Advancing the Development of Pediatric Therapeutics (ADEPT) Workshop Summary

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Disclosures

• The speaker has no financial conflicts of interest to disclose.

Workshop Summary

• Key Concepts
• Innovative Approaches
• Importance of Partnership
• Challenges and Caveats
• Future State and Next Steps
What words come to mind when you think about “Big Data” for pediatric safety?

National System Paradigm Shift

Regulatory science initiatives - EMA planned activity and projects:

1. The Task Force should identify all sources of big data and define the main drivers, in which they can be responsed to work to
2. The Task Force should produce a list of recommendations and big data roadmap
3. The Task Force should describe the current status of expertise, future needs and challenges
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Key Concept: Big Data and Safety

- Types of Questions
  - Exposure – depends on the data source
  - Outcome – depends on the completeness
  - Confounders – consider wide info sources (omics)

- Types of Information
  - Clinical characterization – use patterns
  - Population level estimates of risk
  - Patient level estimates of risk

According to US Food and Drug Administration
What does big data offer?

- **Breadth** – large numbers of individuals get us closer to the underlying source population
- **Depth** – increasing amount of data on each individual increases the chance that we will have measures of likely confounders
- **Diversity** – different types of data offer the potential to “cross check” findings for any particular data source
- **FDA-Sentinel system**: more than 100 million patient health care data

From: D Martin EMA big data workshop

What is unique about Big Data for pediatrics?

- Age by itself is not a barrier (if date of birth is known)
- Issues around exposure to medical products during pregnancy and birth outcomes
  - Complex to link moms and babies to assess birth outcomes
  - Health plan data challenges in days after birth
    - Coded for the mom or baby?
- Unique patterns of care?
  - Critical information dispersed (no data source has a clear)
  - Hospital, pediatrician, insurer, birth registry, vaccine registry
  - Do kids see more specialists leading to more data dispersion?
  - Care at school?
- Regulatory constraints/ research with minors
Key Concept: Big Data and Safety

• Driving Force
  — Need for Certainty – Fit for Purpose
  • Risk – to restrict use
  • Efficacy – to expand use

• Areas of Opportunity
  — Patient reported outcomes (surveys, apps)
  — Inference (lessons from machine learning)

Key Concept: Validation

• Validation of Data Elements
  — Medical record review
  — Assessing temporal relationship
  — Completeness of data against expected

• Validation of Findings
  — Multiple sites
  — Multiple studies or independent sites
  — Machine Learning – Internal & External validation

Key Concept: Big Data in Children

• Standards for age, gender, developmental
  — Note
  — Note
  — Note

• Incorporate developmental factors

Key Concept: Big Data in Children

• Family-centric analyses
• Genomics
Key Concept: Big Data in Children

- Long-term safety data
  - Key given long time horizon
- Challenges
  - No unique identifiers
  - Fragmented healthcare
  - Mobility and life changes (i.e. college, military)

Innovative Approaches to Big Data

other tools for clinical exploration

Videos and Papers at http://iperer.org
Neonatal Sepsis and SpellS

Question: Can we identify neonatal spells prior to onset of nosocomial infection?

- Thommandram et al., built a neonatal spells algorithm [3] for detecting spells activity in real-time

Classifications:
- central apnoea
-onasal apnoea
- obstructive
- obstructive central
- central obstructive
- isolated blood oxygen desaturation
- isolated bradycardia,

Event Stream Processing (Spark Streaming)

- Process with dataframes
- Interactively query with SQL
- Spark SQL
- MLlib
Importance of Partnerships

- Rare exposures & rare outcomes
- Shared knowledge and experience
- Efficient use of limited resources
Key Concept: Partnerships

• Types of questions (hierarchy)
  – Descriptive
  – Safety
  – Effectiveness
  – More complex questions

• Caveats
  – Health care delivery and access to meds differs
  – Clinical definitions may differ (neonate, live birth)

Key Concept: Partnerships

• Steps needed to pursue partnerships
  – Engage children, families, clinicians
  – Strategic collaborations
  – Careful design (exposure, outcomes, confounders)
  – Ethics/Data Protections
  – Sustainability

Link Primary and Secondary Data

OHDSI Open Source Partnerships
Key Concepts: FDA/EMA Partnerships

- Pediatric Cluster
  - PMDA, HealthCanada, EMA, FDA
  - Common approaches
  - Safety signal and responses
- Monthly Pharmacovigilance Calls (EMA/FDA)

Key Concepts: Partnerships

- How to bring the right people together
  - Note

Challenges and Caveats
Key Concepts: Challenges

- Limitations in phenotypes
  - Note
  - Note
- Heterogeneity in pediatric drug response
  - Note
  - Note

Biases and Causality Leakage

- Site/specialty effects:
  - Example: obgyns prescribe prozac
- Causality leakage:

(Examples: mortality prediction from pneumonia, ICU)

From your perspective, what barriers do you see in using “Big Data” to support you (or your organization’s) work?
Key Concepts: Ethics/Regulatory

- How actionable are results - regulatory
  - Depends on certainty of data
  - Future state – need standards on certainty, precision
  - Benefit:Risk Considerations
  - CURES – Real World Evidence
- How actionable are results – clinical
  - Depends on certainty of data
  - Guided by regulatory (off-label)
  - Available ≠ Accessible

Key Concepts: Ethics/Regulatory

- Changes in clinical and regulatory processes
  - Note
  - Note
- “Big Data” serve regulatory processes
  - Note
  - Note

Key Concepts: Ethics/Regulatory

- Adjustments that can be made
  - Recognize importance of trust
  - Where data reside is key
  - Advocate for appropriate ethics oversight
Next Steps/Future State

Genomic Based Mechanism of Action

- Cystic fibrosis is caused by one of nearly 2000 mutations.
- CF drug, ivacaftor which targets G551D mutation in the CFTR gene (4% of CF population).
- Delivers increases in FEV1 ~10%.

Indication gradually expanded to covers further mutations

The future
- Challenge of determining the level of evidence required to extend indications when further mutations are identified.

Looking to the Future

Visualization of the topology of complex data from the U-BIOPRED consortium of adult severe asthma cohorts

Cohorts are generated following the integration of multiple biomarkers
- How are the individual components validated?
- How reproducible are the cohorts?
- How is data weighted within the algorithms to define the cohorts?
- How do you identify the stability of the cohorts over time?
- Are the cohorts translatable to a defined patient population?

Aim: how do we generate certainty for regulatory decision making?

Implications for Effective, Safe AIs

Regulation
- Identify scenarios that matter.
- Require that data relevant to those scenarios are collected.
- Seek explanation, but not transparency.

Research/Tech
- Design systems to provide explanation.
- Determine how to extract information relevant to scenarios (including proxies).
Utility: During Drug Development Life Cycle
- Provide evidence to support acceptability of efficacy extrapolation for a given indication
- Support proof of concept
- Inform need for juvenile toxicity studies
- Identify settings for opportunistic PK studies
- Identify trends in short- and long-term product safety

Utility: Overall Product Safety
- Identify previously unrecognized, unlabeled serious ARs
- Capture product safety
  - Broader population (e.g., wider age range, more co-morbidities, variable disease severity, variety of concomitant drug use)
  - When co-prescribed with other drugs
  - With off-label use
  - With accidental exposures
  - Related to excipient content

Utility: Capturing Long-Term Safety
- Identify trends in safety of products
  - Taken chronically during childhood or over a lifetime
  - Taken for shorter duration but during critical stages of development
- Detect ARs
  - Reversible versus permanent
  - Manifest months to years after product exposure

What are the most important next steps?