Role of iDMC for complex clinical trials

Thomas Jaki

University of Cambridge Lancaster University
Background

- Academic Statistician
- Regularly sit on iDMCs (both academic and industry studies)
- Expertise in complex clinical trials
The role of a DSMB

- To review accumulating data from patients taking part in a clinical trial on safety (and possibly efficacy)
- To advise the trial sponsor regarding the continuing safety of current and yet to be recruited patients
- To advise the trial sponsor on the continuing validity and scientific merit of the trial
So what about complex trials

Modify an ongoing trial
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- based on accrued data at interim, or
- allows adding of arms, or
- regional (sub)protocols contributing to master trial

...to enhance flexibility
So what about complex trials

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by design

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− allows adding of arms, or
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to enhance flexibility

without undermining the study’s integrity and validity.

(Chow et al. 2005)
Implications for iDMC

- May be asked to “execute” adaptations decisions
Implications for iDMC

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  - ⇒ more in a later talk

- Multiple treatments/populations/maturity of data
RECOVERY when it started

- Standard of Care
- Hydroxychloroquine
- Dexamethasone
- Lopinavir / Ritonavir
- Azithromycin

- in hospitalized patients with suspected or confirmed COVID-19 (all ages)
RECOVERY today

Standard of Care

- Hydroxychloroquine: ✗
- Dexamethasone: ✔
- Lopinavir / Ritonavir: ✗
- Azithromycin: ✔

Severe disease

- Tocilizumab: 
- Convalescent plasma: 

Children < 44 weeks

- Corticosteroids: 

Children > 44 weeks with PIMS-TS

- Intravenous immunoglobulin: 
- Synthetic neutralising antibodies: 

T. Jaki
Challenges for safety monitoring

- Increased risk of spurious findings
- Release of results
- Dependence of decision making
- Expertise of iDMC
- ...
DSMB models for complex trials

Overarching DSMB

Figure: Potential model for iDMCs for complex trials.
DSMB models for complex trials

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Overarching DSMB

Specialist(s) Candidate 1

Specialist(s) Candidate 2

Specialist(s) Candidate 3

Figure: Potential model for iDMCs for complex trials.
DSMB models for complex trials

**Figure:** Potential model for iDMCs for complex trials.
Pooling internal (but also external) evidence (Mütze and Friede, 2020)

Evidence could be included

- informally (e.g. by considering data side by side) or
- formally (e.g. by using meta-analytic approaches)
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⇒ Avoid naive pooling due to Simpson’s paradox!
Discussion

- Platforms add organisational complexity
- Adaptive designs add complexities about decision making
- When combining information ensure doing it appropriately