



COVID-19 Clinical Trials: End Points!

April 24, 2020

COVID-19 Endpoints

- Most endpoints are ordinal in scale
- Most are combining together different clinical states of disease progression
- Relatively short timelines
 - Given enrollment rates and sample sizes and need, maybe 21 days is “long”
- Some “integrate over time” some do not
- Trying to make it easy to collect; objective; clinically relevant

Disease States

- **Severe:** In ICU, maybe on ventilator, need organ-support
- **Moderate:** Hospitalized; not ICU; Not organ support
- **Mild** (COVID suspected or proven): Ambulatory, non-hospitalized
- **Healthy:** Do not have COVID-19

WHO/NIH Ordinal Scales

WHO Ordinal Scale

- 1: Death
- 2: IMV or ECMO
- 3: NIV or HFNC
- 4: Hospitalized w O2
- 5: Hospitalized w/o O2 w/ in-patient needs
- 6: Hospitalized w/o in-patient needs
- 7: Not hospitalized w limitations
- 8: Not hospitalized w/o limitations

NIH Ordinal Scale

- 1: Death
- 2: IMV or ECMO
- 3: NIV or HFNC
- 4: Hospitalized w O2
- 5: Hospitalized w/o O2 w/ in-patient needs
- 6: Hospitalized w/o in-patient needs
- 7: Not hospitalized w limitations
- 8: Not hospitalized w/o limitations

Other Endpoints

- Mortality (ordinal scale!)
- (Death, MV, alive/not MV)
- (Hospitalized/death, not hospitalized)
- Time-to-liberation (all ordinal!)
 - Time to leave ICU; off MV; leave hospital
- ICU-Free days:
 - Composite of “alive & free of organ support” & “in-hospital death”
 - Death –1, 0, 1, 2, ..., 21 (death, 0 days free OS, 1 day free OS, ..., 21 days free organ support)

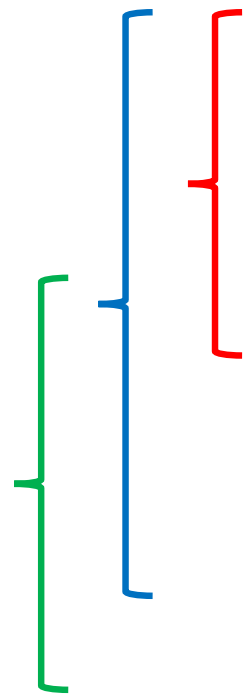


Timing?

- NIH is day 15
- Have seen “worst-vale of NIH Scale” over 15 days
- ICU-Free days integrates timing
- “Ideas” of a model that incorporates “AUC” over 21 days

State by Endpoint

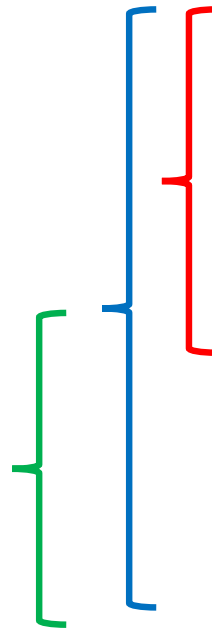
- **Severe**
- **Moderate**
- **Mild**



NIH Ordinal Scale
1: Death
2: IMV or ECMO
3: NIV or HFNC
4: Hospitalized w O2
5: Hospitalized w/o O2 w/ in-patient needs
6: Hospitalized w/o in-patient needs
7: Not hospitalized w limitations
8: Not hospitalized w/o limitations

State by Endpoint: ICU-Free Days

- **Severe**
- **Moderate**
- **Mild**



State over 21 days	ICU-Free Days
Death	-1
Alive, 0 organ-support free	0
Alive, 1 organ-support free	1
Alive, 2 organ-support free	2
Alive, 3 organ-support free	3
...	...
Alive, 20 organ-support free	20
Alive, 21 organ-support free	21

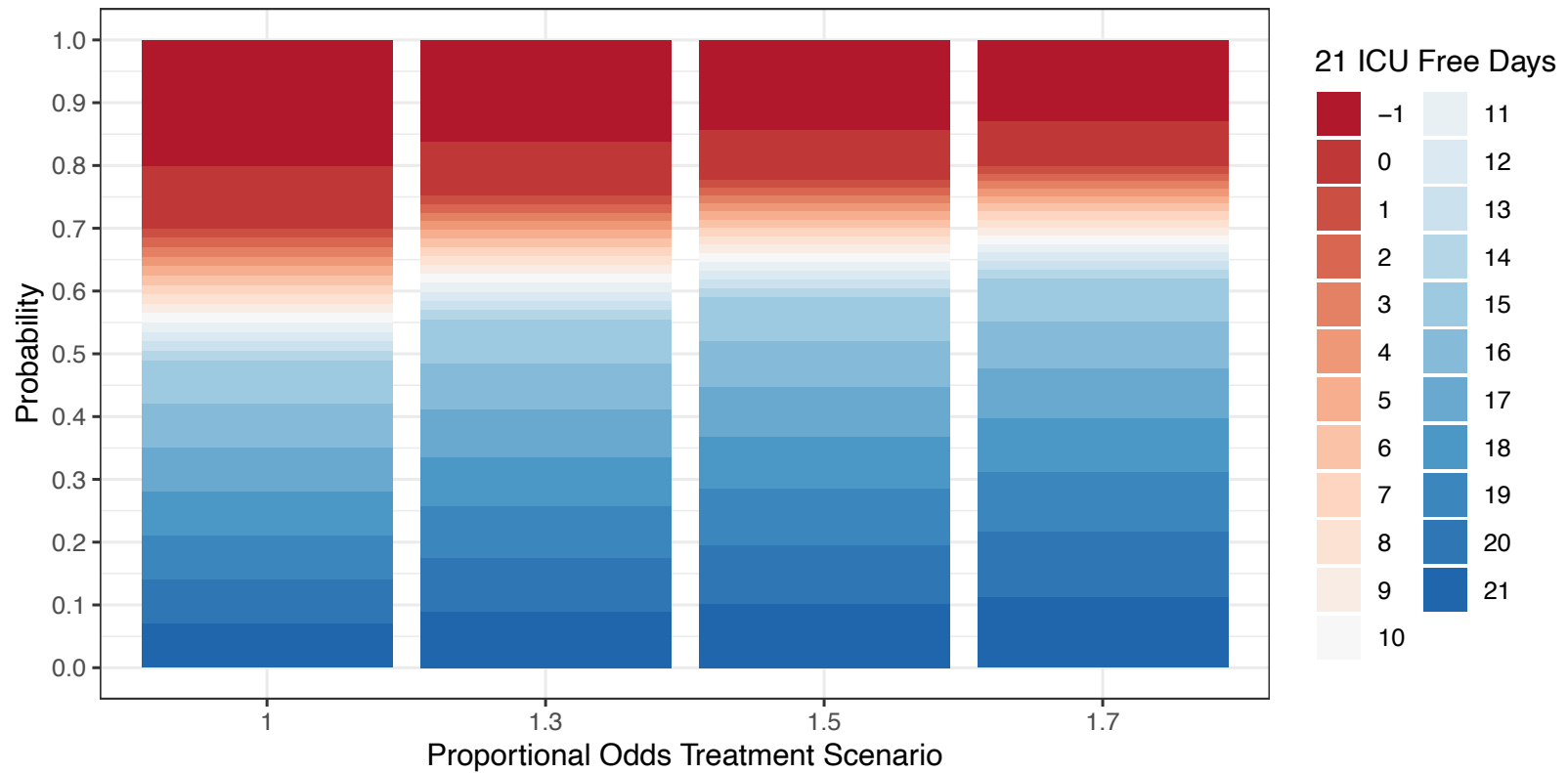
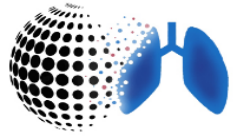
Analysis Methods for Ordinal Scales

- Wilcoxon Test
 - Non-parametric, no effect size, harder model
- Proportional-odds model
 - Easy to model; effect size across endpoint “odds-ratio”
 - Proportional odds assumption
 - Every jump is the “same”
- Numerical averaging
 - Yuck
- Utility Analysis of “Ordinal States”
- Cox-Model???
- Dichotomize?

Bayesian Proportional Odds Model

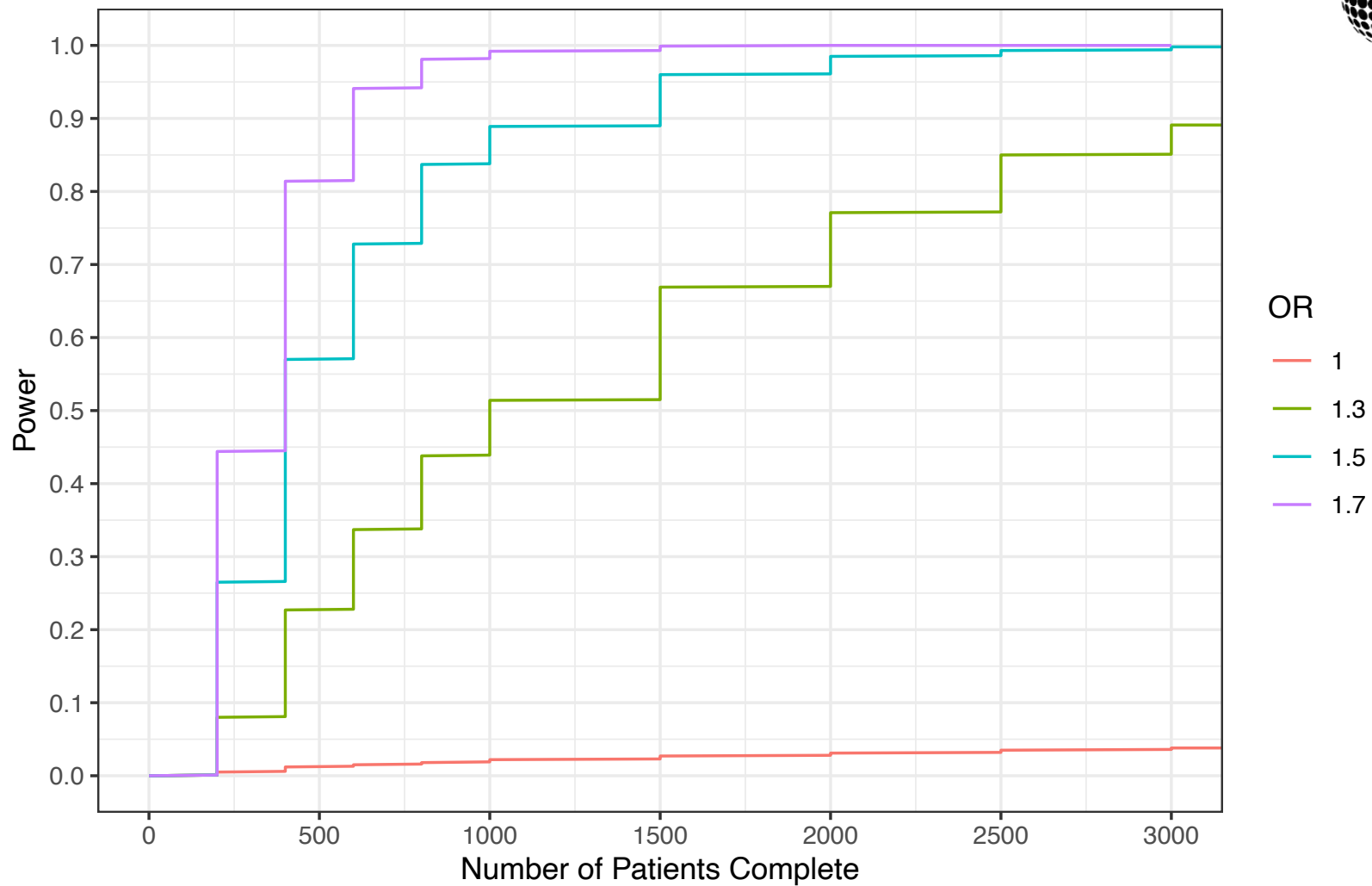
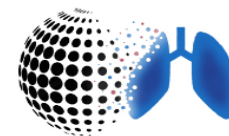
- Modeling easy
- Dichotomous logistic-regression for 2 values
- Interpretation of odds-ratios good clinical interpretation
- Covariates easy, interactions easy...
- Allows adaptations, predictive probabilities, ...

REMAP-CAP Simulations

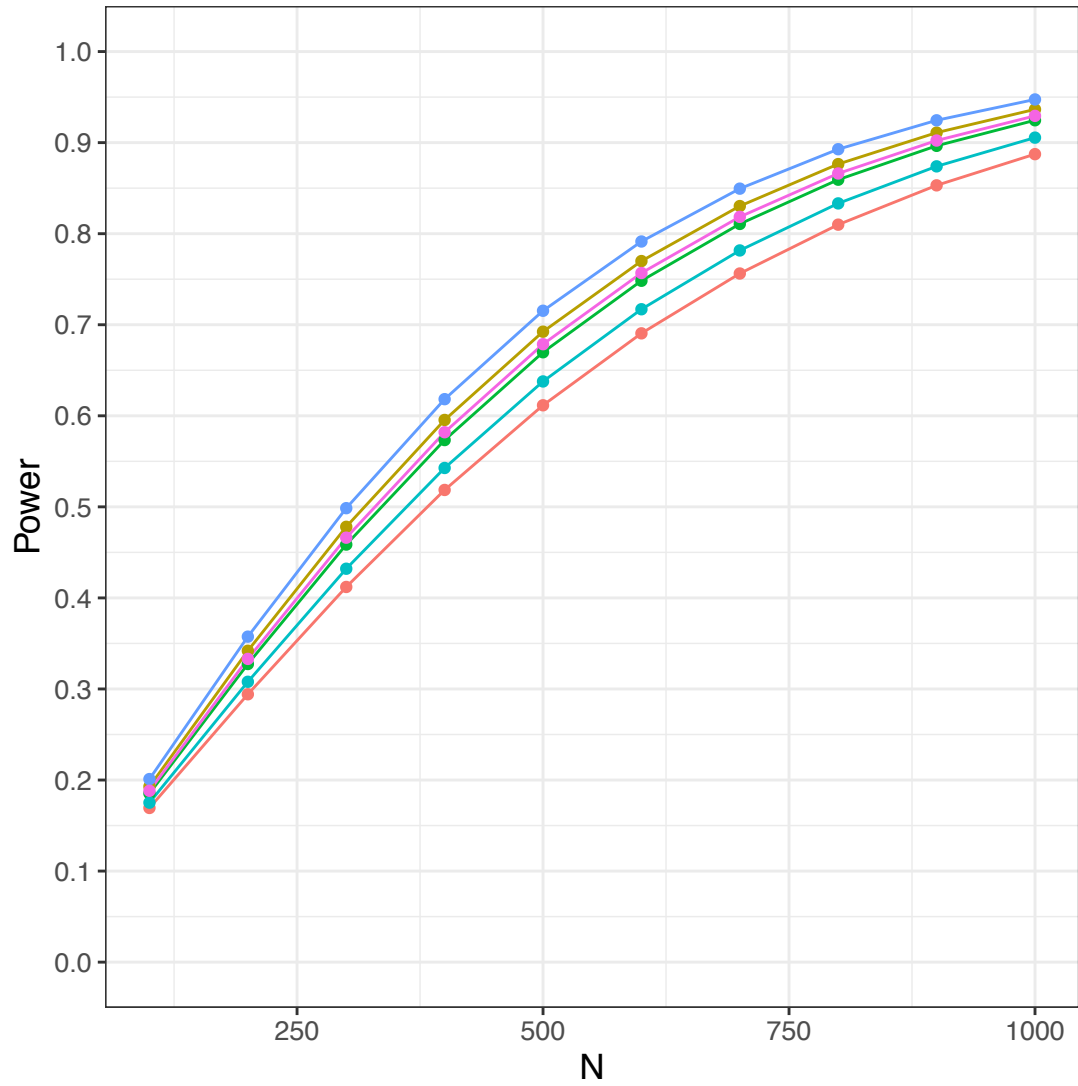


1v1 Domain: Power vs Patients Complete

One Effective Arm



OR = 1.5



Ordinal vs Dichotomous vs...
1:1 trial; Pr(OR > 1) > 97.5

Proportions in each outcome category

- (0.5, 0.5)
- (1/3, 1/3, 1/3)
- (0.5, 0.25, 0.25)
- (0.5, 0.45, 0.05)
- (0.25, 0.25, 0.25, 0.25)
- (0.5, 0.166, 0.166, 0.166)



Bayesian Proportional Odds Bayesian Code

<https://ftp.berryconsultants.com/BayesPOModel/>

Huge Thanks to Lindsay Berry and Elizabeth Lorenzi for the code!