Industry Perspectives on ATHN and the Data...

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Overview

- What’s the perspective of industry on ATHN and the ATHN dataset?
  - Regulatory/safety related issues
  - Non-regulatory/safety issues

- What lessons learned can industry impart?
  - Less is often better than more
  - Small wins up front are critical

- What would it take for industry to feel comfortable with ATHN and the data?
  - Quality and completeness
  - Demonstrated success
What’s the perspective of industry on ATHN and databases?

• Pharma is generally obsessed with numbers...
• Key questions or numbers include
  • Epidemiology
    • Trends in patient counts, HTC vs non-HTC
  • Treatment paradigms
    • On demand, prophylaxis, ITT
    • Children, Adolescents, Adults
  • Product use and utilization
  • Safety signals (AE incidence)
    • Thrombotic events
    • Immunogenicity (PTP, PUP, other)
What’s the perspective of industry on ATHN and databases?

- Data sources are abundant...
  - Clinical trials
    - Product studies (phase I-III, phase IIIB/IV)
    - Class/cohort studies (Intl. ITT, RODIN, SIPPIT,...)
  - Registries (HTRS, FIX, EACH-2, SACHA, GTR, STER,...)
  - Surveillance/epidemiology
    - CDC (UDC 1.0, Inhibitor study, Babies...)  
    - EUHASS (PTP, PUP), UKHCDO (switch)  
    - Market Research Bureau (MRB) annual report
    - WFH survey
    - Other HTC-based and patient-based surveys
      - Utilization (HUGS) and shipment (HHC)
      - Payor (CMS, Solucient, Premier, Innovus, ...)
What’s the perspective of industry on ATHN and databases?

- Regulatory-related issues
  - Efficacy
    - Post approval trials (phase IV, observational, registries)
  - Safety and adverse event reporting
    - General
      - Baseline safety or immunogenicity (EUHASS model)
    - Product-specific
      - Post approval trials (PASS, registries)
      - Literature
      - Spontaneous (unsolicited) reports
Post-approval efficacy/safety studies

- **Post-approval requirements**
  - Agreed upon with FDA/EMA prior to launch
  - Can include Risk Evaluation and Mitigation Strategies (REMS)
  - Typically need to be addressed with global studies and detailed data collection around treatments and outcomes

- **Post-approval studies**
  - Protocol driven (phase IIIb/IV)
  - Observational
    - Post-approval safety studies (PASS)
    - Registries (disease or product)

- **Management**
  - Internal (trial ops, project/site/data management, statistics)
  - External (CRO, ATHN?)
  - Hybrid

Execution of PMS studies is critical since continuing marketing authorization is at stake.
• Objectives

  • Monitor the safety of treatments (Hemophilia and CBD)
  • Inform clinicians, regulators and other interested parties of the treatment patterns and AEs reported
  • Establish a database of EU HTCs
  • Establish a directory with information/pubs on clotting factors
  • Set up a Rapid Alert System to immediately notify professionals if a severe or unexpected AE is reported

• Scope

  • 3 years from 10/1/08

• Funding

  • 60% EAHC
  • 40% 9 companies

[www.euhass.org accessed 9/13/2012]
<table>
<thead>
<tr>
<th>Diagnostic categories included in EUHASS</th>
<th>Events to be reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia A (&lt;40% FVIII:C)</td>
<td>Allergic or other acute event</td>
</tr>
<tr>
<td>Hemophilia B (&lt;40% FIX:C)</td>
<td>Transfusion transmitted infections</td>
</tr>
<tr>
<td>vWD (type 1 if vWF:Rco &lt;15%)</td>
<td>Inhibitors</td>
</tr>
<tr>
<td>vWD type 2 or 3</td>
<td>Thromboses</td>
</tr>
<tr>
<td>Afibrinogenemia</td>
<td>New cardiovascular events</td>
</tr>
<tr>
<td>Hypofibrinogenemia</td>
<td>New malignancy diagnoses</td>
</tr>
<tr>
<td>Dysfibrinogenemia</td>
<td>Deaths</td>
</tr>
<tr>
<td>Factor II deficiency</td>
<td></td>
</tr>
<tr>
<td>Factor V deficiency</td>
<td></td>
</tr>
<tr>
<td>Factor VII deficiency</td>
<td></td>
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<tr>
<td>Factor X deficiency</td>
<td></td>
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<tr>
<td>Factor XI deficiency</td>
<td></td>
</tr>
<tr>
<td>Alpha 2 antiplasmin deficiency</td>
<td></td>
</tr>
<tr>
<td>Combined FV/FVIII deficiency</td>
<td></td>
</tr>
<tr>
<td>Combined FII/FVII/FIX/FX deficiency</td>
<td></td>
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**EUHASS Reports**

- Quarterly report of adverse events
- Annual report (AE rate by diagnosis, trx status, clotting factor)
- Distribution
  - Participating centers
  - Pharmaceutical sponsors
  - National patient groups (via EHC)
  - EMA/FDA
  - Healthcare professionals (via EAHAD)
### 3 Year Update (WFH 2012)
- 74 centers, 26 EU countries
- 14,467 hemophilia A patients (6,210 severe)
- Inhibitor rate

<table>
<thead>
<tr>
<th>Group/Product Type</th>
<th>Inhibitors</th>
<th>Incidence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe PUPs – rFVIII</td>
<td>65/250</td>
<td>26%</td>
<td>20-32</td>
</tr>
<tr>
<td>Severe PUPs – pdFVIII</td>
<td>6/40</td>
<td>15%</td>
<td>6-30</td>
</tr>
<tr>
<td>Severe PTPs – rFVIII</td>
<td>17/8896</td>
<td>0.19 /100 pt yrs</td>
<td>0.11-0.31</td>
</tr>
<tr>
<td>Severe PTPs – BDD rFVIII</td>
<td>-</td>
<td>0.38 /100 pt yrs</td>
<td>0.14-0.82</td>
</tr>
<tr>
<td>Severe PTPs – FL rFVIII</td>
<td>-</td>
<td>0.15 /100 pt yrs</td>
<td>0.08-0.27</td>
</tr>
<tr>
<td>Severe PTPs - pdFVIII</td>
<td>8/3573</td>
<td>0.22 /100 pt yrs</td>
<td>0.10-0.44</td>
</tr>
</tbody>
</table>

Adverse event reporting and registries

- Registry definition
  - An organized system using observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition or exposure, and that serves a predetermined scientific, clinical or policy purpose(s).

- AE reporting requirements
  - “If the registry receives sponsorship in whole or part from a regulated industry, then the sponsor has mandated reporting requirements including stringent timelines.”
  - “The process for detecting and reporting AEs should be established in collaboration with the sponsor and any oversight committees.”
  - “Sites should be trained about how to identify AEs and to whom they should be reported.”

Figure 2: Best Practices for Adverse Event Reporting to FDA in Registries of Postmarket Products

- Follow good public health practices for reporting new or serious AEs (recommended practice, not mandated).
- Notify company and/or FDA about new or serious AEs.
- Report AEs in FDA periodic reports or PSUR if applicable.
- Aggregate study findings of adverse events.
- Does the registry receive sponsorship or financial support from any regulated industry?
- Does the registry have data collection with individual patient interaction?
- Trains site(s) in identification and reporting of AEs, including events of special interest and SAEs.
- Establish rules, roles, responsibilities for involved parties for oversight and reporting in conformance with registry design and applicable regulations.
- Are SAEs in temporal association with a drug under study recognized by a knowledgeable person?
- Is there a reasonable possibility that the drug caused the SAE?
- Notify responsible entity (e.g., company) as soon as possible, ideally within 24 hours.
- Company determines if the SAE is "unexpected" (based on labeling) in terms of type, specificity, or severity.
- Company reports SAEs considered unexpected and possibly related to own drugs to FDA within 15 calendar days of original report; reports for device-related deaths, serious injuries, or malfunctions are due within 10-30 calendar days.

Key elements
- Reporter information
- Identifiable patient information
- AE diagnosis
- Description/narrative
- Seriousness
- Relatedness/causality
- Suspect drug or biologic (with dose, time intervals)
- Concomitant medications
- Outcome/resolution

Reporting options
- Individual physician/HCP or The "Registry"
- To sponsor/manufacturer or To FDA (MedWatch)

Timing of reporting
- Serious AE
  - Within 24 hrs to manufacturer
  - Manufacturer has 15 days to investigate and report to FDA
- Non-serious AE
  - Periodically to manufacturer
Example: HTRS Registry

- Society owned registry supported by NNI since 1999
- Observational registry under IRB approval/informed consent
- Collects bleed and treatment information over time with outcomes on individual patients
  - Detailed data on specific dosing/exposure, con meds, and timing of AE relative to exposure
- Safety management plan
  - Specific requirements based upon sponsor’s SOPs
  - Triggers
    - Positive affirmation (Adverse event Y/N) links on bleed, surgery, ITT and follow-up forms
    - CRO surveillance for other triggers like hospitalization, mortality, new diagnoses (line infection) or procedures (port removal)
- Online AE forms
  - CRO routes SAE to all manufacturers electronically (<24 hrs)
  - All AE related to sponsor reported periodically
What’s the perspective of industry on ATHN and databases?

- Other industry interest in ATHN and dataset/platform
  - Investigator/society driven research
    - Cohort studies
    - Investigator initiated studies (IIS)
  - Key drivers for success
    - Network size and ease of communication
    - Standard nomenclature (inclusion/exclusion)
- Other issues to consider
  - Feasibility
    - Site/patient participation
    - Investigator agreement on objectives, scope, outcomes
    - Timeline to activate, complete, and publish
  - CRF over an EDC complexity (annual visit -> cohort, UDC,...)
  - ATHN study/project/site management (vs CRO partnership)
Example: Cystic Fibrosis

- CFF founded 1955 by consortium of patients and physicians
- Leading organization in the US devoted to cystic fibrosis
  - 80 chapters and branch offices nationwide
- Funds and accredits Care Center Network and research
  - 110 accredited CF Care Centers including 260 CF clinics
  - CFF Therapeutics (2000) - not for profit managing drug discovery and development
  - Therapeutics Development Network (1998) – 80 site research consortium with 13 transitional (early phase) specialty sites
  - CFF Registry (1960’s) captures ~ 26,000 (87%) US patients
- Networking (patients, families)
- Cystic Fibrosis Services (pharmacy)
- Advocacy initiatives
- Investment in research

Cystic Fibrosis Foundation Annual Reports and other materials accessed at www.cff.org
Example: Cystic Fibrosis

Median Predicted Survival Age, 1988-2010
Over 5 Year Bands

Survival by Birth Cohort

Percent Surviving

Age (Years)

1986-1990
1991-1995
1996-2000
2001-2005
2006-2010
What’s the perspective of industry on ATHN and databases?

- Other industry interest in ATHN and dataset
  - “ATHN Reports” plus...
    - Epidemiology (includes UDC/HRSA data)
    - Treatment paradigms (prescription data)
    - Product use and utilization (ATHNAdvoy)
      - Adherence/compliance, alignment with prescribed
      - Validation against 340B shipment data
  - Issues to consider
    - Necessary data elements required (core data set)
    - Extent of site participation (core/extended data)
    - Data elements uniformly captured (% complete)
    - Depth of historical data (trending, inhibitor status)
    - Actual use/utilization captured (vs prescription only)
What lessons learned can industry impart?

- Less is often better than more
  - Simpler cohort, fewer data fields, shorter duration and outcome
  - Simpler site then patient recruitment, lower site burden
  - Smaller site/project/data management footprint required
  - Easier to manage data quality (vs quantity)
- Small wins up front are critical
  - MedWatch reporting with electronic data transfer
  - EUHASS-type project
  - Engagement through demonstrated success
    - Multiple small cohorts
    - Publications track record (inclusive authorship policies)
    - Logistical kinks worked out (project mgmt, data, stats)
  - Hypothesis generating is fine...
    - “An answer” in 1-2 years over “the answer” in the future
What would it take for industry to feel comfortable with ATHN and the data?

- Assurance around quality of core data set
  - Transparency around quality and completeness of core data set
  - Impacts perception of quality for prospective projects
- Demonstrated success in developing/conducting studies
  - Resources for research/safety monitoring and studies
    - Research operations manager (even if CRO partnership)
    - Trial operations staff (or establish CRO partnership)
    - Stats/epidemiology (less important up front)
  - UDC/UEHASS/Cohorts
    - Rapid alignment around data elements and outcomes
    - Short project initiation timelines (grant/concept to FPFV)
    - Data demonstrating success (on time completion, results)
THANK YOU SO MUCH!