Development of a Consolidated Pediatric Rheumatology Observational Registry*

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*The views presented in this presentation do not necessarily reflect those of the Food and Drug Administration.

Assessing Longer Term Safety for Products Approved for Children with JIA

- Products for polyarticular JIA are generally approved following approval for the analagous adult indication, i.e., RA, and a clinical trial in children
- Clinical trials, by their nature, are limited in duration and in the number of patients studied.
- Rare and uncommon adverse events are not always fully characterized at the time of approval.
- Therefore, in the past, FDA has asked pharmaceutical companies to study larger numbers of children in longer term treatment trials and in observational registries:
  - Postmarketing commitments prior to FDAAA.
  - Post marketing requirements since implementation of FDAAA, September, 2007

Postmarketing Registries

- Assess safety in “real-life” clinical practice

- Utility of registries
  - Identify safety signals of rare/uncommon adverse events.
  - Characterize longer term safety.
  - Assess event rates for safety signals discovered in spontaneous postmarketing reports.
  - Assess relative risk compared to other widely used therapies.
  - Identify factors that modify safety risks.
  - Known numerator and denominator from which to calculate event rates.
  - For rare events may not be able to precisely define risk but may be possible to estimate maximum risk, e.g., event rate is no more frequent than x /10,000 patients.

Ongoing and Completed Observational Registries

- ENBREL® (etanercept) AMGEN
  - Long-term use of Enbrel in at least 500 JRA patients for ≥ 3 years.
    - Etanercept alone (n=403) or Etanercept + MTX (n=198)
- HUMIRA® (adalimumab) Abbott Laboratories
    - 800 patients, 4 years to 17 years of age,
    - 10 year follow up period.
- ORENCIA® (abatacept) Bristol-Myers Squibb
  - 500 patients: more intense evaluation first 3 years; annual follow-up thereafter for malignancies, autoimmune disease, serious infections, for a total of 10 years.
- CELEBREX® (celecoxib) Pfizer
    - Prospective Observational Registry.

Challenges

- Currently, pediatric rheumatology observational registries are implemented product-by-product for indication for JIA.
- Pediatric rheumatologists have noted the limitations of the product-by-product approach to registries.
- Limitations of current pediatric rheumatology observational registries:
  - Fail to capture children who switch from one medication to another. Important data across medication changes are lost in product-specific registries.
  - Limited number of patients with JIA. It is difficult to enroll an adequate number of JIA patients into an individual product registry for the growing number of approved products for JIA.
  - Enrollment criteria may exclude important groups of patients.

Rationale for a Consolidated Registry

- A consolidated registry would enroll children with JIA on a variety of different medications and follow them long term
- A consolidated registry of JIA patients could support collection of longer term safety data and other information in children receiving a variety of approved products for JIA.
- Consolidated registry would allow assessment of postmarketing safety of a new product approved for JIA, including a “built-in” control group to allow detection of safety signals.
- Children could be followed even as their medication is switched to other treatments.
- A registry could allow less restricted enrollment criteria to include a more representative experience.
- Research opportunities could be incorporated to advance the subspecialty.

May 12-13, 2009 Meeting

- FDA convened an open public meeting to bring together key stakeholders to discuss challenges and opportunities.
- Prior to the meeting FDA worked with representatives of pediatric rheumatology community (CARRA) and industry (PhRMA and BIO) to assure their active participation
- FDA also included active participation by representatives of European pediatric rheumatology (PRINTO), patient groups (AF), ACR, NIH

May 12-13 Meeting (cont.)

- Discussed:
  - lessons learned from existing registry experience, including CORRONA, JIA registries from Netherlands, UK .
  - Considerations from epidemiology perspective: signal detection, considering confounders
  - How a consolidated registry would fit into current regulatory framework
- Considered challenges of transition from product-specific registries to a consolidated registry.
- Considered funding challenges and potential approaches.
- Considered:
  - Structure of a registry, data collection and concerns about proprietary data;
  - Detecting safety signals;
  - Research opportunities.

May 12-13 Meeting: Outcome

- General consensus that a consolidated registry is desirable and should be developed
- Considerable additional work required concerning funding, governance, IT infrastructure, data standards, discerning safety signals
- Next steps:
  - CARRA representatives to write a manuscript for publication describing the meeting
  - CARRA representatives to organize a steering committee to move forward with implementing the registry

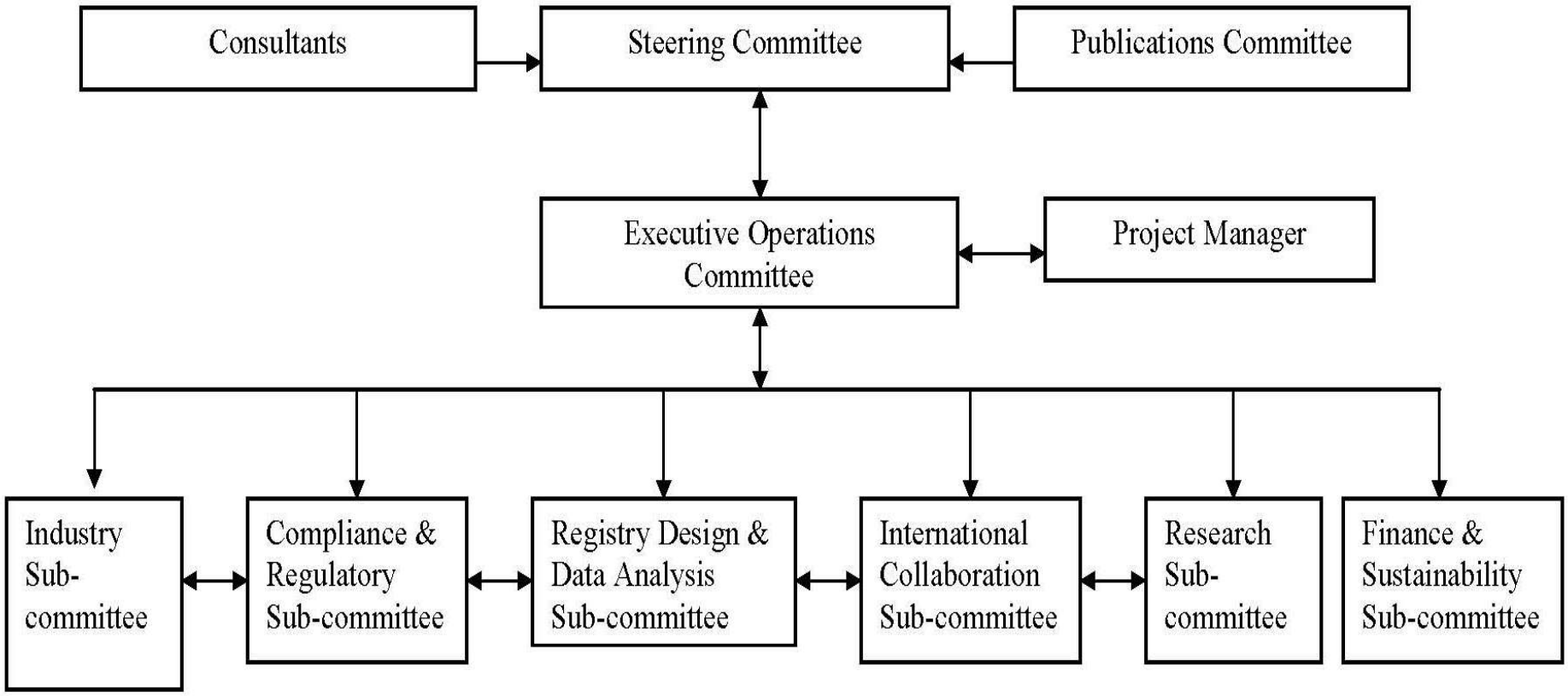
Consolidated Registry Task Force

- Task force organized to develop the registry has met by phone call and face-to-face at ACR annual meeting in October
- Membership intended to include all stakeholders:
  - Regulatory agencies: FDA, EMEA
  - Pediatric rheumatologists (CARRA, PRCSG)
  - European pediatric rheumatologists: PRES, PRINTO
  - Industry: PhRMA, BIO
  - Potential funding agencies – NIH (NIAID, NIAMS)
  - Patient organizations (AF, Friends of CARRA)
  - Professional organizations: ACR
- Includes members with expertise in statistics/epidemiology, information technology

Task Force Guiding Principles

- Priorities are safety surveillance, regulatory compliance, feasibility and research.
- Design registry to be scalable and flexible such that size, applications and functionalities can be added and changed as technologies and needs change
- Harmonization of data definitions with other registries in the US and international registry initiatives to allow sharing of data

JIA Consolidated Registry Task Force Organizational Chart



Overview of Registry Initiatives

Database Architecture

Go Grant
CARRAnet

Federated Database
Site databases

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Centralized database with Permissioned Sharing
Multiple privacy options
Data Validation
Biospecimen IT (i2b2/SHRINE)

Basic Data Entry
60 sites

Data Elements

CER Challenge Grant
CARRA Rx

JIA Consolidated Registry Task Force

CER
JIA, SLE, JDM, Scl, Vascu, Rare Diseases

- Epidemiology
- Outcomes
- Protocolized care

Safety surveillance and Regulatory data for Post-Marketing Compliance

US
International

Consolidation of data elements
Harmonization of data definitions

Sustainability

Financial Support Models

Public Private Partnerships

- Federal
  NIH
  AHRQ
  DHHS
  CDC
- Non-profit
  e.g., AF
  ACR
  FoC
  Disease-Spec Org
- Industry
  Pharma
  Biotech

- Comparative Effectiveness Research
- Safety and Pharmaco-Surveillance
- Clinical Trials
- Epidemiologic Research
- Translational Research
- Quality

JIA Consolidated Registry Task Force Workplan Timeline

	Activities	Oct-09	Nov-09	Dec-09	Jan-10	Feb-10	Mar-10	Apr-10	May-10	Jun-10	Jul-10	Aug-10	Sep-10
Steering Committee:	*Chairs: Kimura and Sandborg*												
	ACR Launch												
	Project/Work Plan												
	Funding for Task force												
	Benchmarking												
	Governance of Registry												
	Funding Model for Registry												
Compliance and Regulatory Committee	*Chairs Sobel and ?*												
	Data Elements for Compliance for FDA approval												
	Feedback from FDA Compliance and finalize data elements												
	EMEA input												
	Final review of data elements												
Industry Committee	*Chairs Sobel and Jahreis*												
	Data definitions of adverse events and serious adverse events												
	Pharma monitoring requirements for post-marketing data elements												
	Process for adjudication of risk attribution												
Registry Design Committee:	*Chair: Kimura*												
	Benchmarking existing safety registries												
	Identify and assemble all data elements												
	Create data definitions												
	Data analysis approach												
International Collaboration Committee:	*Chairs Wulfrat and Ruperto*												
	Idenftify common data definitions												
Research Committee:	*Chairs*												
	Coordinate with CER and CARRAnet Grants												
External/Independent Advisory Board:													
	Identifying members for Ext Adv Board												
	First meeting of Ext Adv Board												

Regulatory Issues

- Important to make sure that participation in the consolidated registry will meet regulatory requirements
  - Currently there is general agreement that a consolidated registry can be an effective way to collect long-term safety data that would meet regulatory needs in most cases
  - As new FDAAA law is implemented it will be important to make sure registry can satisfy those provisions
- Compliance issues:
  - FDA Compliance group has responsibility for assuring proper conduct of studies conducted as post-marketing requirements
  - To meet regulatory requirements it will be important to have assurance that data are accurate with provisions for data collection, cleaning, monitoring

Governance Issues

- Steering committee will discuss how various committees and sub-committees will be structured
- Independent Scientific Advisory Board
  - To include individuals without potential conflicts of interest

Funding

- Currently CARRA has obtained NIH funding that will help set up the infrastructure for the registry
- GO grant to fund CARRAnet
  - Will provide database architecture and initial entering of patients
- Comparative effectiveness grant to fund CARRA-RX
  - To study outcomes, epidemiology and protocolized care in a variety of pediatric rheumatic diseases
  - Will provide a robust dataset for the registry

Timelines

- Steering committee hopes to complete its work within 12 months
- Many issues still to be decided:
  - Funding
  - How/whether to incorporate existing registries into the consolidated registry
  - How to cooperate with other groups, e.g., European registry/registries

Summary

- A consolidated pediatric rheumatology registry has the potential to address several problems associated with product-specific registries
- Efforts to develop a registry have support and cooperation from variety of key stakeholders
- Essential to address key issues including funding, governance, database architecture & data elements, safety signal detection