Clinical trials: Role of a DSMB

15th Advanced Course of Vaccinology
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Penny M. Heaton, MD
Director of Vaccine Development

BILL & MELINDA GATES foundation

Vaccine Development: "Catalyze development of low cost vaccines that reduce under 5 mortality"

Starting Point

6.6M deaths under 5 / yr (2012)

GAVI budget $6.3B (2016-2020) [1]

Objectives

1. **Accelerate timelines for development of novel vaccines (e.g., next generation rotavirus, HIV, maternal immunization, malaria, combination vaccines, etc.)**
2. **Achieve 50% cost reduction for priority vaccines, with first focus on IPV, pneumococcus, penta, rotavirus**
3. **Get robust and timely surveillance data**

1) Vaccine spend only. Excludes GAVI spend tied to VIS (e.g., Cholera Stockpile, YF Campaigns) as well as cash programs and business plan.

Source: Under 5 mortality from WHO/Unicef 2012; GAVI budget source: FP&A analysis

Vaccine Development

Objectives

1. Accelerate timelines novel vaccines
2. Achieve 50% cost reduction for priority vaccines
3. Get robust, timely surveillance data; assess impact

Standard approach to "end-to-end" vaccine development adapted from industry

Clinical Development (DSMBs)	CMC/ Manufacturing Development	Regulatory Strategy	Surveillance

Agenda

- What is a DSMB and why are they important in vaccine clinical trials?
- Under what clinical trial scenarios are DSMBs needed?
- How is a DSMB implemented?
- Case Studies

What is a DSMB and why are they important in vaccine clinical trials?

- Provide a means for unbiased data evaluation and study changes if required
- Independently monitor safety, efficacy (overwhelming benefit, futility analyses, sample size re-estimation), and study conduct/progress
- Evaluate accumulating data in a blinded and/or unblinded fashion according to:
  - Pre-specified criteria
  - Clinical judgment
- Mandated to ensure the safety of study participants
  - To ensure 'no unavoidable increased risk for harm'
  - To ensure that a trial continues 'long enough to answer its scientific questions

Under what clinical trial scenarios are DSMBs needed?

Clinical Trial Scenarios for which DSMBs are Needed

- The study endpoint is such that a highly favorable (e.g., overwhelming efficacy) or unfavorable (adverse event; futility) result may ethically call for early study termination
- There is prior information or a strong suspicion that the vaccination/treatment may cause harm
- The study is being conducted in a vulnerable population such as children, pregnant women, or the very elderly
- The study is being conducted in a population with an increased risk of death that may be unrelated to the study endpoints
- The study is large, of long duration, and multi-center

While all trials require safety monitoring, most do not require a DSMB

Examples:

- Studies for vaccines/treatments in early stages of development
- Studies assessing outcomes not including mortality or serious morbidity (e.g., relief of symptoms)
- Studies of short duration

DSMB Implementation – See appendix for details

How do DSMB's typically operate?

- Membership
- Charter
- Relationship with other important committees
- Reimbursement

DSMB Membership

What are the desired qualifications for DSMB members?

Who should Chair a DSMB?

DSMB Membership

- 3 to 7 members (odd number to permit majority rule in voting)
- Experts in the disciplines needed to interpret safety and efficacy data from the trial and weigh risk vs. benefit
  - Disease area and vaccine expertise
  - Experience in clinical trial conduct and methodology
  - Biostatistician
  - Bioethicist
-  Individuals with prior DSMB experience (very important for Chairperson!)
- From regions in which study is being conducted
- Ad-hoc specialists or consultants may be utilized as non-voting members
- Members should not otherwise be involved in the conduct of the study; no conflicts of interest

How do DSMBs typically operate?

- Agendas
  - Introductory meeting: Review protocol, discuss Investigators' Brochure, review Charter, define quorum, and agree on voting rules
  - Subsequent agendas set by DSMB Chairperson
- Meeting Format
  - Open session – study staff including investigator and Sponsor present updates including enrollment, demographics, and blinded AE summaries
  - Closed session – DSMB plus biostatistician evaluate unblinded data as needed
  - Executive session – DSMB (voting members only) discuss and decide recommendations for study continuation or termination
  - Open session – DSMB reconvenes with study staff and Sponsor and provides recommendations

DSMB Charter - Stopping Guidelines

- Pre-specified statistical guidelines for study termination
  - Early termination
  - Sample size re-estimation – Have an adequate number of cases occurred to evaluate the study hypotheses and reach a conclusion?
- Clinical judgment always considered
- Voting rules: Majority rule, not consensus
- Possible recommendations
  - Modify protocol
  - Suspend one or more study arms
  - Increase sample size
  - Stop early because of safety concerns, overwhelming efficacy, or futility
  - Stop; data are adequate to evaluate primary hypotheses

Case Studies - Instructions

- 3 groups; 15 minutes
- Select a DSMB Chairperson
- Open session – read the case study
- Closed/executive session
  - Discuss
  - Vote
- Chair presents recommendation (5 minutes each)

Maternovax Study GBS-210

Randomized double blind placebo controlled phase III evaluation of pentavalent Group B Streptococcal (GBS) conjugate vaccine (MaternoVax-GBS®) in healthy pregnant women. The vaccine is being administered in the first and second trimester to women in Soweto, South Africa for the prevention of early and late onset neonatal GBS disease, maternal chorioamnionitis, and premature labor.

GBS is a leading cause of pneumonia, sepsis, and meningitis in the neonatal period with a case fatality rate of 10 to 30 percent.

Maternovax Study GBS-210

- Enrollment Update
  - 25,552 patients enrolled to date with a target enrollment of 50,000
  - Deaths: There have been 242 deaths in the study cohort.
  - SAEs: - 25 of these have been classified by the investigator as being possibly related to receipt of study vaccine.
- Protocol Exemptions, Deviations, and Waivers- There have been 800 protocol deviations all for lack of a follow-up visit for mother and infant post-partum.
- Question for the DSMB: Are the data on safety to date consistent with a recommendation to continue the study?

BioBoost Study ZX-110

- This is a randomized double blind placebo controlled phase II evaluation of CpG adjuvanted pandemic Influenza H7N9 vaccine (InfluZap®) in healthy adults.

  H7N9 is an influenza strain that normally circulates among birds although some variants are known to occasionally infect human populations. This virus first infected humans in March 2013, in China. As of April 11, 2014, 419 cases have been reported with a mortality rate of approximately 30 percent.

  CpG is a relatively novel adjuvant that has been evaluated in preclinical and clinical studies of several infectious diseases and cancer vaccines but has not yet been approved by any regulatory authority for licensure of a commercial product.

BioBoost Study ZX-110

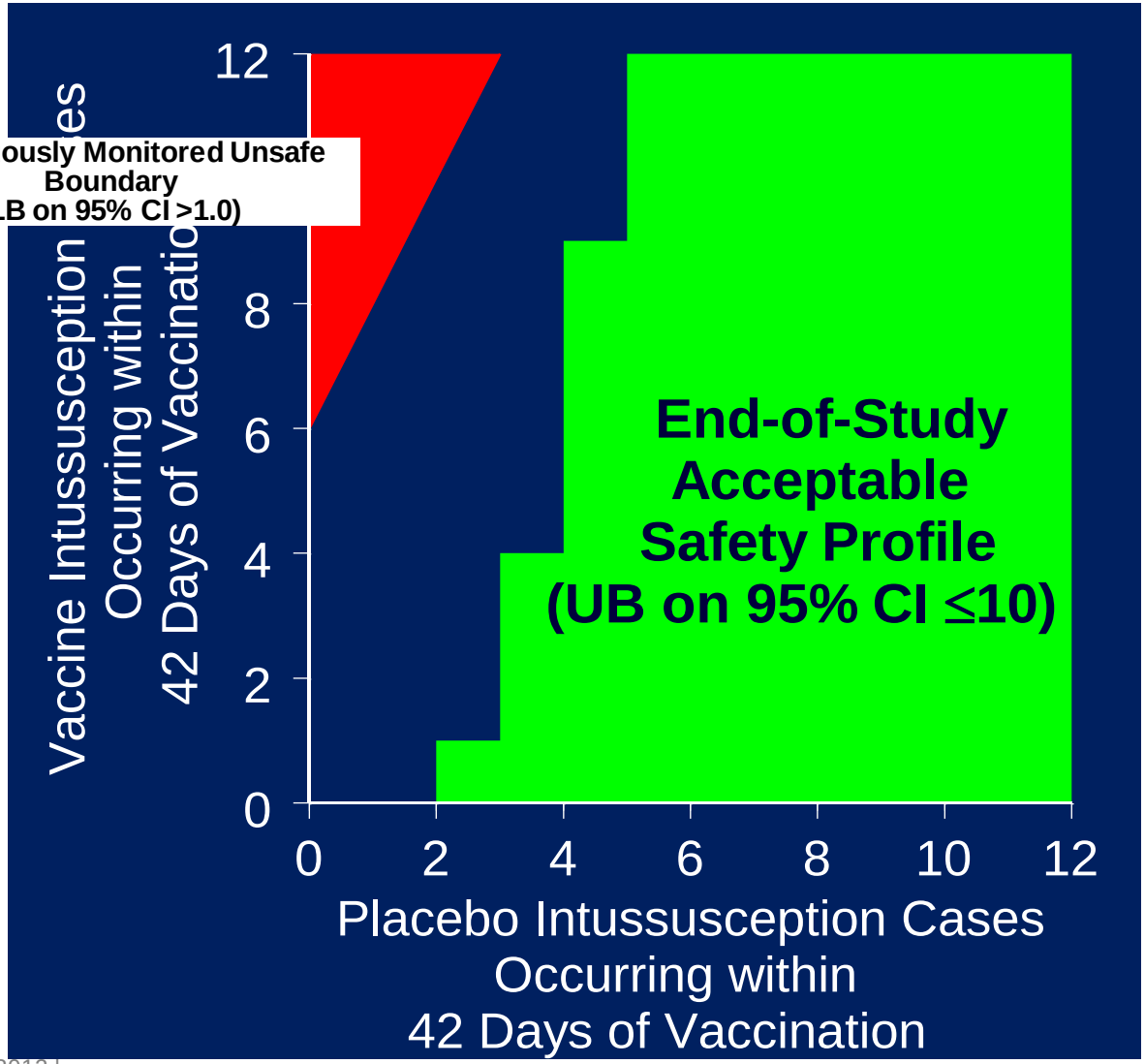
- Enrollment Update
  - 52 patients enrolled to date with a target enrollment of 100 (50 per group) . Enrollment is three months behind initial projection.
- Deaths: No deaths in the study cohort
- SAEs:
  - 3 hospitalizations - auto accident, elective thyroidectomy, Wegner's granulomatosis
- Question for the DSMB: The DSMB has been asked to make a recommendation as to whether or not the study should continue. Options include:
  1. Continue the study
  2. Place the study on hold pending further evaluation
  3. Stop the study
- If the study is placed "on hold" and enrollment stopped, what would the criteria be for restarting the study enrollment?

Rotavirus Vaccine Study V-065

- This is a randomized double blind placebo controlled phase III evaluation of the safety and efficacy of a human-bovine reassortant rotavirus vaccine
- Rotavirus is the leading cause of gastroenteritis-associated hospitalization and responsible for half a million deaths annually
- A different rotavirus vaccine (human-rhesus reassortant) had previously been approved and recommended for all infants in the US. It was voluntarily withdrawn from the market because of a side effect called intussusception.
  - The risk of intussusception was increased in the first week after doses 1 and 2.
- Two other companies had different rotavirus vaccines in late stage development. They decided to move forward with large (60,000 to 100,000 infants) phase 3 trials to evaluate safety with respect to intussusception and confirm the efficacy of their vaccines against severe rotavirus disease.

Rotavirus Vaccine Study V-065: Stopping Guidelines

- Each potential case of intussusception was to be adjudicated as it occurred.
- All positively-adjudicated cases were referred to the Chair of the DSMB
- The cases were unblinded according to treatment group (vaccine or placebo) and reviewed according to statistical guidelines and clinical judgment



Rotavirus Vaccine Study V-065

- Enrollment Update
  - 32,296 patients enrolled to date with a target minimum enrollment of 60,000 (30,000 per group).
- Intussusception: There have been 3 cases of intussusception in the study as follows:
  - 5 month old male infant 32 days after the second dose
  - 8 month old male infant 54 days after the third dose
  - 2.5 month old female infant 10 days after the first dose
- SAEs and deaths: As expected in a study of this size, there were several hospitalizations and some deaths. None were judged by the investigator to be associated with study vaccine or placebo.
- Question for the DSMB: Please review the study status to date and make a recommendation as to whether or not the study should continue based on the data presented above.

Appendix

DSMB Charter - Overview

- Typically the Charter is initially drafted by the lead study clinician in close collaboration with the biostatistician
  - Finalized with the DSMB Chairperson and members

- EMA and FDA guidelines for DSMBs are available (effective in 2006)
  - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003635.pdf
  - http://www.fda.gov/OHRMS/DOCKETS/98fr/01d-0489-gdl0003.pdf

Recommended: Data Monitoring Committees in Clinical Trials: A Practical Perspective by Ellenberg et. al., 2002

DSMB Charter - Contents

- DSMB membership and general qualifications
- Meeting organization and schedule
- DSMB roles and responsibilities
  - Pre-defined stopping guidelines
- Definition of quorum; rules for voting
- Communication channels to Sponsor and other study committees
- Appendix – example study reports

DSMB Charter - Meeting Organization and Schedule

- Meeting frequency depends on several factors including enrollment rate, schedule of analyses, and type of safety issues
  - Schedule meetings at some minimum frequency to evaluate study data
- Agendas
  - Introductory meeting: Review protocol, discuss Investigators' Brochure, review Charter, define quorum, and agree on voting rules

    ***Note: Discuss expected adverse events and common causes of death expected in the study population
  - Subsequent agendas set by DSMB Chairperson
- Format
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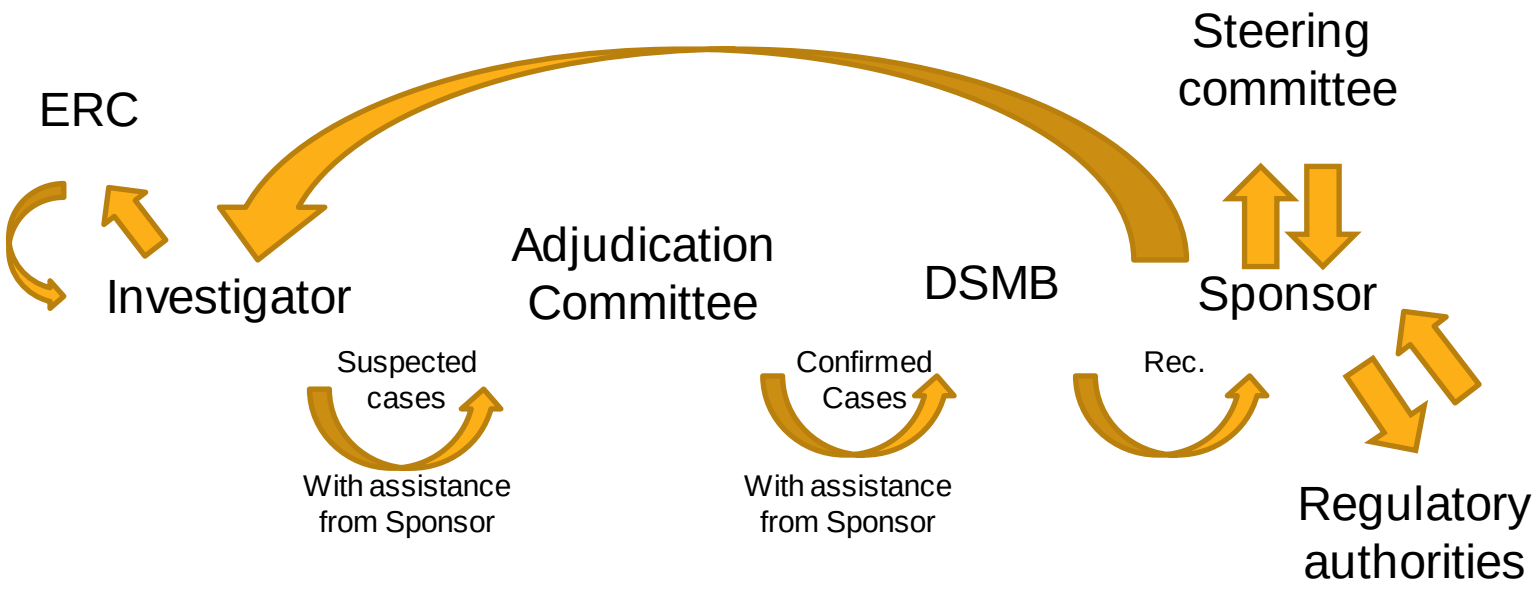
Communication channels between DSMB and other study committees



DSMB Reimbursement

- DSMB members are international experts in their fields
- General reimbursement guidelines
  - Per diem
  - Travel
  - Honorarium (published guidelines in US by specialty)