

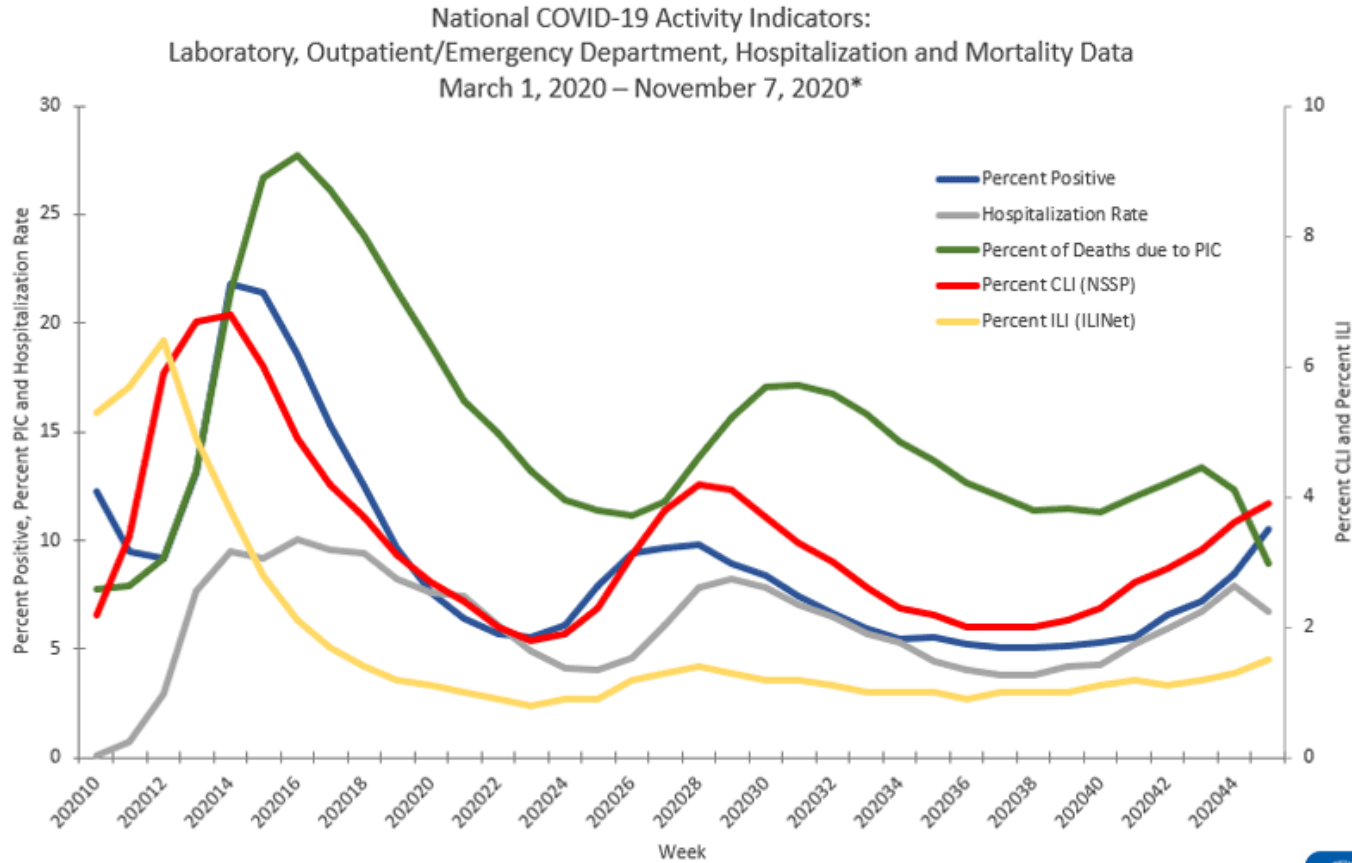
Impact of COVID-19 on HCT Center Outcomes



Committee

Kwang Ahn
Christopher Dandoy
Miguel Perales
John Wingard
William Wood

The impact could vary by when you look & what indicator of COVID-19 burden you use



*Data are preliminary and may change as more reports are received.

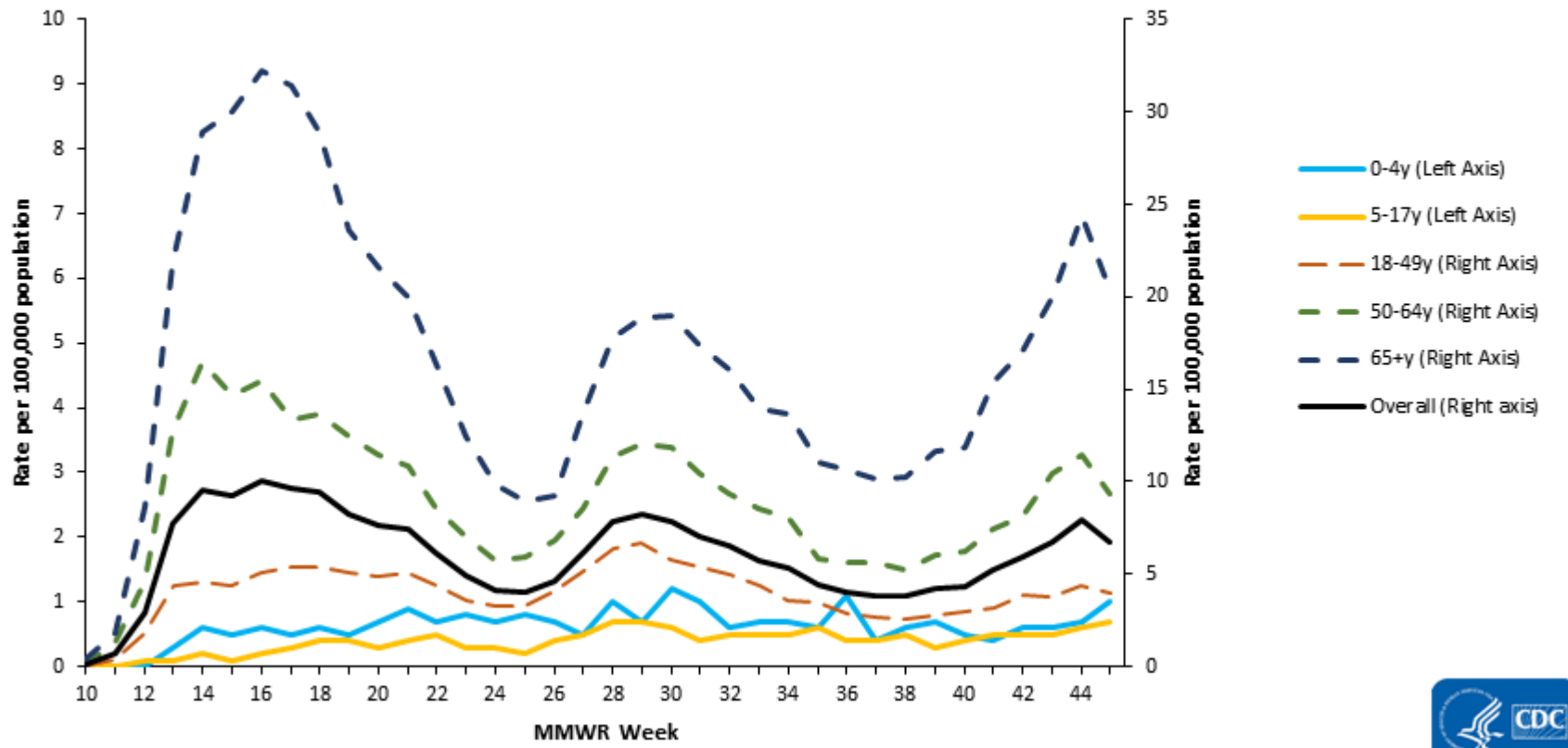


What is the best indicator??

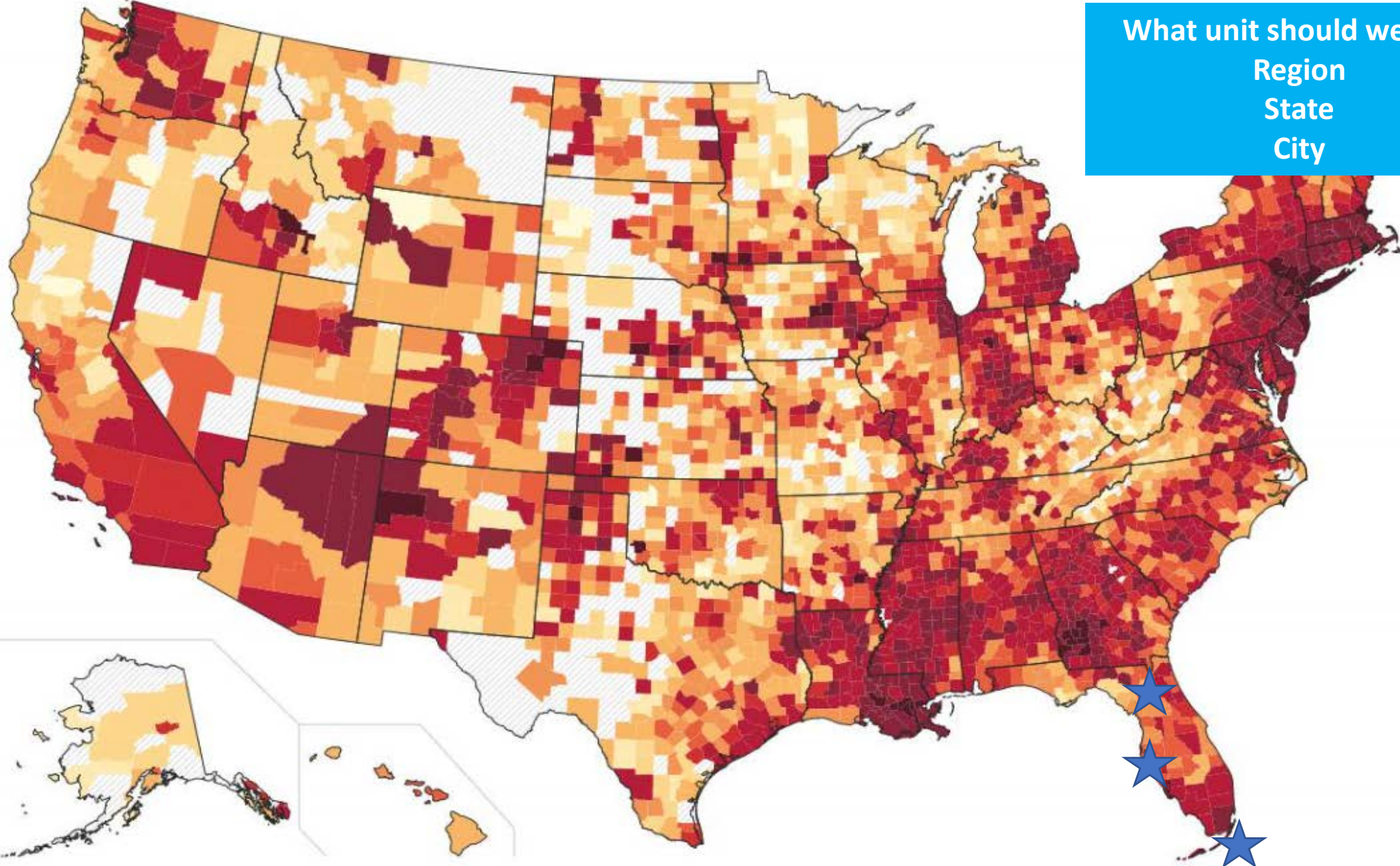
- Infection
- Hospitalization
- Death

The impact could vary by the type of patients a center treats

Weekly COVID-19-associated hospitalization rates by age group — COVID-NET, March 1–November 7, 2020



The impact of the pandemic could vary by where your center is



What unit should we use?
Region
State
City

The impact of the pandemic could depend on what kinds of patients/diseases a center treats

- **Other factors that may affect Impact:**

- Risk factors for both disease & COVID-19
- High vs low socio-economic status
- Family donor vs MUD

➤ **These factors may be very different in two centers with the same COVID-19 burden**

Center 1

Children

Mostly affluent patients

Mostly White, European extraction

Center 2

Older adults

Mostly under-resourced patients

Mostly non-White

COVID-19 probably also has indirect effects

- **Pre-HCT**

- Delays, perhaps bridging treatment
- Abridged risk assessment
- Best donor/graft choice may not be available
- Effect of cryopreservation of donor graft

- **Peri-HCT**

- Blood product shortages
- Loss of housing options, early return to local community and truncated follow-up by transplant team
- Constraints on health care resources (eg, ICU & transplant bed availability, staff adequacy, etc)

- **Post-HCT**

- Less oversight of ongoing care, monitoring of immunosuppressive regimen & infectious complications
- Potential delays in identifying GVHD, starting treatment, or suboptimal evaluation
- Less ability to conduct education, encourage health promoting behaviors, & screen for early & late complications
- Less availability of social networks to assist in care needs

➤ Much of the quality measures put in place by centers to promote quality may be disrupted by forces outside of their control

CIBMTR is now collecting information about some of these factors in the COVID impact reports

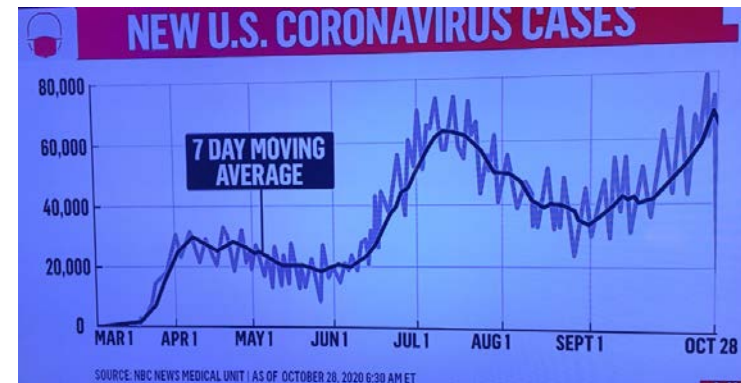
Taking all these considerations into account, the impact of COVID-19 on center HCT outcomes is:



Questions we will need to ponder about what data to put into analysis (1)



- **Did COVID-19 affect center mortality rate?**
 - Is the effect significant?
 - Can we define a “dose dependent” effect?
 - Is it transient or persistent?
- **What is the best marker of COVID-19 burden?**
 - Infection? Hospitalizations? Deaths?
 - Should we measure COVID-19 burden at the center or in the community where the patient lives
- **What is the best way to account for location?**
 - Should COVID-19 activity be broken down by region, state, a smaller geographical unit?
 - Should we also consider burden in the patient’s local community, where it differs from transplant center
- **What is the best proxy for the indirect effects of COVID-19 burden on a center?**
 - This is difficult to measure
 - is it even possible to measure?
 - ? Would a decrease in transplant volume at the center be a surrogate?
 - ? Will the center’s responses in the COVID-19 impact reports provide a gauge of the impact



Questions we will need to ponder about data to put into analysis (2)



- **What additional data do we need to collect in our CRDFs?**
 - COVID-19: date, outcome
 - GVHD & IS: date of GVHD onset, GVHD severity, date IS stopped
 - Center: zip code & its relationship to whatever COVID-19 unit of location we select
- ✓ **CIBMTR has begun to collect COVID-19 impact reports (with plan to be used in the 2021 report)**
 - How complete are the supplemental data collection forms during March-September & later?
 - This was at a time when center data staff was mostly working remote; ability to collect the data was suboptimal & varied by center
 - As of Oct 18: 57% not yet completed, 30% no impact, 12% impacted
 - Update Nov 19: Period March through Aug 24: Allogeneic HCT – 57% complete
Period Aug 24 through Nov 19: Allogeneic HCT – 37% complete

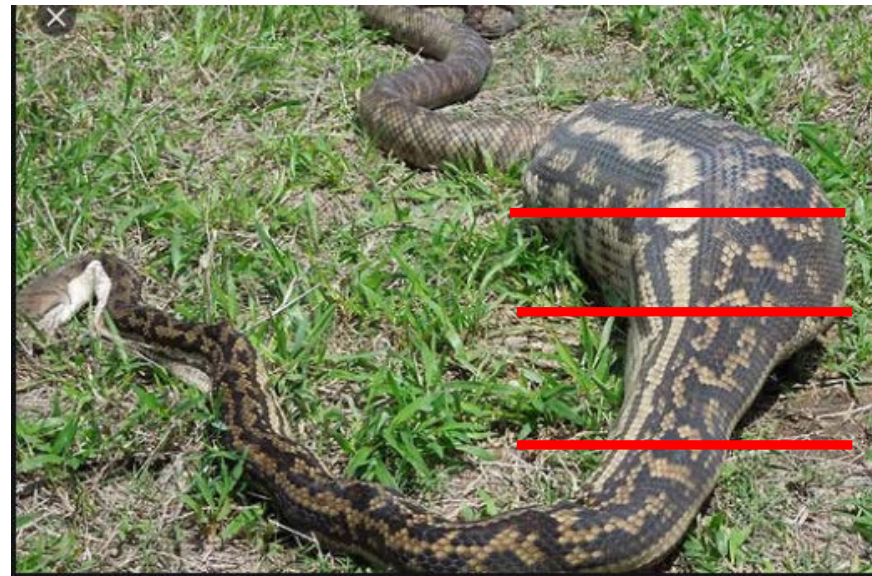
Questions we will need to ponder about data to put into analysis (3)

How to think about assessing the possible impact of COVID-19 on rolling 3-year HCT time periods



| Report | Pre- & Peri-HCT care | Post-HCT care | What HCT phase was impacted & for what years? |
|------------------|----------------------|---------------|--|
| 2020 (2016-2018) | No | No | none |
| 2021 (2017-2019) | No | Yes | 2019 post only |
| 2022 (2018-2020) | Yes | Yes | 2019 post; 2020 Pre/peri/post |
| 2023 (2019-2021) | Yes | Yes | 2019 post; 2020 Pre/peri/post; 2021 post yes;?pre/peri |

Ask this snake if he has a bellyache



Does this hurt?

2022 & 23: yeah, a lot

2021: yeah, a little

2020: not really

How we might approach the best type of analysis



- A pseudo-value approach (the traditional method used for HCT outcomes) makes it difficult to test time dependent covariates
- A time-dependent analysis might be best to use?
 - What time-dependent effects should be considered in analysis?
 - Calendar time: to adjust center experience with the pandemic
 - COVID-19 changes over time in the region
 - Time after HCT: first 100 days, 3-6 months, 6-12 months
 - Time on IS
 - Time dependent complications: especially acute & chronic GVHD
 - Time when COVID-19 infection occurs in individual patients
 - How can these time-dependent effects be tested?
 - Use Cox regression model to test the impact of the time dependent effects
 - Fit continuous function of time to determine potential breakpoints
 - Test interactions among the time dependent variables

Analysis Option #1



- Construct a Cox regression model
 - Develop a baseline model using currently known significant variables from previous years
 - Then, introduce the time dependent effects in stepwise manner to determine their function & significance of effect on outcomes.
 - Test interactions.
 - If time-dependent individual patient COVID-19 infection is significant, then we may censor at time of COVID-19 infection
 - If use COVID indicator, the center location rather than the patient location would simplify the analysis
- Additional advantages of a time dependent analysis:
 - Cox model can use all available follow-up time even if <1 year (important for HCT completed in second half of CY2019)
 - Modeling will use patients as the unit of analysis (to establish impact of pandemic), rather than centers (to determine performance)

Analysis Option #1



- How will the results be used?
 - If the analysis does not suggest an impact from the pandemic, CIBMTR will proceed with the standard pseudo-value regression model
 - If the analysis finds an impact, CIBMTR will need to determine whether the pseudo-value regression model analysis plan can be revised to accommodate the time dependent effects & potential interactions.
 - If analysis confirms impact & pseudo-value regression model cannot be adapted or too many time variable effects exist, CIBMTR will make recommendation to HRSA to defer specific cohorts from inclusion in the model
 - It may be appropriate for CIBMTR to include a disclaimer regarding the limitations to fully adjust for potential effects of the pandemic on the analysis & results

Analysis Option #2 (suggested by us non-statistical clinicians)



- Can we use year-over-year mortality (pre-pandemic vs post-pandemic) & if CY2019 outcomes are lower, adjust for un-explainable variation in the model to understand center's performance?
 - Can we separate a decrease in survival related to COVID-19 pandemic from that which is due to true performance decrease?
 - In any given year 5-10% of centers go from one performance category to another

After the analysis is done..



Possible outcomes

- We may be able to successfully model the impact & adjust accordingly
- We may not be able to successfully model the impact & we may be forced to conclude that the impact may influence outcomes in ways that are not predictable nor can be adjusted
- If the second proposition is our conclusion, is it fair to publish center outcome results that may well be skewed by a factor outside its control which defeats all of the quality measures put in place to optimize quality?

Next steps



- We need to decide **now** what additional data to collect & engage centers in collecting it
 - We are right now asking centers to get us their data as soon as they can for this purpose.
- The analysis models will need to be developed in 2021 (for the CY 2019 transplants)
 - Modeling to test the impact of COVID-19 for HCT recipients of HCT in CY 2019 should begin as soon as data are reported to CIBMTR (Jan/Feb 2021) to permit time to develop revised final analysis plan by May 2021
 - Currently, plan to begin the data preparation phase sooner than later to do the Cox model testing with a revised analysis plan if appropriate. Communications will follow.
- Important to note
 - The 2021 analysis will be impacted only by post-HCT care in CY2019 patients
 - The 2022 analysis will be impacted additionally by all facets of pre-, peri-, & post HCT care in CY2020 patients
 - Each subsequent year's analysis will be impacted in ways not yet known

Questions



- Are there factors or effects we are missing or have not accounted for?
- What is the best way to account for COVID-19 effect
 - Infection, hospitalization, or death rates?
 - Should we account for variability over time?
 - Is it best to measure at the location of the center or the patient
 - Region, state, town
- What is the best proxy for the indirect effects of COVID-19?
- What are your thoughts about the possibility that we may not be able to successfully model the impact & we may be forced to conclude that the impact may influence outcomes in ways that are not predictable nor can be adjusted?
- What else?