

# Cohort Studies from the ATHN Database – (Where can we go? How can we get there?)

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# Agenda

- ATHN: Launching into the Future
- Potential approaches to facilitating research
  - TIMI as a model for sequential trials
  - Implications of launching distinct cohorts
    - Data depth and quality
    - Financial
- Your thoughts: What research approaches and initiatives should we pursue?

# ATHN's Future

- ATHN aims to be the most convenient, accessible and sought-after network and database to facilitate research in bleeding disorders (and at some future time, thrombotic disorders)

# Database as of 9-5-11 by Demographics

Category	# of Patients	% of Patients
TOTAL AUTHORIZED PATIENTS	5141	100.00%
BY SEX		
Male	3588	69.79%
Female	1553	30.21%
Total	5141	100.00%
BY AGE		
0-2 years	242	4.71%
3-12 years	1535	29.86%
13-17 years	964	18.75%
18-21 years	551	10.72%
22-24 years	227	4.42%
25+ years	1622	31.55%
Total	5141	100.00%

# Database through 9-5-11 by diagnosis

PRIMARY DIAGNOSIS GROUP	# of Patients	% of Patients
Factor VIII Carrier	27	0.53%
<b>Factor VIII Deficiency</b>	<b>2036</b>	<b>39.60%</b>
Factor IX Carrier	12	0.23%
Factor IX Deficiency	609	11.85%
von Willebrand Disease	1146	22.29%
Rare Disorders	166	3.23%
Platelet Disorders	565	10.99%
Thrombotic Disorders with Identifiable Causes	182	3.54%
Venous Thrombosis	90	1.75%
Other/Unknown	308	5.99%
Total	5141	100.00%

**Why sponsors might be interested:  
Before ATHN it was hard to find 2000  
FVIII deficient patients!**

# How to Utilize ATHNdataset

## Reuse Standard Building Blocks Across Research Projects

### Feasibility Studies

- Site selection
- Hypothesis generation
- Power calculations

### Observational

- Leverages a quality dataset

### Cohort Studies

- Study data enriches the dataset

### Controlled Trials

- Case control studies and randomized trials

# ATHN's Role in Supporting Research

- Providing infrastructure powered by WebTracker
  - Integrated, translatable universal components
- Capacity Building
  - Funding for data entry personnel
- Cooperating and facilitating projects
  - ATHN Project Review Panel / communication to network
- Research Think Tank (July 2009)
  - ATHN as honest broker for feasibility studies
  - National platform to define and track cohorts
  - Eligibility screening
  - Consent tracking
  - Simplify reporting of safety information to FDA/sponsors
  - Quality of data

# ATHN's Sweet Spot: Cohort Studies

- Single Sponsor or potential role for consortia of sponsors
- All or subset of HTC's could participate in any given study
- Design to leverage standardized data already being collected at sites
  - Avoid double data entry
  - Work to ensure that the basic data entered forms robust basis for entering cohorts
    - Using hemophilia as an example
      - Severity
      - Factor(s) previously used
      - Inhibitor history (to some degree of detail)
- Data collected for this baseline purpose enriches the overall ATHN dataset

# Cohort study definition

- A group of subjects followed longitudinally.
- USUALLY prospective, at least in part
- Corollary
  - “Followed” implies collecting data from time to time.
- Many famous and infamous examples in epidemiology
  - (Neufeld favorites include the Bogalusa, Muscatine and Framingham Heart Studies)

# TIMI Consortium as an Inspiration if not a Model

- Not-for-profit academic research consortium of cardiology sites launched to facilitate multicenter clinical trials in coronary artery disease in 1984
- Thrombolysis In Myocardial Infarction (TPA trials).
- TIMI 1, TIMI 2, TIMI(n)
- Now up to TIMI trial 55 or so, 28 years later
- Each trial has an infrastructure, database, project managers, and a variable group of investigators
- Each trial has specific and distinct funding source
- Consistent endpoint definitions are a great strength
  - TIMI composite endpoint – “fatal or non-fatal MI, sudden death, or unstable angina”
  - TIMI perfusion grade, etc

# TIMI example, continued

- Because the trials are distinct, one can start before the prior one finishes. If more personnel and space are needed, this is accounted for as direct (staff) and indirect (rent) costs of starting the next trial.
- The infrastructure is familiar to sites. Training is facilitated at the central office.

# “What was TIMI 10?”

- **TIMI 10A/B**
- **Assessment of the clinical pharmacology of tenecteplase in humans with AMI**
- Evaluation of pharmacokinetics and gross safety and efficacy of TNK in 113 patients with AMI:
  - prolonged half-life allows for single-bolus administration,
  - TNK is highly fibrin specific with encouraging patency and safety profiles.
- A prospective angiographic comparison of single-bolus tenecteplase with accelerated alteplase in 886 patients:
  - rate of TIMI grade 3 flow at 90 minutes with tenecteplase 40 mg was comparable to that of accelerated alteplase

## Cohort Studies: Which to Pursue?

- Chronic co-morbid conditions such as obesity, cardiovascular disease or diabetes in an aging hemophilia population
- Rare bleeding disorders, e.g., Factor XIII deficiency
- Adults on prophylaxis
- Phase IV studies of newly FDA-approved drugs
- Adults with mild disease
- High titer inhibitor patients
- Tolerized patients
- PUPs
- Long acting vs. short acting products

# Adverse Event Reporting

- EUHASS – like reporting (European Haemophilia Adverse event Surveillance System presented at data summit 2009)
- Patient data drawn from the ATHNdataset
- Proof of concept required
- Benefits for FDA and industry
- Potentially industry-funded

# “Cohorts sound like a great idea! How do we start?”

- Job for today – think hard about some starting projects
- Finish defining and enforcing minimum elements for the most minimal ATHN dataset (with sensitivity to the costs of
  - Extensive data collection (this is why we need a minimum set)
  - Avoiding re-work to maximum degree possible
- Collect, audit baseline data (do we have it right?)
- (Raise money)
- Move from present state (finally launched!) to productive future.

# What should we start on?

- What is the “low hanging fruit?” for ATHN1 and ATHN2?
- ATHN to hire a statistician within the next few months to manipulate, evaluate the database, helping with concept generation.
- The CDC project might or might not define some of the early cohorts for ATHN

# What Distinguishes Cohort studies

- Specific Consent by participants (data broader than the limited dataset)
- Separate hypotheses and endpoints
- Distinct funding stream
  - Internal
  - Corporate Sponsors
  - Grants (including investigator-initiated studies)
- Baseline data for all participants might need to be more robust than it is now
- Specific additional work for the sites
  - (Implies additional resources needed at sites)

# How will this work, exactly?

- Each cohort needs to be defined and fleshed out as a protocol.
- Each cohort that requires patient identifiers (or potentially samples or interventions) will require IRB and consent process.
- The ATHN database tracks to which studies patients are consented, and these consented groups have pooled data for analysis.
- Sites will need budgetary arrangements with ATHN for each funded study. Ideally these will be standardized.





# Four examples

- 1. North American Chronic ITP registry (observational)
  - Retrospective and prospective, investigator initiated, philanthropic funding
  - 17 sites, 550 subjects
  - Q 6 month data updates, few specified data elements (bleeds, plt counts, treatments)
  - \$100 per patient total for duration of 4-5 year study
  
- 2. Thalassemia Longitudinal Cohort (observational)
  - Retrospective and prospective, NIH sponsored
  - 17 sites, 426 patients
  - Annual data update, dozens of specified data elements
  - \$600/patient /year for year 1, then \$300/year

# Examples, continued

- 3. UDC –
  - Prospective
  - Not strict per-patient reimbursement; hard to compare exactly. Our site got approximately \$130/patient per year, but this was highly variable based on size of site and region
  - Unfunded mandates which ideally would not be part of the ATHN cohorts (or why would anyone participate?)
  - Not exactly a single cohort, multiple purposes, multiple diseases.
- 4. HTRS registry
  - Post-marketing data on safety in patients eligible to receive rVIIa.
    - Retrospective (data of variable quality) and longitudinal
    - Generous reimbursement per data form

# Cohorts of enlightened self-interest (e.g. HTCs and 340B programs)

- Data to support the value of care in HTC model
- Data to counter claims of pharmacy benefit manager organizations about prescribing
  - “Dispense to prescription”
- Using data to improve outcomes
  - (What outcomes?)
  - Adherence data? ATHN/Advoy

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**THIS IS WORTH A PILOT STUDY – need weights, prescribed and dispensed doses. Goal 100,000,000 units at, say, 10-20 centers<sup>23</sup>**

# New CDC Database (after 10-1-11)

- Opportunities for more than one cohort
- Compare the UDC dataset
  - Hemophilia by severity
  - VWD
  - Inhibitor patients (vs not)

# We need your ideas and help!