Breakout Session #5: Neonatal Abstinence Syndrome

John Van Den Anker, Moderator

International Neonatal Consortium

EUROPEAN MEDICINES AGENCY
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10 YEARS

Participants of the Neonatal Abstinence Syndrome (NAS) Breakout

JOHN VAN DEN ANKER, MODERATOR

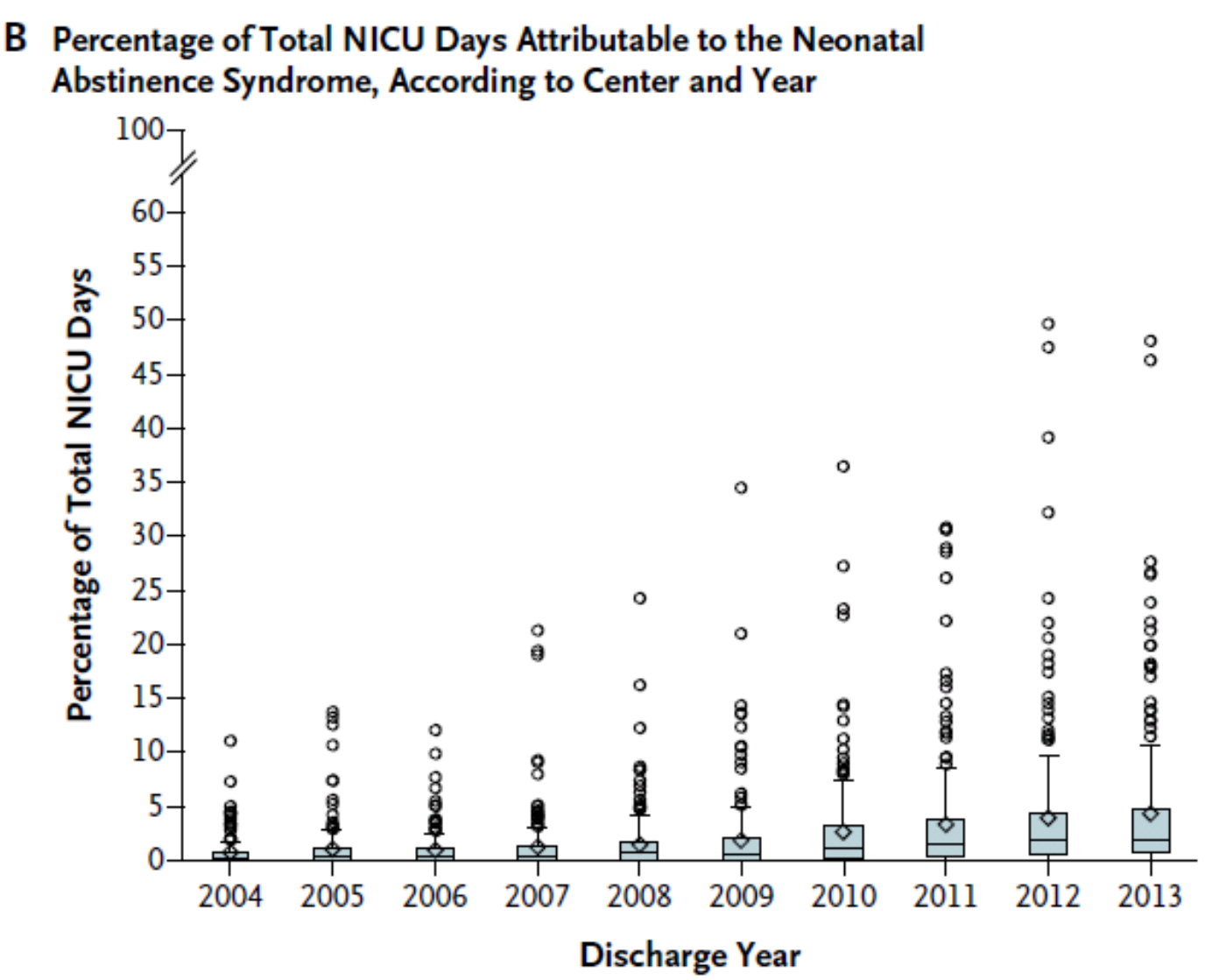
- KAREL ALLEGAERT
- CHRISTINE GLEASON
- PAM SIMPKINS
- MERRAN THOMSON
- PAOLO TOMASI
- ALICIA WEST, C-Path
- TOM YOUNG
- WAKAKO EKLUND

By WebEx

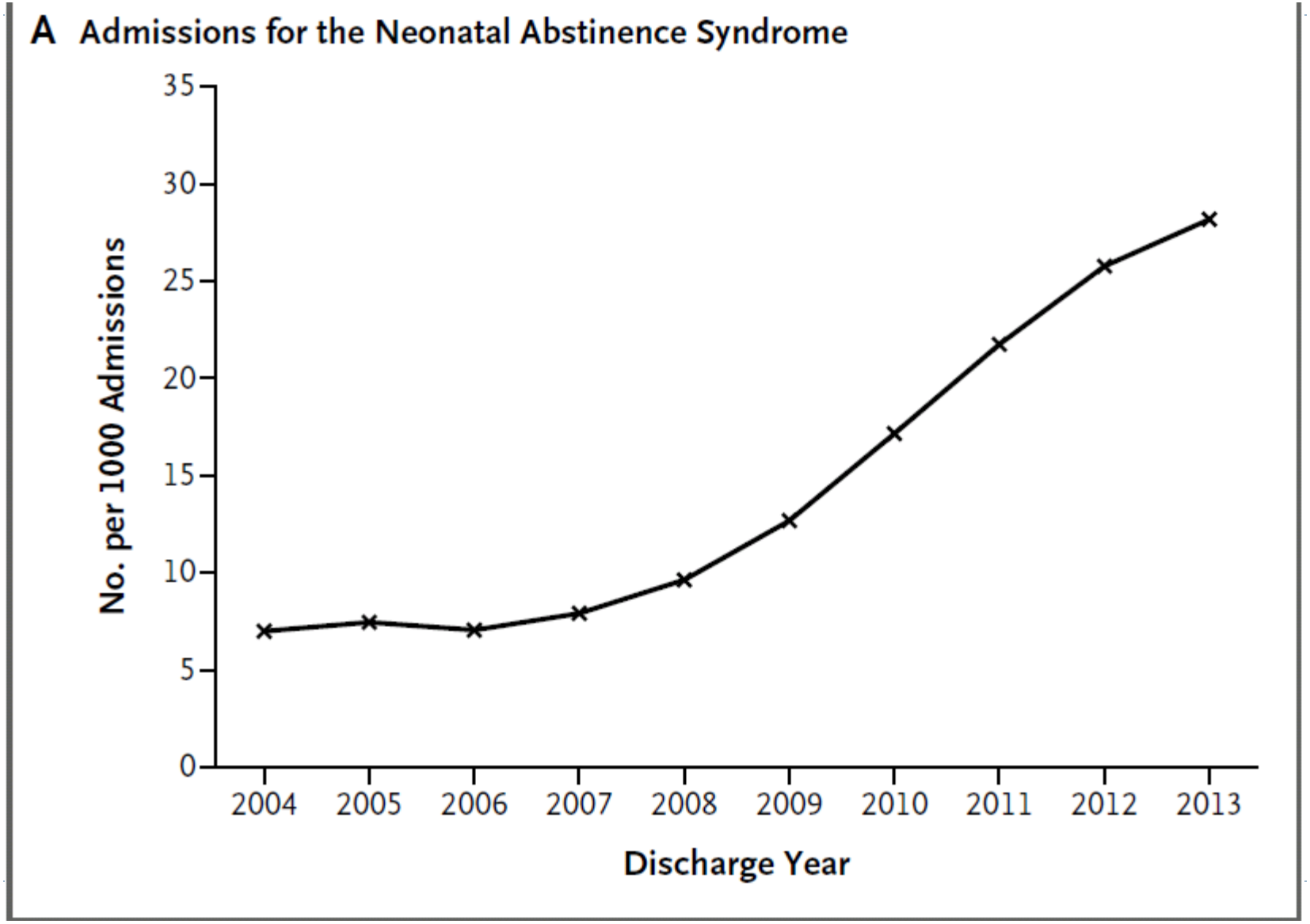
CECILIA FALKENBERG

ROBERTO DE LISA

Increasing Incidence of the Neonatal Abstinence Syndrome in U.S. Neonatal ICUs



Tolia, V.N., et al. The New England Journal o f Medicine, 2015

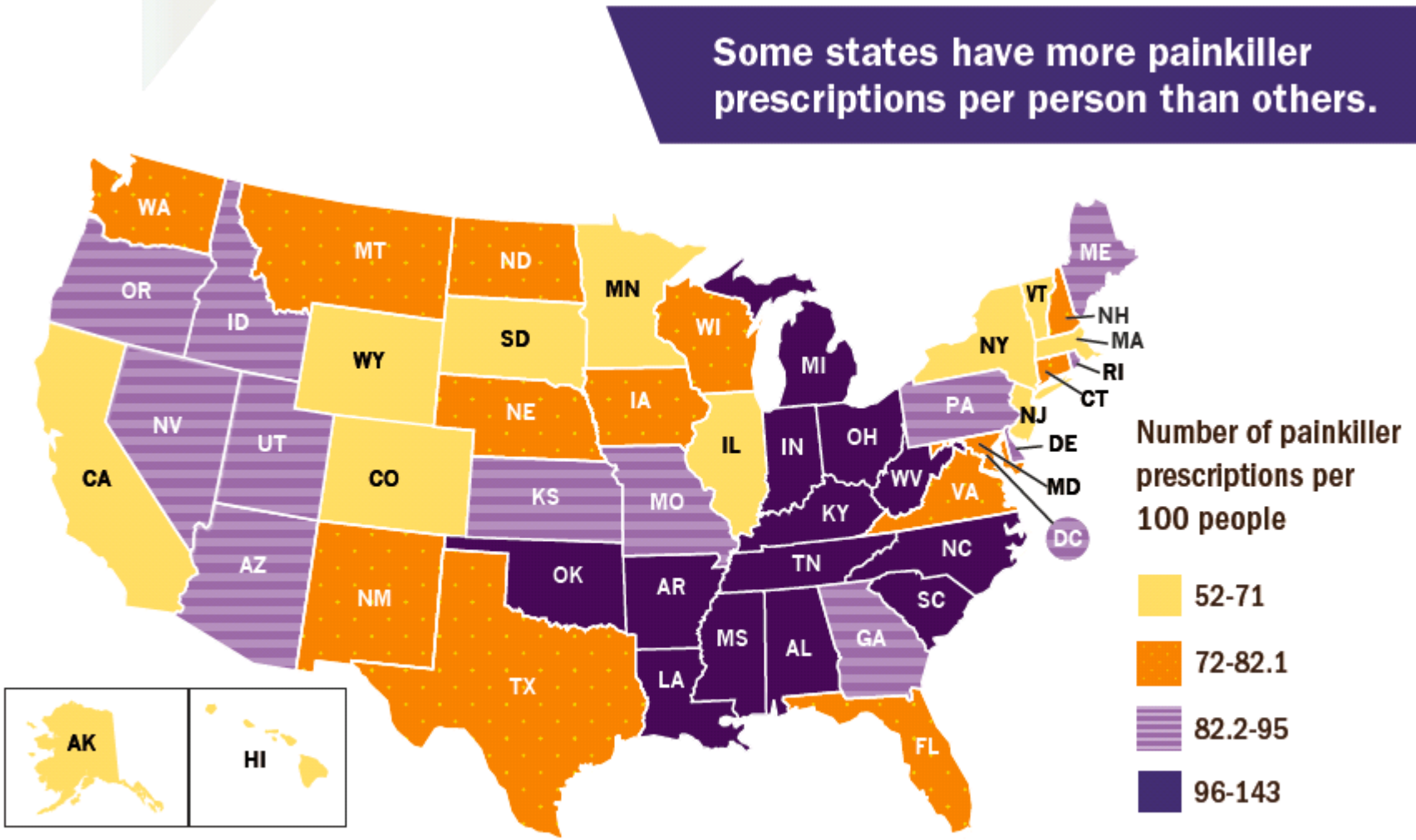

A Admissions for the Neonatal Abstinence Syndrome
No. per 1000 Admissions
0
5
10
15
20
25
30
35
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
Discharge Year

FACTS

- A baby is born with NAS every hour, and its symptoms can last for months and lead to weeks of hospitalization. Symptoms include seizures, breathing problems, fever, difficulty sleeping, tremors, stiff limbs, difficulty feeding, irritability, and dehydration.

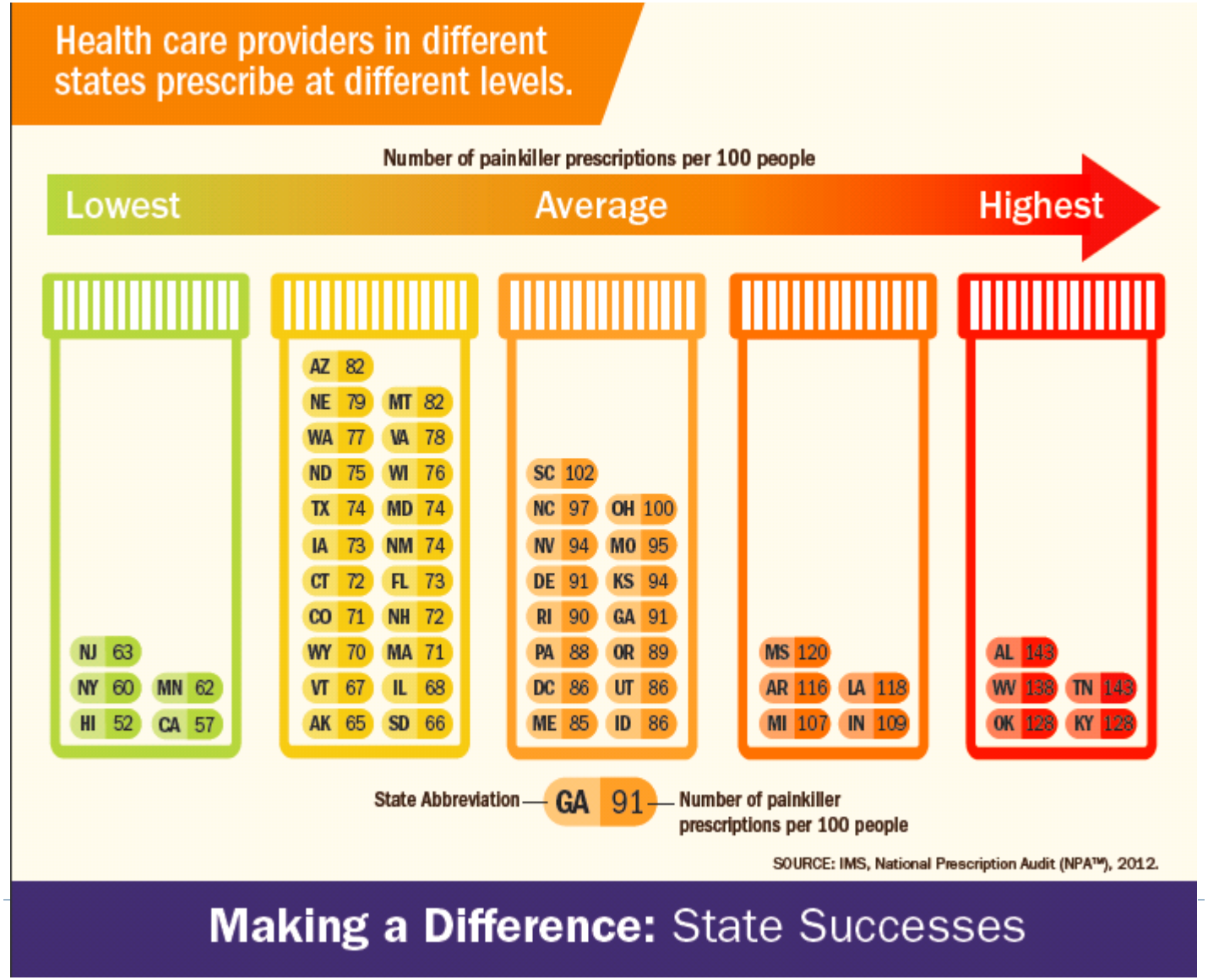
- It also found that aggregate inflation-adjusted hospital charges for newborns with NAS grew from $732 million in 2009 to $1.5 billion in 2012. Medicaid was the primary payer for over 80% of these charges.

Painkiller Prescriptions By State



SOURCE: IMS, National Prescription Audit (NPA™), 2012.

Opioid Painkiller Prescribing
Where You Live Makes a Difference



Response to Breakout Question #1

- **For neonatal abstinence syndrome (NAS), what indication is in most need of effective therapies? Include an estimate of the incidence and severity**.

1. IN UTERO (sudden withdrawal)
2. POST NATAL (iatrogenic postnatal)
   - Chronic exposure and weaning off
   - We are using less and less opiates in the NICU
   - Can we validate a biomarker???? This would help greatly

Response to Breakout Question #2

- **For NAS, what non-clinical studies need to be carried out prior to designing clinical trials of new and/or existing drugs?**

  - What juvenile animal toxicity studies are needed? **Yes, we do in the area of drug withdrawal, genetic and gender differences need to be investigated**
  - Are animal models available for the indication (e.g. gestational age equivalent)? **Majority of these studies were done in the 1970's , then no request for juvenile studies, decided to ask the experts at the EMA for their input in the area of either prevention or treatment.**
  - Can the non-clinical data be extrapolated to inform clinical development, including initial dosing? **If the non-clinical data are relevant absolutely using modelling and simulation**

Response to Breakout Question #3

- **For NAS, what information would be needed before starting a clinical trial?**

- Can existing pediatric or adult studies be extrapolated to neonates? **In utero exposure is a rather unique situation but we surely should try to use existing information**
- Could a master protocol be developed for use when evaluating treatments for this indication? **Yes, but it will be crucial to find the best way to measure withdrawal and to define the short term endpoint. Social factors confound too much long term endpoints**
- **<u>Essential parts will be:</u>**
- **the length of treatment**
- **in utero genetic test to determine which intervention or no intervention will work best in every individual neonate**
- **also tailor treatment based on a to be defined target, standardize the study population so that we can isolate / control – genetics**
- **we will learn why some respond and some don't; This would be huge.**

Response to Breakout Question #3

- Would the use of different drug classes alter the inclusion/exclusion criteria? **No**
- Do the inclusion criteria drive formulation, mode of administration and/or dose? **No**.
- **Oral or transdermal are the only two acceptable routes of administrations**
- What parameters are needed for constructing a meaningful modelling and simulation tool?
- **Good PK and PD and PGx. A quick genetic test that will allow targeted, tailored drug therapy if needed**

Response to Breakout Question #4

- **Are there impediments to establishing a master protocol (do multiple approaches exist – comparative effectiveness studies)? Is there equipoise?**

- **A must be consider: drug + non-pharmacological intervention (swaddling, dark rooms, breast feeding, massage, keeping the mom with the baby)**

Response to Breakout Question #5

- **What potential biomarkers and clinical trial endpoints could be used for treatment of NAS?**

  - Are adequate clinical outcome measures available? If not can they be developed? **length of stay, seizures, Finnegan score, need appropriate and repeated training of staff to assure reliable use**

  - Are any prognostic, predictive, pharmacodynamic, and safety biomarkers available? **No** Are any regulatory ready? **No – but we can develop them!**

  - **We need to discover the biomarkers that need to be used 1. selection of patients to be treated; 2. assess efficacy of treatment. INC can work to validate the biomarkers.**

Response to Breakout Question #6

- **What long-term outcome measures are available to assess the safety and efficacy of the therapy?**

  - Too many confounding factors
  - Cumulative post natal narcotic drug exposure?
  - With the master protocol can at least compare the outcomes for each drug; there is only a long term safety outcome not an efficacy outcome

Response to Breakout Question #7

- **In light of your responses to Questions 1-6, where are the gaps in knowledge and how would you prioritize the studies needed to approach the treatment of NAS?**

- **Gaps**

- Don’t understand the genetics and biology of acute narcotic withdrawal is
- Don’t have a good biomarker for severity
- Need an animal model with genetics and biomarker to assess severity
- There is a bill being proposed!

THE PROTECTING OUR INFANTS ACT

- **Help Infants Suffering Due To The Opioid Crisis: Cosponsor The Protecting Our Infants Act**

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Updated Survey Results