BREAKOUT SESSION #1

Addressing challenges in conducting neonatal studies

- *What would you recommend to improve the feasibility of conducting neonatal PK trials and obtaining CSF samples?*
- *Should neonates be enrolled at the same time as older children in PK trials or only after safety/PK is assessed in older children?*
- *Should PK trials be single or multiple dose in neonates?*
- *What would you recommend to streamline neonatal safety trials*
- *How long should safety follow-up be for neonatal trials*
- *Are master protocols feasible for any indications in this population*
- *If the available data for neonates does not include CSF data, should dosing recommendations based on that data be included in the labeling*

REPORT OUT #1

- Recommendations to improve feasibility
- Recommendations regarding enrolling neonates concurrently with older children
- Recommendations regarding single or multiple dose PK studies
- Recommendations regarding streamlining neonatal safety studies
- Recommendations regarding length of safety follow-up for neonates
- Recommendations regarding the use of master protocols
- Recommendations regarding neonatal CSF data and labeling

REPORT OUT #1

Recommendations regarding enrolling neonates concurrently with older children

- Seems very reasonable if the drug class is one that we have a lot of experience with. Concerns with a new class, particularly if there were safety concerns in adults.

REPORT OUT #1

Recommendations regarding single or multiple dose PK studies

- For multiple dose, may need to be able to dose escalate in the trial or know that you are administering a therapeutic dose.
- Variability in a single neonate is observed commonly and multiple dose sampling per subject may be desirable from a clin pharm perspective

REPORT OUT #1

Recommendations regarding neonatal CSF data

- General feeling among pediatricians that knowledge of CSF penetration relative to MIC is very important for the treatment of sick neonates, the reality is that many antibacterial drugs that are used in clinical practice are lacking CSF penetration data.
- There is a rabbit model of meningoencephalitis in rabbits, but unclear if there is data from neonates to support the model.
- A CSF opportunistic sampling substudy when an LP is being done clinically open at all sites when a larger pediatric study is open.
- Value in sampling Ventricular reservoirs and why aren’t we doing it more often? How about a single dose study in these infants?

- Unclear if a PWR for neonatal CSF data would be helpful – maybe if it was part of a PIP and all lined up from the industry perspective.
- Not consensus whether CSF data was critical for neonatal labeling going forward – certainly desireable. “Keeps Danny B up at night”.

REPORT OUT #1

Recommendations regarding streamlining neonatal safety studies

- Standardization of adverse event reporting and standardized approaches to common AEs when they occur – perhaps standardized CRFs
- Sample size – depends on drug, first in class and safety in adults impacts
- Comparator arm – trade off is fewer neonates exposed to study drug
- Adverse events – Agency will focus on those plausibly related to study drug

REPORT OUT #1

Recommendations regarding the use of master protocols

- In the few successful protocols, an independent group takes the lead and sponsors are in and out
- Questions about ownership of data can be worked out.
- BARDA RFI has prompted an ongoing discussion in adults – some of the discussions focus on changes in standard of care over time, access to data for sponsors to meet reporting requirements.
- Nimbleness and efficient administrative structure will be important.

BREAKOUT SESSION #2
Addressing challenges in informed consent for children

- **Trust** – How best to foster trust between parents, providers and research staff?
- **Timing** – How best to ensure sensitivity to the stressful situation of a critically ill/medically fragile child?
- **Tools** – What tools have been most helpful in conducting the IC process with parents of fragile/ill children?
- **Trial** – What accommodations have been successful in improving study participation/retention with regard to a more meaningful IC process
- **Training** – What type of training is needed to improve the process of obtaining IC in sensitive situations?

REPORT OUT #2

- **Trust**
- **Timing**
- **Tools**
- **Trials**
- **Training**

REPORT OUT #2

Recommendations regarding enhancing trust between providers, investigators, study staff and parents

- Improve trust: Design questions to help empower parents to get the information to better understand and frame the clinical trial participation decision.
- How to enhance and improve “shared decision making” about participating in a study
- Find parents on Facebook groups about the trial
- Parents identify with each other. Facilitate their connection to others who chose to participate in the clinical trial they are considering

Trust (continued)

- Informed consent: Is there value to getting the word out about what clinical trials are and about informed consent (NCI? “I can”)
- Knowledge is power, and the Internet can empower parents

REPORT OUT #2

- Recommendations regarding necessary tools to improve the IC process in sensitive situations

- Role playing about how to get consent well. Use coordinators and patient advocates to forge effective approaches
- Use social media to put parents considering trials in touch with parents who were in them
- Video tapes of role playing with approach and consent
- Training in being sensitive to parents– solvable problem. People may be clueless about how to talk to the parents. Don’t delegate to a college student there for the summer. Get the right people. Don’t “down-delegate”

Talking to parents about participating

- People with more expertise in sensitivity– that has the attributes necessary to communicate well with parents
- Find someone with good interpersonal skills
- Do people in these roles make sufficient money? Should they be paid more.
- A lot of research people are more introverting – not good at talking to parents– don’t use them!
- Institution’s willingness to build infrastructure
- Role-plays
- Electronic tools?
- Have the kids take video- I-cam

REPORT OUT #2

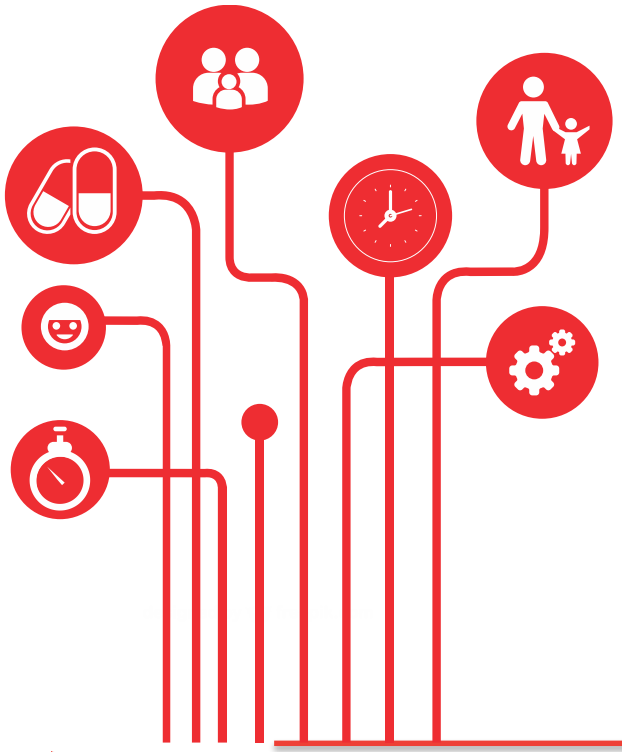
- **Recommendations regarding training to improve the IC Process in sensitive situations**

- Do role playing with patient coordinators and patient advocates around getting consent. Give feedback on recruitment.

Signed consent from both parents need not be a barrier. Can apply the “reasonably available” criteria to the signature. Other parent agrees but is not able to get to a place to to sign and there is a narrow window of time to start the antibiotic.

Other recommendations

- More focus group work?
- Maybe do work with more specific patient types
- Go to the NICU to talk to these parents– get a focus group or interviews right then and there
- Kids who have participated in clinical trials



BREAKOUT SESSION #3

Making pediatric antibacterial drug trials more feasible and efficient

- **How could obtaining PK trials in children be made more efficient and provide adequate data?**
- **How could comparative trials in children be made more efficient and provide adequate data (assuming efficacy is extrapolated)?**
- **Are there changes to clinical trial infrastructure and administration that would be helpful?**
- **Are there greater opportunities for buy-in from payers and alignment across regulatory agencies?**

REPORT OUT #3

- **How could PK trials in children be made more efficient and provide adequate data?**
  - What strategies to reduce the number of blood draws / burden of enrollment would you recommend (e.g. sparse sampling, single vs. multiple dose, opportunistic blood sampling, filter paper sampling, other)?
  - Could pediatric PK trials begin earlier in drug development (e.g. after a phase 2 trial or one phase 3 trial is completed in adults)?
  - Are there circumstances when PK data can be obtained in all pediatric age groups simultaneously rather than sequentially?

REPORT OUT #3

- **How could comparative trials in children be made more efficient and provide adequate data (assuming efficacy is extrapolated)?**
  - Are there changes in I/E criteria that could be made (e.g. prior antibacterial drugs or concomitant medications)?
  - Are there other changes in study design and conduct that could be made (e.g. data collection requirements and visit windows, comparator arm, timing of endpoint, use of biomarkers, other logistics)?
  - What are the factors that impact sample size? Can sample size be reduced?
  - Are there circumstances when comparative trials can be conducted in all age groups simultaneously?
  - If an antibacterial drug is approved for two indications in adults, are there circumstances when children with both diseases could be enrolled in the same comparative trial?
  - How can we most efficiently address unmet needs for MDR pathogens in children?

REPORT OUT #3

- **Are there changes to clinical trial infrastructure and administration that would be helpful?**
  - What is the best mechanism for educating hospitalists, neonatologists, surgeons and referring physicians about the value of new antibiotics and the need for clinical trials?
  - How could the potential advantages of a clinical trial network be realized (e.g. would companies be willing to use a common protocol and network of sites for both PK and comparative safety and rotate drugs in and out)?
  - How could the need for better funding for clinical trial sites be addressed?
    - How can sites be better supported in both understanding their real costs of participation and obtaining the necessary training to efficiently negotiate appropriate study budgets?
    - What is the best way to ensure that families are adequately compensated for the time and travel necessary for participation?

REPORT OUT #3

- **Buy-in and Alignment**
  - Are there opportunities for obtaining payer buy-in earlier in the development process, such that regulators and payers accept the same level of evidence of efficacy?
  - Are there opportunities to achieve alignment between global regulatory agencies with regard to pediatric study plans?

REPORT OUT #3

- **Simultaneous enrollment of all age groups above two**
  - **Sequential enrollment under two**

REPORT OUT #3

- **Assuming efficacy can be extrapolated from the adult trials, proceed with safety trials for pediatrics**
  - **Simple safety and PK studies can be designed a lot easier than full efficacy trials**
    - **Note: do not exclude collecting efficacy endpoints, but these may not necessarily be the same endpoints as in full adult efficacy trials.**

Pediatric Trials in Antibacterial Drug Development

NEONATAL INFECTION

Facilitator: Brian Smith (Duke)
Scribe: John Farley (FDA)

Michael Cinoman (Cempra)
Maria Cortina-Fernandez (EMA)
Ian Friedland (Achaogen)
Rachel Greenberg (Duke)
Gary Noel (J&J)
Amanda Paschke (Merck)
Tom Smith (FDA)
Bud Weiderman (Children's National)
Kunyi Wu (FDA)

INFORMED CONSENT

Facilitator: Rose Tiernan (FDA)
Scribe: Diane Bloom (InFocus)

Breck Gamel (Patient Advocate)
Tonoah Hampton (FDA)
Robert Hernandez (Cempra)
Paul Jones (FDA)
Skip Nelson (FDA)
Brian Perry (Duke)
Jonas Santiago (FDA)
Edward Spindler (The Medicines Co.)
Charlie Thompson (Pfizer)
Chris Wheeler (FDA)
Lynne Yao (FDA)

PEDIATRIC DRUG TRIALS

Facilitator: *Jamie Roberts* (CTTI)
Scribe: Ethan Hausman (FDA)

John Alexander (FDA)
Jeff Blumer (University of Toledo)
John Bradley (University of San Diego)
Ed Connor (Critical Path Institute)
Roger Echols (id3c)
Prabha Fernandes (Cempra)
David Friedland (Wockhardt)
Dionna Green (FDA)
*Hasan Jafri (MedImmune)**
Lenny Krilov (Winthrop)
Erin Moore (C3N)
Sumathi Nambiar (FDA)
Doug Rank (Cerexa)
Mike Sharland (St. George University)
Sunita Shukla (FDA)