EUHASS

(European Haemophilia Safety Surveillance)

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Disclosure

- Consultancy: CSL Behring, NovoNordisk
- Travel and honoraria to give lectures: Baxter, Bayer, Biogen, Biotest, Octapharma, Pfizer

- EUHASS financial support from Industry:
  Baxter, Bayer, Biotest, CSL Behring, Grifols, Kedrion,
  Novo Nordisk, Octapharma, Pfizer, SOBI/Biogen
  Partial support: BPL, LFB

All above payments were to the University of Sheffield

Background: AEs in Haemophilia

- Patients with haemophilia have suffered more from AEs than any other group
- Haemophilia treaters deal with the effects of AEs daily
- Reporting systems have been available for years but are poorly used
- It is not all about inhibitors in PUPs
- It is not all about FVIII replacement therapy

Some Current AE Issues

- Inhibitor in haemophilia A PUPs
  - 2nd vs 3rd generation: PedNet, UKHCDO, FranceCoag vs EUHASS
  - PD vs Recombinant: FranceCoag vs PedNet, EUHASS
- Inhibitors in PTPs
  - Full length vs B-domain deleted
- FXI concentrate thrombogenicity
- Do fibrinogen concentrates cause thrombosis?
- Perioperative FVII concentrate related thrombotic risk
- Product thrombogenicity in 2A von Willebrand disease
- Variant CJD risk with UK cryoprecipitate since fibrinogen concentrate is not licensed for acquired disorders in the UK

EUHASS
(European Haemophilia Safety Surveillance)

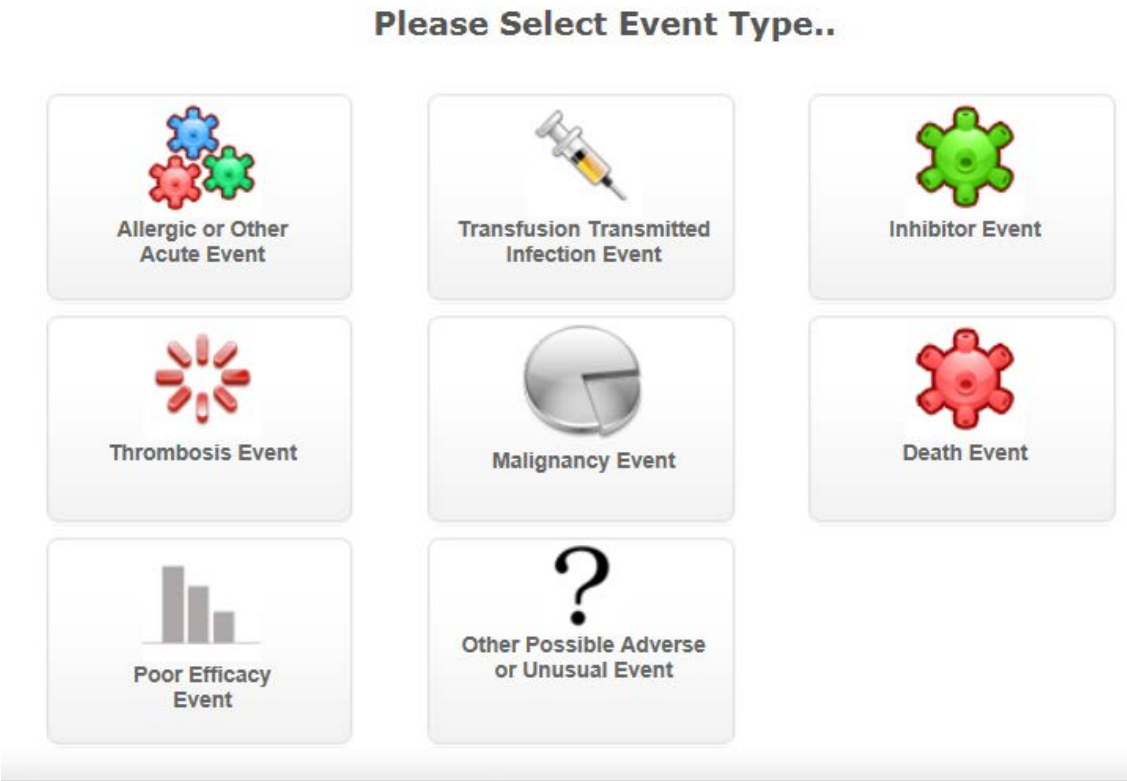
- Adverse event surveillance scheme
- European
  - Identical system in Canada (CHESS)
- Sentinel centres
- Prospective
- Electronic
- English language
- Started 1st Oct 2008

EUHASS practicalities

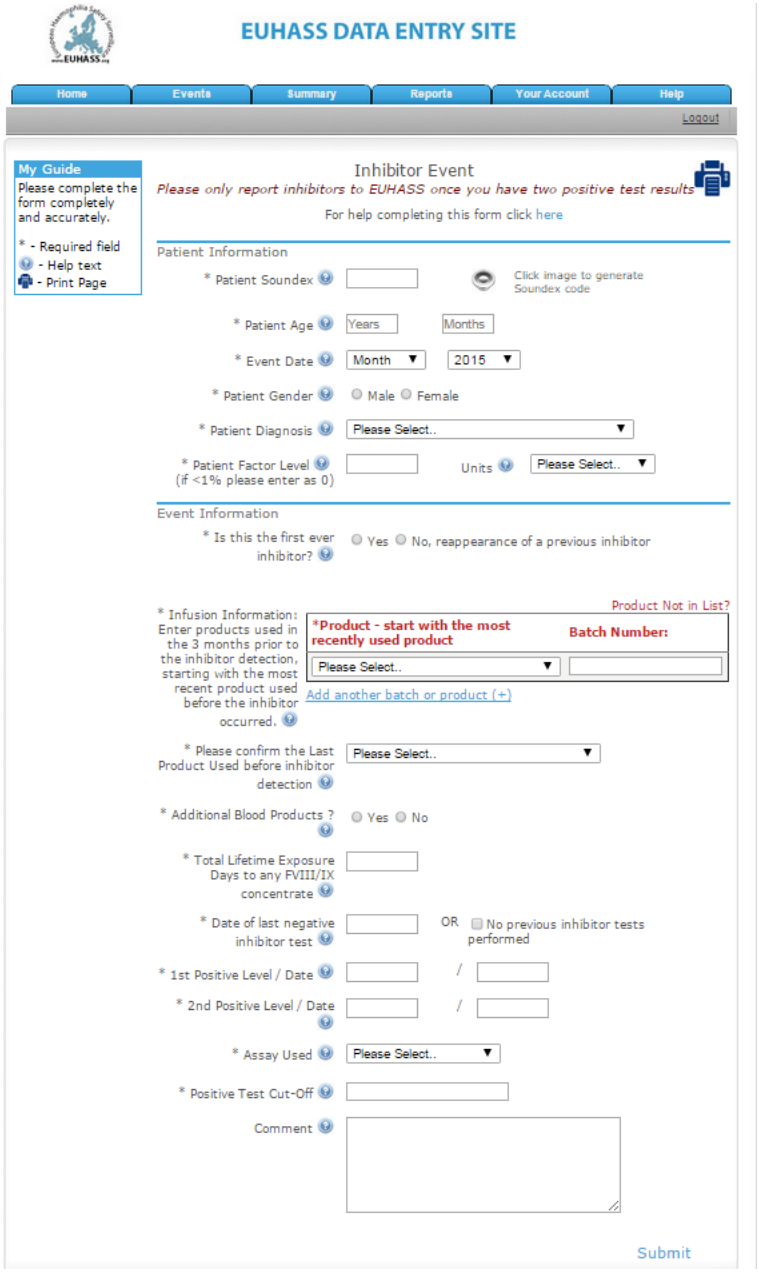
- Project lead: M Makris, Project manager: E Gilman
- Data ownership: EAHAD (Professionals organisation) and EHC (Patients organisation)
- IT management: MDSAS Ltd based in Manchester and also supporting UKHCDO and CHESS
- Funding
  - 2008-2011: European Commission (60%) + Industry (40%)
  - 2011-2012: EAHAD
  - 2012-2015: European Commission (60%) + Industry (40%)
  - 2015+ Industry

EUHASS Participating Centres

EUHASS: data on adverse events



Makris M, et al. Thromb Res 2011; Suppl 2:22



EUHASS data entry form for inhibitor reporting.

Specific help information for each data point. This is text +/- video guidance

Patients for Surveillance

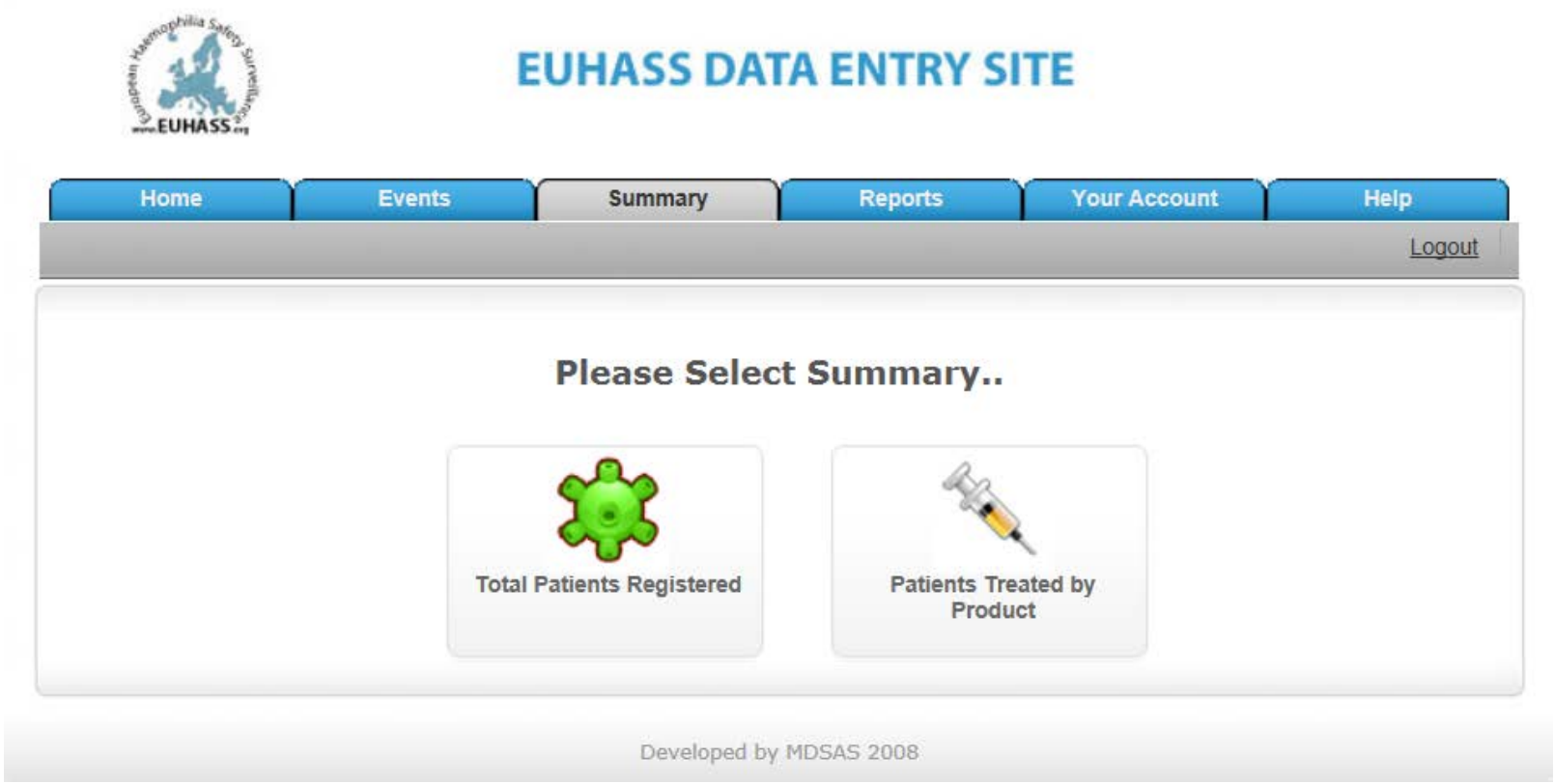
- Haemophilia A and B – all severities
- All VWD 2, 3 and severe type 1 (<15% VIII:RCo)
- Other coagulation factor deficiencies

- Since 2012:
  - acquired disorders haemophilia and VWD
  - Severe inherited platelet disorders

Data submitted

- Event specific
  - Generic and event specific questions
  - Events reported live when they occur, or
  - 3 monthly
- Cumulative data on surveyed population
  - Annually
  - By diagnosis
  - By clotting factor concentrate

EUHASS: No. of patients at risk



EUHASS Data: First 5 Years

1 Oct 2008 – 31 Dec 2013

- 78 haemophilia centres
- 26 European countries
- 35,567 patients

EUHASS Patients Under Surveillance Jan 2013- Dec 2013

	Total	Severe	Concentrate treated during the year
Haemophilia A	**15,926**	**6,750**	**8,049**
Haemophilia B	**3,365**	**1,169**	**1,525**
Other bleeding disorders	16,276	1,989	2,022
Total	**35,567**	**9,908**	**11,596**

Adverse Events Reported

	Year 1-5
Centres reporting	78
Allergic/Acute reactions	113
Transfusion-transmitted infections	0
Inhibitors – first occurrence	259
Inhibitors – recurrence	31
Thrombosis within 30 days of concentrate	73
Thrombosis with no concentrate in 30 days	51
Malignancies	262
Deaths (from any cause)	434
TOTAL	**1223**

Data checks

- Automatic logic tests at the time of data submission
- Project lead informed live at time of event reporting. Follow-up questions and comments added to events
- Lists of events and at risk patient data sent back to centres to confirm accuracy. Only confirmed results used

Publications

- Background
  - Makris et al. Thrombosis Research 2011; 127 (suppl 2):S22-S25
- Method for PUP inhibitor Analysis
  - Fischer et al. Haemophilia 2012; 18:e241
- Inhibitors in severe PUPs and PTPs
  - Fischer et al. Thrombosis and Haemostasis 2015; 113:968-975
- Inhibitors in moderates and milds
  - Fischer et al. Thrombosis and Haemostasis (in press)
- Overlap between registries
  - Fischer et al. Haemophilia (in press)

Reports

- 3monthly
  - Mainly with lists of events
  - Jan-Mar 2015: Released May 2015
- Annual report
  - With some analysis on rates
- Product specific reports
  - 63 reports issued

EUHASS strengths

- Large
- Prospective
- Simple
- Live reporting at time of event possible
- All bleeding disorders
- All adverse events
- All products
- All European countries

EUHASS weaknesses

- PUP inhibitor rates depend on constant usage
- Limited data collected
- No central testing of inhibitors
- No audit of data by visiting centres
- Anonymous
- Variability in reporting on time
- Not GCP level reporting
- No long term funding
- No efficacy data

Clinical trial product reporting

- Centres participating in clinical trials sign confidentiality agreements that essentially prevent them from reporting adverse prevents to registries by product name

- EUHASS has a single product category called “Unlicensed Clinical Product”.
- EUHASS does not know the name but collects the event

- Proposal: Allow centres to report adverse events with trial products by name but ask registries not to make this public until a product is licensed

Registry overlap

- So far not a big problem
- We know the centres participating in the different registries and the time the centres participated in the different registries
- Duplicate reporting in EUHASS prevented by soundex coding

From 2014 onwards

- UKHCDO is the UK National registry. Has an adverse event reporting system which is initially identical to EUHASS.
- Any reported event from participating centres gets anonymised and passed electronically to EUHASS
- For any inhibitors the UKHCDO asks for much more detailed information which is not passed onto EUHASS