

# Global Health Trials Discussion Forum: Data Safety Monitoring Boards

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# DSMB Discussion Topics



- ▣ Why? The Purpose of a DSMB?
- ▣ When? For which kinds of clinical trials?
- ▣ How? What should be in a DSMB Charter?
- ▣ What? Examples of DSMB recommendations?

# Purpose of a DSMB

- How does a DSMB differ from routine safety monitoring?

# When needed?



- In vivo artemether-lumefantrine therapeutic efficacy studies
- Phase 1 Bioequivalence study? E.g. FDC vs loose TB treatment (Rifampicin, Isoniazid, Pyrazinamide, Ethambutol)
- Randomised controlled trial comparing SP with artesunate plus SP?
- Sulfadoxine-pyrimethamine (SP) Intermittent Preventive Treatment in pregnant women?
- Artemether-lumefantrine drug-drug interaction studies with nevirapine or protease inhibitor based antiretrovirals in HIV infected patients.
- OZ439-mefloquine drug-drug interaction study.

# Key elements of DSMB Charter

- ▣ Who?
- ▣ How many?
- ▣ How often?
- ▣ What data?
- ▣ Unblinding?

# DSMB recommendations

▣ Examples?

# To stop a study early – risk:benefit (10-fold increase between 1975 and 2005)

- **Harm:** ILLUMINATE – increased risk major cardiovascular events and death in torcetrapib group @ 18 months (n~5000).
- **Benefit:** pre-operative beta-blockade before vascular surgery showed 2/59 bisoprolol vs 8/53 control had major cardiovascular events
- **Futility:** ARDS Network found only 1% probability of showing superiority of higher vs lower PEEP in 2<sup>nd</sup> interim analysis of 549 of planned 750 patients
- **New non-study information:** increased risk of major CVE with celecoxib in men with prostate cancer

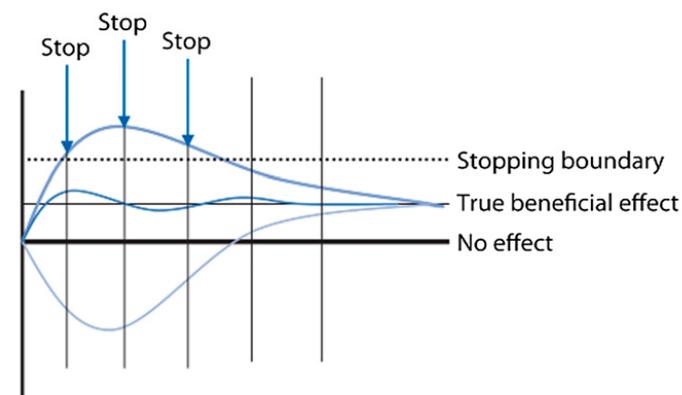
# Why is stopping trials early problematic?



# Why is stopping trials early problematic?

- Effects of multiple testing and overestimation of treatment effects.
- Comprehensive assessment of treatment impact limited
  - Long term outcomes
  - Patient important outcomes
- Publication bias -> impact on guidelines
- Freezing effect: Tough to launch new trial on QN if study stopped early

Theoretical Distribution of Randomized Controlled Trial Results as Data Accumulate



POISE n=8000

30% decrease in non-fatal MI  
33% increase in overall mortality  
2-fold increased risk of stroke

# Lessons learnt?