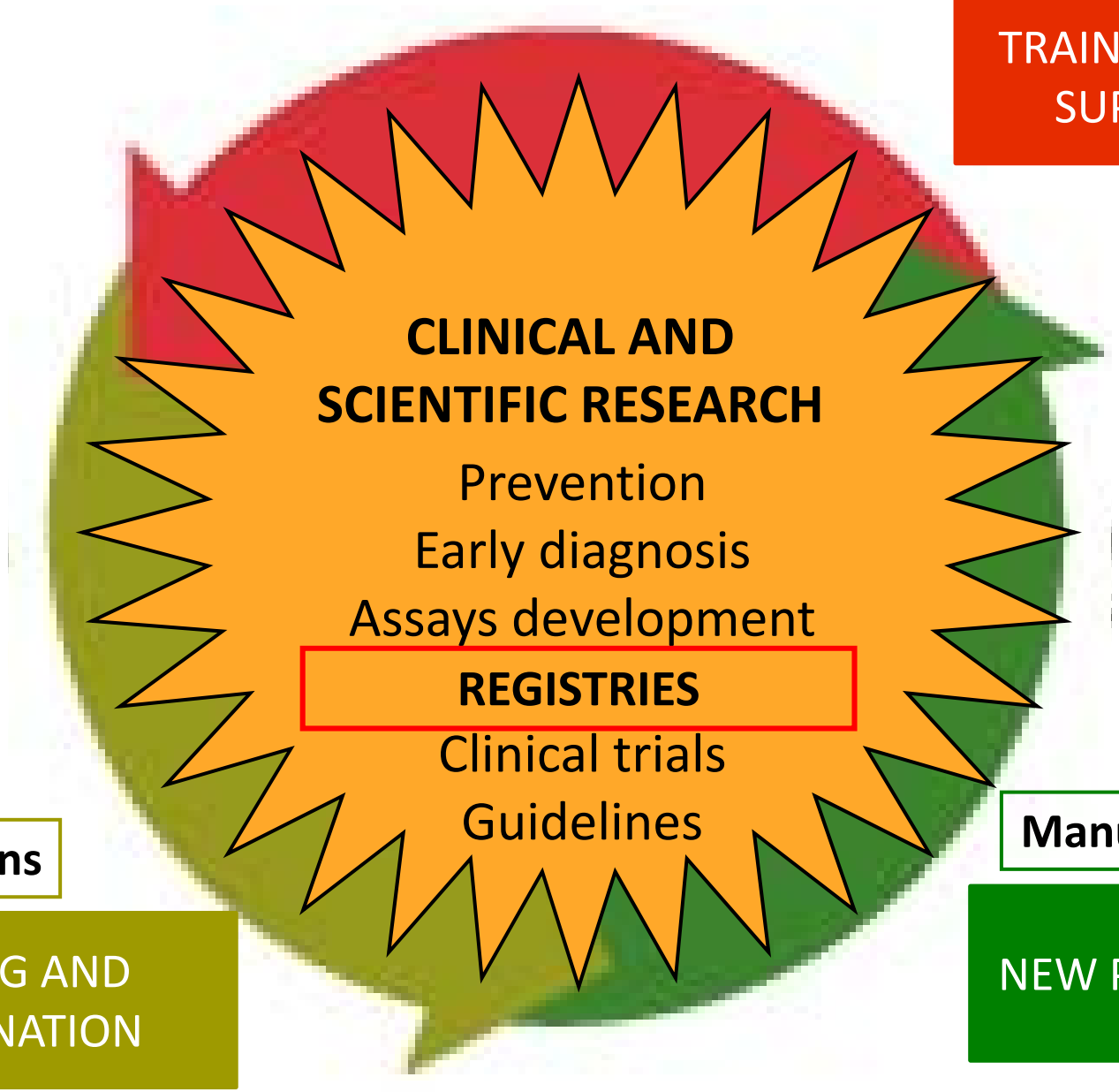
# Main limitations in rare diseases

Lack of data

Low prevalence

Limited clinical experience and availability of treatments

# The needs




**Patients association**

TRAINING AND SUPPORT

**Institutions**

FUNDING AND COORDINATION

**Manufactures**

NEW PRODUCTS

**In 2010 the Agency for Healthcare and Quality (AHRQ) published the second edition of the landmark handbook REGISTRIES FOR EVALUATING PATIENT OUTCOMES**

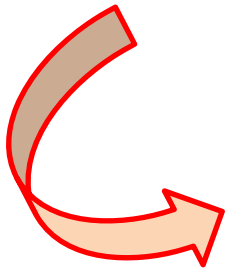
A registry can be defined as

"an organized system that uses **observational study methods** to collect **uniform data** to **evaluate specified outcomes** for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes

R. Gliklich, N. Dreyer, eds. "Registries for Evaluating Patient Outcomes," second edition, (Agency for Healthcare Research and Quality, Rockville, MD, September 2010).

# Why we need registries?

**Disease/patient registry** are powerful tools with considerable potential for rare disease research



- Observing course of disease
- Prevalence
- Understanding variations in symptoms
- Relationship between the laboratory phenotype and clinical severity
- Treatment schemes
- Long-term outcomes with different treatment schedules
- Side effects/safety issues of treatments
- Cost-effectiveness of treatment

«Good information is the best medicine»
Donald A. B. Lindberg, Director of National Library of Medicine

# Needs in Hemophilia

The arrival of new hemostatic products requires:

- new design of appropriate clinical trials
- improvement and harmonisation of registries
- a well documented post marketing surveillance

Rigorous and prolonged independent surveillance studies may replace some of the pre-approval studies and speed up the approval process and improve the identification of complications and side-effects

# FVIII, FIX and RCDs ISTH - SSC project: Standardization of post-registration surveillance

**THE MANDATE:**

- Standardisation of methods for monitoring long-term safety/efficacy of novel long-acting products or new hemostatic agents for treatment of hemophilia
- The Project Group is composed by physicians, regulatory agencies (EMA, FDA) and patients associations (WFH, EHC, NHF)
- This project will be structured in two main steps:
  1. **setting up a minimum set of data for monitoring safety and efficacy and obtaining approval of this template by Regulatory agencies and Institutions**
  2. performing an observational study of at least 5 years
- The present project is focusing on the first step

# Safety evaluation

ACTIONS TAKEN:

•A minimal data collection scheme was drafted starting form the analysis of the available registries/databases

•It contains information on safety of each patient using standard or new drugs in order to carry on a post marketing surveillance

ACTIONS IN PROGRESS:

•Members of the committee are evaluating this questionnaire (P. Collins, S. Pipe, M-Makris, A. Srivastava, F. Peyvandi)

•The data collection scheme will be sent to FDA and EMA and to manufacturers for their comments

•Data collection scheme will be available on ISTH website for comments from scientific community

# Harmonised data collection system

**FIRST STEP**

**EMA request for the first 100 ED**

- TYPE AND NAME OF CONCENTRATE
- DATE OF FIRST INFUSION
- INHIBITOR TESTING SCHEDULE →
- INTENDED TREATMENT REGIMEN
- DATE AND REASON FOR EACH ED
- TOTAL NUMBER OF EXPOSURES PER YEAR
- MEAN DOSE PER Kg PER PATIENT/YEAR
- ADVERSE EVENTS
- LONGER ACTING PRODUCTS: monitoring of renal and hepatic function (annual check-up) and immunogenecity against PEG and any other fragment used

testing schedule

| | Previous product | Test product ED1 | Test product ED10-15 | Test product ED50-75 | Test product ED ca 100 |
|---|---|---|---|---|---|
| **Inhibitor* (after washout)** | X (new patient - not in pre-authorization studies) | X baseline inhibitor testing prior to first infusion | X | X | X |
| **Recovery** | X | | X | X | X |

*Testing should also be carried out if there is any suspicion of an inhibitor

# Harmonised data collection system

**SECOND STEP**

**Collection of information on any adverse events every 6 months**.

Specific information on:

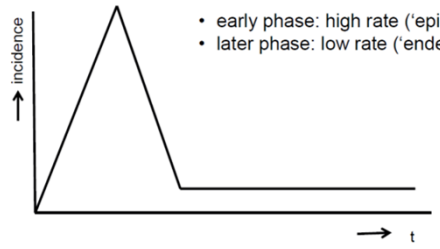
- INHIBITOR, DEATH, MALIGNANCY, THROMBOSIS, NEW INFECTION, ALLERGY, OTHER
- LONGER ACTING PRODUCTS: monitoring of renal and hepatic function (annual check-up) and immunogenecity against PEG and any other fragment used

# Sample size

3 categories of patients will be included:

- PUPs
- PTPs who never used the product in study
- PTPs from pre-authorization studies with the product in study

The nature of post FVIII exposure inhibitor incidence is 'biphasic' [1]




## Epidemic phase

- The measured outcome is cumulative incidence (events/people)
- The sample size is based on the predefined inhibitor risk to be excluded

## Endemic phase

The rate itself is the effect measure (events/person-time)

- The sample size is dependent on the predefined of inhibitor development to be excluded
  he person-time accrued in the study

**THE INCIDENCE OF INHIBITOR TO BE EXCLUDED SHOULD BE PRE-DEFINED**

| | Observed number of inhibitors allo | | |
|---|---|---|---|
| | 0 | 1 | |
| Cumulative incidence ruled out* | | | |
| 4 | 91 | 137 | 178 |
| 5 | 72 | 110 | 142 |
| 6 | 60 | 91 | 118 |
| 7 | 51 | 78 | 101 |
| 8 | 45 | 68 | 88 |
| 9 | 40 | 60 | 78 |

| | Observed numbers of inhibitors allowed | | |
|---|---|---|---|
| | 0 | 1 | 2 |
| Incidence rate (per 100 person-yrs) | | | |
| 2 | 185 [16%]† | 279 [23%] | 362 [30%] |
| 3 | 123 [29%] | 186 [45%] | 241 [57%] |
| 4 | 93 [40%] | 140 [59%] | 181 [73%] |
| 5 | 74 [48%] | 112 [69%] | 145 [82%] |
| 6 | 62 [54%] | 93 [76%] | 121 [88%] |
| 7 | 53 [59%] | 80 [81%] | 104 [91%] |
| 8 | 47 [63%] | 70 [84%] | 91 [94%] |

1. DiMichele DM, et al. Design of clinical trials for new products in hemophilia: communication from the SSC of the ISTH. J Thromb Haemost 2015

# Storage of data

- **National registries** have been proposed as the source of post-marketing surveillance data
- National registries are essential in order to give a high standard of care
- National registries must have:
  - robust organisation with national steering committee that includes patients
  - good IT infrastructure and quality data collection
  - mechanism for patients to report their side-effects
  - independent and long-term financing (secured by healthcare provider)

# Data analysis

- Analysis should be performed
  - at each country separately, followed by a meta-analysis at a central data coordinating center (e.g., at or supervised by regulatory agencies)
  - by independent academic figures and EMA could make decision on the base of these analyses with access to the data
- Data analysis could be performed:
  - annually
  - at statistically predetermined intervals
- Particular attention should be paid to the overlapping and duplication of patient information from multiple sources (registries, clinical trials)

# Dissemination of results

- Independent academic figures should interpret and publish data on peer-reviewed scientific journal
- Following, EMA should publish reports

# Summary of the needs

- Common structure for all registries to collect data on key parameters to enable cooperation between databases and countries
- Establishment of national registries in all European countries
  - Country specific incidence/characteristics of care
  - Comparative evaluation of care in Europe
- Central body to coordinate registries and provide forum to meet and discuss issues of mutual interest (incl. funding)
- Countries rather than centres should participate in international registries