Large Industry Perspective on Ethics and Inclusion

Federal Task Force on Research for Pregnant and Lactating Women

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Disclosure and Disclaimer

- Robert Ternik is an employee and shareholder of Eli Lilly and Company.

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Current Environment - Industry

Studies in Pregnancy

- Pregnancy is a practically universal exclusion in RCT's
  - Risk to Woman
  - Risk to Fetus
- Exception is in treatments specifically for pregnancy
- High Hurdle to prospect of benefit for investigational drugs in RCT
- Observational Data/Registries

Studies in Lactation

- Lactation Studies can occur in
  - Clinical Environment
  - Research Environment
  - Volunteer Environment
- Each situation invokes many factors in defining
  - The Human Subject
  - Prospect of Benefit
  - Consent

In both areas, regulatory and ethical complexity coupled with a challenging risk-benefit equation that involves both the woman and fetus or woman and child creates a unique challenge to the pharma industry. This is true for all stakeholders.

Current Environment - Industry

- As illustrated at the initial PRGLAC meeting August 21-22, 2017, there are limited industry sponsored (IS) interventional studies (data presented here accessed 25NOV2017)
  - pregnancy (268 IS of 1645 total)
  - lactation (17 IS of 103 total)
- Sponsoring and funding for data registries across pharma is inconsistent and confounded by
  - Enrollment challenges (stigma, incentive, legal risk)
  - Lack of experience (sponsor and HCP)
  - Study Design (bias, sampling, timing)
  - Data Quality (controls, sampling timing, exposure uncertainty-child)
- Achieving Consistency in Research
  - Difficult due to variability in risk tolerance, benefit proposition, capability

Perspective on Clinical Research

Sponsor Responsibility: Characterize benefit-risk profile of the product in the indicated population to inform the HCP and patient

- The indicated population rarely includes a pregnant woman and/or her fetus, or lactating women and/or her breastfeeding child
- Detailed medical and ethical benefit-risk assessments are complex
- Negative legal and social ramifications are significant
  - Fear of Liability
- Consequence is exclusion or discontinuation in Clinical Trials
  - Limited and inconsistent information for HCP's and patients to make treatment decisions, especially for new medicines

When to Study – How to Decide

- Products being developed for use in pregnancy or lactation as the indication
- Prevention of vertical disease transmission
- Circumstances for which the FDA (2005 Guidance) recommends clinical studies in lactating women[1]
  - When use in lactation can be anticipated
- Post Marketing Registries/Observational Studies

- Decisions made on a case by case basis by sponsors
  - Mechanism of Action
  - Benefit - Risk Analysis (including liability)
  - Timing in the overall drug development cycle
  - Feasibility of trial – relates to capability
    - Enrollment, Duration, Data Quality

Risk Analysis- Conceptually

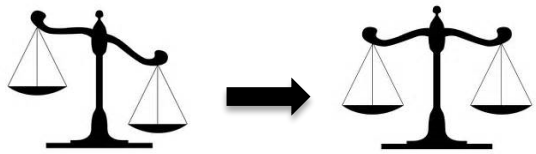
- These matter to all stakeholders
  - Different weighting by perspective

$$\sum_{1}^{N} \left(\begin{array}{l} \text{Pregnant Woman} \\ \text{Fetus} \quad \text{Lactating Woman} \\ \text{Regulatory} \quad \text{Child} \\ \text{Ethical} \\ \text{Liability} \quad \text{Social} \end{array} \right) =$$

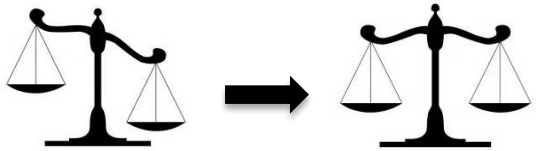
Are these simply additive?

Or at best

- How do we balance the equation?



Improving the Benefit Risk Analysis - Opportunity



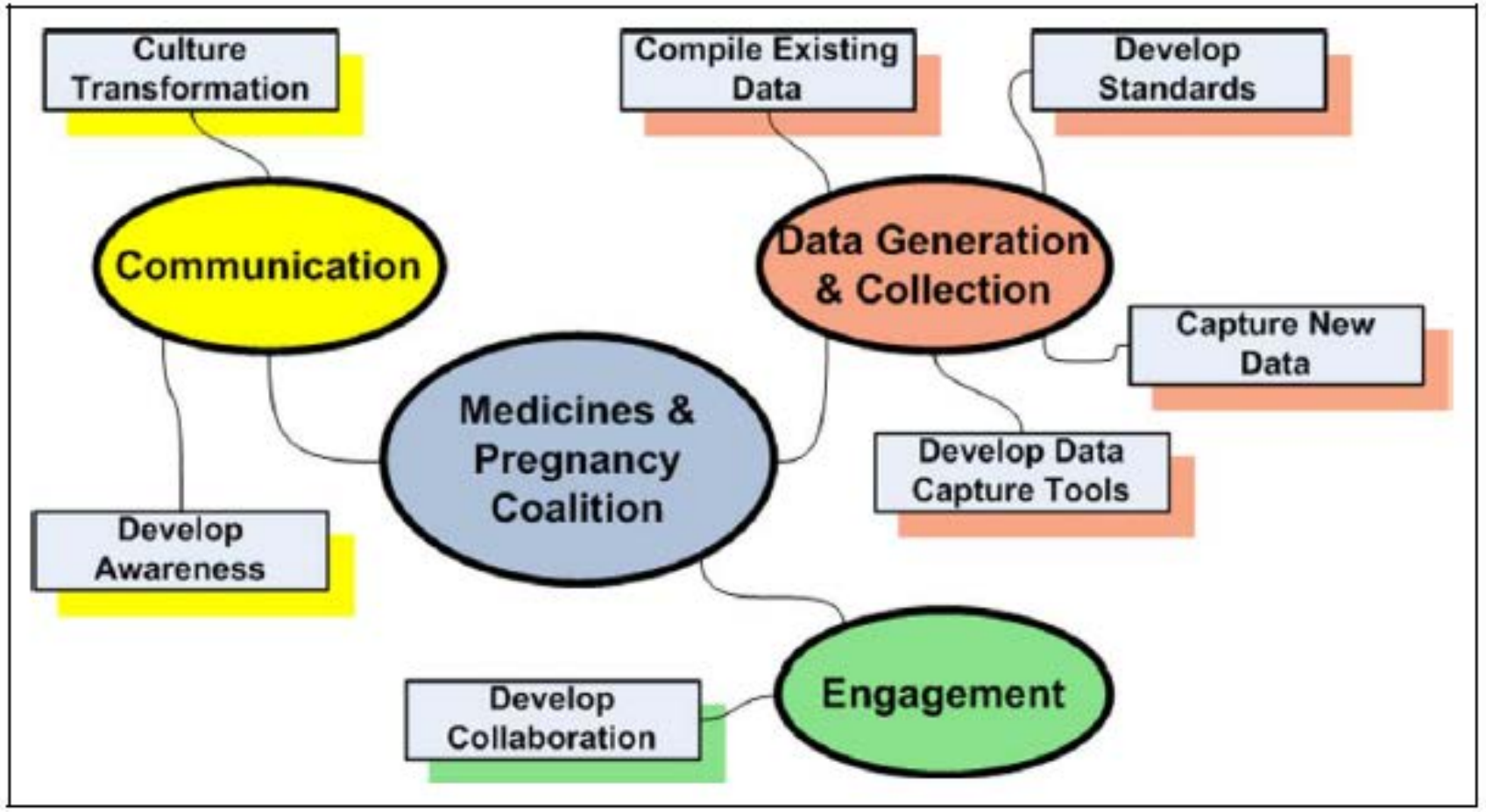
- **Assessing Benefit**
  - Quantifying and communicating the benefits of treatment, breastfeeding etc...
    - More extensive data collection on outcomes and benefit
    - Consistent protocols
- **Informing Risk**
  - Better use of pre-clinical tox data
    - Mechanistic, Animal, Modeling
  - Drug excretion into breast milk
    - Physico-chemical modeling for risk
  - Placental transport of drug to fetus
    - Modeling and simulation
    - Representative alternative models
  - Best Practices for post market PK data collection
- **Addressing Liability Concerns**

Path Forward - Recommendations

- Collaboration across stakeholders (Engagement)
  - Patient/Participant Voice is key
  - Leverage the strengths of the various stakeholders
- Communication
  - Awareness and Cultural Transformation
    - Pediatrics as a model? - Protection THROUGH research not FROM research
- Methodology
  - Consistency
    - Data collection, storage, analysis and access
- Leadership
  - Define roles for key stakeholders
  - Develop regulations, guidance, protections and incentives for ALL stakeholders

Industry wants to play it's role in providing information to HCP's and Patients, and needs the support and collaboration of all stakeholders

Path Forward Proposals



Path Forward Proposals

- ConcePTION – Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now

References

1. FDA Guidance for Industry - Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling, Draft, February 2005
2. Clemow DB, Dewulf L, Michaels DL, et al. A proposed framework to address needs of clinical data for informed medication use in pregnancy. Therapeutic Innovation & Regulatory Science. 2014;48:145-154.