Challenges to DSMB's in Maternal Immunization Studies: Perspective of DSMB Chairs

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Challenges to DSMB

- Safety assessment of two different subjects
  - Expectant Mother
  - Fetus/Infant
- Medical experts needed for both mother and fetus
- Established baseline rates of pivotal adverse events in the population are often not available
  - Mother: Preeclampsia, Renal Dysfunction, C-section, etc
  - Infant: Prematurity, SGA, Congenital Anomalies, etc
- Established clear stopping rules in charter
- Ability of the PI to capture all data needed to assess AEFI
  - Labor and Delivery Records Needed
  - Nursery/Pediatric Records needed from Infant

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What to do when a stopping rule is met?

- Data from **placebo** recipients will not contribute to the stopping rules.
- Reactogenicity data confirmed by the investigator as being entered by the participant **in error** will not contribute toward a stopping rule.
- The stopping rule will **PAUSE** randomization and study intervention administration for the impacted vaccine candidate in all dose levels and age groups.
- The **DSMB** will review all appropriate data.
- For all vaccinated participants, all other **routine study conduct activities**, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, **will continue** during the pause.

Back-up Slides

Stopping Rules for Prototypic study in Charter

1. If any vaccinated participant develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.

2. If any vaccinated participant develops a Grade 4 (ER or hospitalization) local reaction or systemic event after vaccination that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

3. If any vaccinated participant develops a fever >40.0°C (>104.0°F) for at least 1 daily measurement after vaccination that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

4. If any 2 vaccinated participants report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

5. If any participant dies or requires ICU admission.

Establishing Baseline Rates of Coincident Events

	Number of coincident events since a vaccine dose			Baseline rate used for estimate
	Within 1 day	Within 7 days	Within 6 weeks	
Guillain-Barré syndrome (per 10 million vaccinated people)	0·51	3·58	21·50	1·87 per 100 000 person-years (all ages; UK Health Protection Agency data)
Optic neuritis (per 10 million female vaccinees)	2·05	14·40	86·30	7·5 per 100 000 person-years in US females (table 2)[16]
Spontaneous abortions (per 1 million vaccinated pregnant women)	397	2780	16 684	Based on data from the UK (12% of pregnancies)[34]
Sudden death within 1 h of onset of any symptoms (per 10 million vaccinated people)	0·14	0·98	5·75	Based upon UK background rate of 0·5 per 100 000 person-years (table 2)[28]

Table 6: **Predicted numbers of coincident, temporally associated events after a single dose of a hypothetical vaccine, based upon background incidence rates**

Black S, Eskola J, Siegrist CA, Halsey N, MacDonald N, Law B, Miller E, Andrews N, Stowe J, Salmon D, Vannice K, Izurieta HS, Akhtar A, Gold M, Oselka G, Zuber P, Pfeifer D, Vellozzi C. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. Lancet. 2009 Dec 19;374(9707):2115-2122. doi: 10.1016/S0140-6736(09)61877-8. Epub 2009 Oct 31. Erratum in: Lancet. 2010 Jan 30;375(9712):376. PMID: 19880172; PMCID: PMC2861912.

TABLE 5 DMC Best Practices

Practice	Description
DMC independence	Procedures for DMC functioning should be formulated in a manner to protect DMC independence.
Membership	DMC, collectively, should be multidisciplinary, well informed, and experienced in DMC processes. Members should be independent and free of meaningful conflicts of interest. The DMC should be demographically representative of populations addressed by the trial.
Maintaining confidentiality	The DMC and ISRG should have sole access to emerging data on safety and efficacy; exceptions should be made only on a need-to-know basis to protect patient interests.
DMC access to efficacy data	DMC should have access to unblinded efficacy as well as safety data on an ongoing basis.
DMC is a collective not a collection	DMC recommendations should be formulated through a consensus process rather than by formal voting.
ISRG responsibilities	The ISRG should ensure the DMC has access to properly timely, reliable, and interpretable efficacy, as well as safety data, on an ongoing basis.

ISRG = independent statistical reporting group; other abbreviation as in Table 1.