Panel I: Pre-Approval Clinical Trial Safety

1) Discuss how various databases presented yesterday might inform the planning, design, hypothesis to be tested, or questions to be explored in a pediatric safety clinical trial.

2) Could these databases be used to adapt to or supplement the information obtained in an ongoing pediatric clinical trial? What mechanism would need to be put in place to do so?

3) What gaps could be better addressed in pediatric safety assessment or quantification given the databases we heard about yesterday?

4) Given the information on exposure patterns, usage, and outcomes collected in these databases, can these databases be helpful in more appropriate sizing of pediatric trials to better meet their objectives?

5) What are the data items (variables) specific to pediatric patients not normally captured for adults that should be included in pediatric trials (e.g. growth, development)?
One issue is that studies under PREA is that we need to extrapolate efficacy, long term safety may not be possible.

Pregnancy registries are sometimes used for post-market safety.

Tough to get patients enrolled into pediatric registries.

Linking trials with genomic subgroups.

Patients who are eligible are hard to identify—maybe not.

In GATC, we actually fund the surveillance staff in order to recruit sufficient numbers.

How we fund safety trials may influence outcomes.

Knowing background event rates is critical to sizing CTs correctly.

Databases all have pros and cons—the.

EMR vendors have large datasets—FDA could start a relationship to ask specific questions.
• FDA needs the raw data and not necessarily the analysis
• There is potential to create case control trials with these large databases such as the HMORN
• Specific granularly with discrete data elements is fairly easy to set up- how many kids with drug x had elevated liver enzymes
• Triggers are potential elements that could point to adverse events
• How much investigation by FTEs needs to be done?
• Not as simple as simply querying 14 hospitals in real-time for these triggers- could take up to 12 months
• Educating industry about what resources are available about pre-market and post-market trials is important
• We need to know who to contact so we
• In Canada, soon there will be limited licenses for drug depending on safety and efficacy. If you want to continue marketing the drug you must find the patients
• There needs to be more collaboration between FDA and HealthCanada- the differences between treatment are fairly minor
Many of the drugs we know what endpoints we are looking for
Enrollment numbers continue to be a problem
Sentinel is looking at these large databases to detect severe AEs that may require the Agency to understand the underpinnings quickly
Would be nice to put say increased lipids or weight gain as a trigger for patients on atypical antipsychotics
There is no mechanism in the US currently that allows us to identify eligible children for trials
The FDA can require sponsor to keep a registry on all patients taking certain products- but sometimes
If the use data says >1 million prescriptions, why can’t sponsors find 1,000 patients to be enrolled?
AE rates differ among populations especially among those with comorbidities, concomitant medications, chronic diseases
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All sponsor has to do at this point is do the trial- not necessarily have a good trial

2-stage adaptive design: first small sample gives you a hint of what final sample size you will need to get a significant outcome

Networks rather than databases are best for

PECARN, PROs, and the neuro-emergency network have been successful at establishing registries, they will capture 80-90% of children on drug x

Industry is on a timeline, can these networks participate in CTs in a timely manner? Are they adaptable

These systems currently are focused on quality control and minimizing medication errors- a switch to focusing on CTs requires more FTEs and permanent surveillance staff

Need to have the proper staffing for the *think time* of doing these analyses

One possibility is suggest to the sponsor that these databases exist for helping answering protocol driven questions
Most EMRs are in ambulatory operations

Partnership with FDA and software developers/EMR vendors would allow FDA to see data modeling

Right now there are no clinical trial data standards

Not having a common data model is beneficial to vendors so they can differentiate themselves

CDISC is standardizing things such as what you call blood pressure and how it is reported in clinical trials

Right now, it would be prudent to create a small **pilot** on critical safety issues and see what is lacking, what problems arise

Active surveillance databases would need to adapt from QC and medication errors to CT safety

CTs could adapt according to what information is accruing in these active databases
It is possible for EMRs to be customized to have a mandatory adverse event to drug field.

Funding needed is for *think time* and not necessarily for building a database from scratch.

One shortcoming of these hospital active databases is that for pediatrics, many children come in for one-time acute care and may not be entered into the database. Children that are in long-term care in the hospital are really the ones where data is being collected.
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Age in months- many databases record age as 0, 1, ...

Dependence of medical devices is normally not a field in EMRs
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If FDA gets enough money, we could put out a pediatric specific RFP.

Right now FDA’s growing relationship with CMS allows us to focus on geriatrics—something similar could be done with pediatrics.

Man power at the agency is needed.

What if we start

Sponsors get their exclusivity bonus after compromising on the CT requirements, and then the CT results.

There is large exposure information, but little safety information.

Safety is not where the money is and is sadly not a priority.

HMORN, Tennessee MediCaid, et all are CERTs with AHRQ meant to help FDA with post-market surveillance—there is one pediatric specific CERT with University of Cincinnati.
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Everyone wants to start with the Cadillac when all you need is a Kia
Active surveillance would allow you to look at data on the fly, see what is missing, then adapt as you see fit
Growth is typically captured in EMRs, but development is not
OTC drugs are not captured in most databases—same with nutritional supplements, herbal/homeopathic remedies
Episodes of care and duration of use need to be captured especially to assess long-term exposure
Concomitant use—e.g., antipsychotics on top of 2-3 other drugs
Panel I: Summary

- Lots of talent in FDA but good studies and good information and hard to get from CTs
- There may be a need for FDA to raise the bar for level of protocol in CTs based on the outside data that we know exists
- Since we know exposure levels, we should be allowed to ask for sufficient trial sizes
- Testimony by “experts” on the feasibility/infeasibility of clinical trial protocols should be trumped by real data in these networks and registries
- What is needed is a network that FDA can talk to for many reasons including verifying that a CT sample of n=x is possible
- More collaboration with HealthCanada is needed
- Next step would be to discuss these recommendations with sponsors
- PeRC may need to start denying waivers for doing studies when the FDA sees a lot of exposure of children in the market
Panel II: Post-Market Safety Surveillance

Discuss the strengths and weaknesses of the different databases presented yesterday for:

1) *pediatric signal generation*?
   This is an approach that uses statistical or review methods to identify a safety signal. No particular medical product exposure or adverse outcome is pre-specified.

2) *pediatric signal refinement*?
   This is the process by which an identified safety signal is further evaluated to determine whether evidence exists to support a relationship between the exposure and the health outcome of interest. Health outcome of interest validation would be a part of signal refinement.

3) *pediatric signal hypothesis testing*?
   This is an evaluation or study conducted to confirm that the postulated signal represents a causal relationship between the pediatric medical product exposure and the health outcome of interest.

4) What 4-5 specific pediatric variables must be present in a surveillance system or database to optimize signal generation? Are there different desirable variables for pediatric signal refinement?

*Terms and definitions here are used for the purpose of discussion and are not necessarily terms or final definitions endorsed by FDA.*
For CESR and other HMO databases are good for both generation and refinement via rapid-cycle or “active” surveillance.

Recently, many researchers have shied away from no pre-specification as it makes it more difficult.

KP “refines” what they are looking for as they “generate” signals.

For FDA, there may be a problem with pre-specifying safety signals and looking for them vs. just data mining, which is more time intensive.

FDA is accustomed to signal generation from AERS (voluntary reports) that someone is constantly data mining looking for patterns.

Sentinel is now focusing on signal refinement.

St. Louis Children’s has a voluntary reporting system, pharmacy team that __________, uses EMRs to bring trigger tools (a pre-specification) to the patient level.

NEISS-CADES can be used for signal generation as no specific drugs are pre-specified. Not a voluntary reporting system but it is limited to outpatient visits and ED use and focuses on acute and common AEs.
For NEISS-CADES, the largest culprit for pediatric hospitalizations was quanadine(?)-antihypertensive used for ADHD patients.

Pediatrrix does not specifically pick-up AEs even though data is being added daily (decreasing renal function, rash) though very serious AEs may be recorded.

Very interesting example was how the active surveillance system at Cincinnati Children’s was able to see a quick increase in pediatric infections within the hospital- it was investigated and found to be a problem with intravenous catheters.

Devices could be added to the voluntary/passive PECARN system- this could be an excellent way of detecting device problems.

Most of the databases, active and passive, are best at looking at pre-specified outcomes since crude counts and data mining (signal generation) is not the most effective way of.

Large databases sometimes are prone to noise and may be hard to find a signal within such a giant sample vs. a smaller, more refined database.

Regardless, you have to pull out all the pediatric data out of larger databases to get proper signal.
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Children’s National, LA Children’s, Cincinnati Children’s- databases with trigger tools are good for signal refinement

Pediatrix (25% of the US’ NICU population) could be queried to see if there is large exposure to a device or drug and if there are any safety issues that have come up

Difficult for St. Louis Children’s inpatient system to be changed to tease out pediatrics since it is geared towards adult care

HMORN, CESR (within Sentinel) are also good for signal refinement

NEISS-CADES, NPDS 1 out of 10 times will be able to refine a signal quickly and cheaply. But 9 out of 10 times these systems may not have the correct data.
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There is a need for both a numerator and a denominator when hypothesis testing.

Sometimes in hypothesis testing, it is vital to talk to patients directly, which adds a lot of time and IRB hurdles.

The more granular the data that is needed, the more time and effort is required.

If you don’t separate out exposure and _____ you will have a lot of false positives.

OSE has been using claims data, etc. for awhile for hypothesis testing.

The new ground is if these outside databases can be used for surveillance.

ICD-9 codes are adult geared and used differently for children, so there is a lot of validation necessary when hypothesis testing.

NEISS-CADES, NDPS are not really for hypothesis testing.

Pediatrix has been used for hypothesis testing, you need to control for many factors in the NICU setting (~4-500,000 babies in the system).

VermontOxford Network is larger (more NICUs) but has less granular data.
One logistical barrier is whether certain outcomes have been validated already—otherwise it may take many months to validate.

Pediatric specific data needs to be a separate query from the larger sample.

Not having the covariates of interest may be a problem, for instance not having a unique device identifier.

Is a denominator even needed for hypothesis testing?
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Age, weight, height are generally captured
Dependence on medical devices
Long-term follow-up
Neurological outcomes like developmental assessment BUT Neurodevelopment is hard to standardize and is usually separate from active surveillance- perhaps helpful in hypothesis testing
Gestational age
Maternal variables
Diagnoses made in the child’s early life
Assessment of compliance or adherence to medication prescribed (perhaps more of a geriatric variable) – a proxy variable could be used for this. For example, to see who is taking a drug x you could see who had come in for a refill of drug x (this assumes compliance)
For Pediatrix, it is known when babies start and end medications
BMI
Sexual activity in adolescents
Chronic conditions- physical comorbidities and neurologic comorbidities
Drug doses
Concomitant medications