European Haemophilia Safety Surveillance System (EUHASS)

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Pharmacovigilance

• Voluntary by health professionals and patients
  – Often not used
  – Too busy, not aware of the scheme
  – Believe adverse event well known
  – Publish own series first
  – Do not report until certain

• Mandatory by manufacturers
  – Post marketing surveillance
  – Small
  – Selected patients
Pharmacovigilance Need in Haemophilia

• Large multicentre
  – to detect rare events
  – rare disease

• Simple
  – Busy clinicians
  – Multicentre
  – English not first language

• Prospective
  – Avoid recall bias

• Single scheme for all products
EUHASS
(European Haemophilia Safety Surveillance System)

- Multicentre European Surveillance System
- In English only, initially
- Electronic only, initially
- Computer system developed in Manchester
- Co-ordinated from Sheffield
- Epidemiology support from Utrecht
EUHASS partners

- Main partner – University of Sheffield
- Associate partners – 4
  - European Haemophilia Consortium
  - University of Milan
  - Van Creveld Clinic, Utrecht
  - UKHCDO Ltd
- Collaborating partners: 42 from 26 countries
- Additional partners: 8
Participating Countries

Austria, Belgium (2), Bulgaria, Cyprus, Croatia, Czech Republic (2), Denmark (2), Finland, France (4), Germany (4), Greece (3), Hungary, Ireland, Italy (7), Latvia, Lithuania, Netherlands (2), Norway, Poland, Portugal (3), Romania, Slovakia, Spain (2), Sweden (2), Switzerland, Turkey (2), UK (3)
Patients for Surveillance

• Haemophilia A and B – all severities
• All VWD 2, 3 and severe type 1 (<15% RCo)
• Other rare disorders:
  – Fibrinogen defects
  – Combined deficiencies of V+VIII, II+VII+IX+X
• Acquired disorders excluded
• Female carriers with low FVIII/IX levels included
Patients Under Surveillance

• Partners who agreed to take part have the following numbers of patients registered:

• Total patients of interest: 14,522
• Haemophilia A: Total: 10,733; Severe: 5,074
• Haemophilia B: Total: 2,094; Severe: 812
• VWD type 3: 304
• VWD type 2: 928
• VWD type 1 (<0.10u/ml VIIIIC or RCo): 463
Reported Events

- Inhibitors
- Infections
- Allergic reactions
- Thromboses
  - DVT/PE
  - New cardiovascular events (MI or Stroke)
- New malignancy diagnosis
- Deaths
EUHASS

- 3 monthly submission of adverse events
- Email reminder at submission time
  - -4, -2, -1 week and time 0
- Ability to enter data live
- Electronic reminders of late submission
  - +1, +2 week emails, then telephone call
- If >21 day delay, then data can not be included in the report which is issued at 28 days after each 3 month surveillance
3 monthly Question

• Have you had in your centre any of the reportable (listed) events?

• If yes, follow-up screens will open up for each event
  – Generic questions
  – Specific questions

• How many patients with severe haemophilia A and <50 exposure days were managed in your haemophilia centre in the last 3 months?
Generic information requested if an event is being reported

- Soundex code
- Month and year of the event
- Age
- Sex
- Diagnosis
- Lowest clotting factor level

- Anonymous reporting using centre identification coding
- Soundex coding where more than 1 centre in the country (prevents duplicates and remains anonymised)
Soundex coding

• Uses an established algorithm
  – Unable to work out the surname from the code
  – Very simply derived using an electronic program

• Examples
• Makris = M262
• Other M262 names: Macgregor, Majors, McGeorge, Mushrush etc
• Klatte = K430
• Other K430 names: Kellett, Kilday, Kalota etc
Specific Follow-up Questions: e.g. for inhibitors

- Only reported when confirmed on 2 samples
- Name of concentrate involved
- Question about whether was the only product used
- Number of exposure days
- Actual inhibitor level on the 2 samples
- Assay used and cut-off
Every 12 months (plus M3)

- Centres will be asked for data on their exposed population

- This will allow incidence rates for adverse events for the different concentrates to be reported.
<table>
<thead>
<tr>
<th></th>
<th>Total patients registered</th>
<th>Severe patients registered (&lt;1% FVIII/IX)</th>
<th>Patients treated with concentrate or FFP or Cryo in last 12 months</th>
<th>Patients treated with bypassing agents in last 12 months</th>
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<tbody>
<tr>
<td>Haemophilia A</td>
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<td>Haemophilia B</td>
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<td></td>
<td>Total patients treated</td>
<td>Severe patients only</td>
<td>PTPs</td>
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<td>&lt;50 Lifetime exposures*</td>
<td>Previously on product</td>
<td>Switched during the last 12 m</td>
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<td>Recombinate</td>
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<td>Benefix</td>
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Reports

• 3 monthly electronic reports of running totals by centre, country and overall cohort
  – distributed to partners and funding partners from industry at same time, EMEA, FDA

• Annual more detailed electronic and paper reporting with commentary
  – Freely available

• Utrecht responsible for all study reports
European Haemophilia Centre Database

• This will be developed and maintained by the European Haemophilia Consortium.
• Will be on the EUHASS website
  – Public: Details of all centres
  – Private: Email contact lists
• Standard demographic details plus how to get 24 hour haemophilia care
• Six monthly updates
• Used to set up a Rapid Alert System
Rapid Alert System

- Uses European haemophilia centre database details
- Includes all haemophilia centres in Europe irrespective of whether they are taking part in the study or not.
- One or more senior staff will be identified in each centre to be notified by the Rapid Alert System
- Activation rules in place
- Immediate Europe wide dissemination of information after discussion with regulators and manufacturers
European Clotting Factor Concentrate Database

- Coordinated from Milan
- Database of all concentrates available in Europe
  - Name, alternate names
  - Properties: plasma source, country of manufacture, donor testing, plasma quarantine, viral inactivation
  - All publications relating to a product
  - Comparisons between products
UK Data

• Parallel system
• Collects more comprehensive data
• Full registry of all patients in the UK, including their factor usage in product and volume
• Negotiating to modify dataset so that all the EUHASS data is collected every 3 months.
• Will be used for validation of the EUHASS data set
• Data ownership will remain with the UKHCDO
<table>
<thead>
<tr>
<th></th>
<th>EUHASS</th>
<th>UKHCDO</th>
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<tbody>
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<td><strong>Countries</strong></td>
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<tr>
<td><strong>Centres</strong></td>
<td>42</td>
<td>80</td>
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<tr>
<td><strong>VWD type 2A</strong></td>
<td>928</td>
<td>648</td>
</tr>
<tr>
<td><strong>VWD type 1 (&lt;10%)</strong></td>
<td>463</td>
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<tr>
<td><strong>Data ownership</strong></td>
<td>EAHAD</td>
<td>UKHCDO</td>
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</table>
Participation of other centres

• The limit of 42 centres was due to logistics of the EU application.
• Study will provide small funding to centres named in the original application.
• No funding will be provided to UK centres as part of the UKHCDO reporting arrangement.
• Other centres will be welcome provided:
  – They agree to provide prospective data
  – They accept they will not get funding
  – Initially additional centres will go on a waiting list but should be able to start within 6 months.
Possible participating centres

• Those in the original application

• Groups as part of a national organisation or region eg UKHCDO

• Individual centres
Project Timeline

• Time M0
  – 1st October 2008
  – M3 - Provide data on number of patients registered and number treated with concentrates in previous 12 months

• Time M4
  – Training at a central European location

• Time M3, M6, M9, M12
  – Submit adverse event data electronically

• Time M12
  – Provide data on number of patients registered and number treated with concentrates in previous 12 months

• Time M13-M36 – Repeat as for the first year
Long Term Plan

• EUHASS will run for 3 years in sentinel centres
• By the end of the project the IT issues of the simple system will have been resolved
• Individual countries will be encouraged to run a EUHASS type of program among all the haemophilia centres in their countries

• Since data collection will be uniform and the methods compatible, it should be possible for European reports to be produced.
Funding

• 60% EU

• 40% Pharmaceutical industry
  – Partners: Biotest, Baxter, Bayer, Grifols, Wyeth, CSL Behring, LFB, Novo Nordisk, Octapharma
Welcome:
Welcome to the European Haemophilia Safety Surveillance project website.

The objective of this site is to provide information about the European Haemophilia Safety Surveillance system. This site will disseminate results about the safety of treatments with coagulation factor concentrates in Europe and will shortly provide information about all the haemophilia centres in Europe.

Click here for more information about the project.

Participating Centres Log In
Log-in to the EUHASS private web site (participating members only).
Site log-in

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