Adaptive Platform Trials in COVID-19

- Pros, Cons, and Potential Implications for Oncology -

Derek C. Angus, MD, MPH

Pragmatic Adaptive Platform Trials

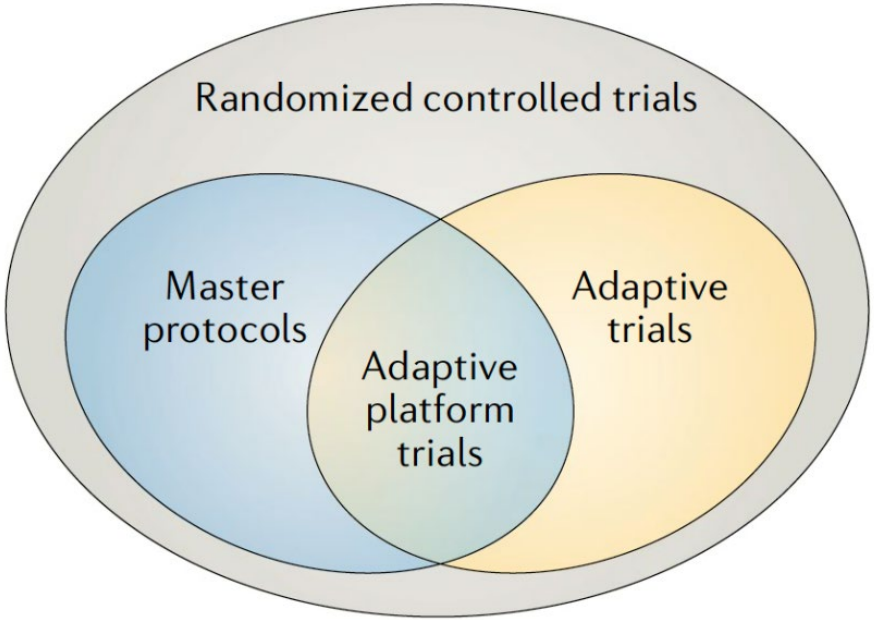
- Uptick in pragmatic adaptive platform trials (APTs) during COVID

- Three notable examples …
  - RECOVERY
  - REMAP-CAP
  - The ATTACC-ACTIV4-REMAP-CAP ‘multiplatform’ RCT (mpRCT) collaborative

- Together, these trials, in the space of ~12 months, have …
  - Enrolled >50,000 patients
  - Generated multiple high-profile findings (published in NEJM, JAMA, Lancet, etc.)
  - Driven the vast majority of current WHO treatment guidelines for COVID

- So …
  - What are they? How do they depart from traditional RCTs? What is good and bad about them? What lessons can be learned?

Adaptive Platform Trials



Woodcock and Lavange. *NEJM* 2017

Adaptive Platform Trials Coalition. *Nature Drug Discovery* 2019

Notable features of the 3 COVID examples …

- All 3 use master protocol with amendments for new study questions
- All 3 use open-label control, but with ‘hard’ primary endpoint to minimize bias
- All 3 emphasize ‘ease-of-use’ and high acceptability at bedside
  - Research questions with broad stakeholder ‘buy-in’
  - Simple entry criteria
  - Lean data collection
- All 3 benefited (massively!) from the UK NIHR CRN Hospital Payment system
  - Healthcare system (UK NHS) specifically incentivized to promote participation
- REMAP-CAP also benefited from ‘embedding’ in both Cerner and Epic
- REMAP-CAP and mpRCT both ran on top of existing clinical trials networks
  - Managed multiple pharma and multiple government funding sources

Notable data and analysis features …

- All 3 keep the ‘statistical complexity’ under the hood
  - In other words, complicated trial design, but ‘simple’ to use at the bedside
  - RECOVERY is frequentist; REMAP-CAP and mpRCT are Bayesian

- All 3 capable (somewhat) of estimating …
  - Subgroup effects
  - Drug-drug interactions

- REMAP-CAP and mpRCT incorporated federated data streams
  - 4 data sources (2 eCRF and 2 E.H.R. systems) with standardized common data model

- mpRCT coordinated multiple DSMBs and trial steering committees

Some trials and tribulations …

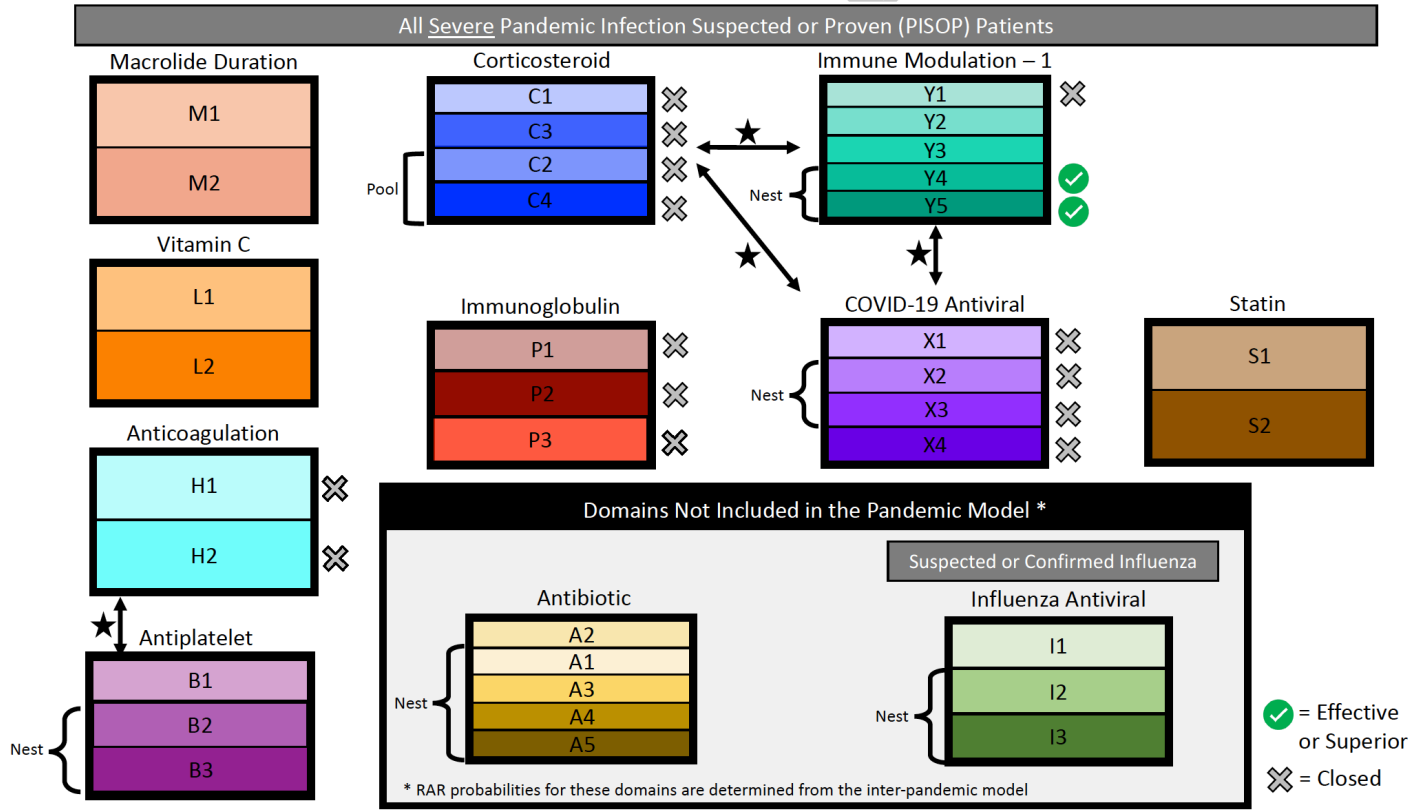
- All 3 have encountered some criticism
  - Opaque/unfamiliar statistics
  - Open-label design

- Relationship with regulatory authorities
  - Successful relationship for INDs, etc.
  - But, required to add ‘traditional’ features to become ‘registration’ grade …

- Sheer ‘weight’ of managing rapid enrollment and continual updates/changes
  - Ex: REMAP-CAP has evaluated 48 separate interventions
  - Massive (and somewhat unanticipated) load on central architecture
    - Trial steering committees, data coordinating centers, analytic cores, DSMBs, etc.

- Overcoming barriers for funders, coordinating centers and trials groups to ‘integrate’

REMAP-CAP severe state (ICU admission with organ failure)



- 194,400 possible regimens, just for COVID, when all domains open!

Lessons learned

- The rate, size and scale of the success of these APTs has been perceived as revolutionary
  - Large number of experienced trialists fairly unanimously believe there is ‘no going back’
  - Similarly positive endorsement from numerous senior regulatory figures
    - (e.g., former and acting current FDA directors)

- But, to facilitate routine incorporation of APTs across the entire clinical landscape, including oncology, several things need more work …

Some things to fix/improve

- Implement a US version of the UK NHIR CRN Hospital Payment system
  - A ‘trial-independent’ incentive scheme for healthcare systems to participate in clinical research
- Move towards federated data solutions
  - Common data model
  - Coordinating centers specify data needs, but draw data from multiple sources, including EHRs
- Re-visit more critically the incremental benefit of traditional ‘sacred cows’ of RCT methods
  - Is placebo always necessary?
  - Embrace ‘everybody wins’ designs to help drive engagement and enrolment, etc.
- Address the right matrix of investigators and funding agencies
  - To permit international collaboration, given competing priorities of different funding agencies and investigators
- Move towards more explicit and understandable reporting