CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Summary and Recommendations of the 2020 Center Outcomes Forum Held on November 20, 2020

Executive Summary

The 2020 Center Outcomes Forum was held on November 20, 2020. The CIBMTR® (Center for International Blood and Marrow Transplant Research) invited representatives of the hematopoietic cell transplantation (HCT) community, the American Society for Transplantation and Cellular Therapy (ASTCT) Quality Outcomes Committee, Foundation for the Accreditation of Cellular Therapy (FACT), National Marrow Donor Program (NMDP), governmental funding agencies, patients, private payers, and statisticians. Discussion focused on three key question related to the Center-Specific Survival Analysis (CSA):

1. Is minimal residual disease (MRD) for acute leukemia (AML, ALL) ready for use as a risk adjustment factor in the CSA?
2. Are there new approaches to account for social determinants of health in the CSA risk adjustment model?
3. Can CIBMTR adequately adjust for the impact of the COVID-19 pandemic in the CSA?

The main discussion and recommendations for each are briefly summarized in the following pages. The final recommendations by topic include:

Recommendations from the MRD Working Group regarding risk adjustment

- CIBMTR should revise the data collection forms used to support the CSA to collect additional information relevant to define MRD status in AML, ALL at the pre-HCT time point.
    - Revised data collection should specifically request whether MRD was assessed for patients in remission, the technique used, the level of sensitivity, and whether MRD was detected.
    - CIBMTR should actively consider revising data collection forms to incorporate pre-HCT MRD status in MDS, CLL and MM as more evidence becomes available.
- CIBMTR should begin education efforts for data professionals and others regarding reporting of MRD status and importance of complete data reporting.
- Using currently collected data, for patients with AML or ALL transplanted in CR, CIBMTR should apply and test the following disease categories in the risk adjustment model:
    - CR (1, 2 or 3+) without MRD tested by high sensitivity method
    - CR (1, 2, or 3+) with MRD
    - CR with no high sensitivity testing for MRD

Recommendations from the Social Determinants of Health Working Group regarding risk adjustment

- Continue inclusion of household income derived from ZIP code of residence and race/ethnicity in the CSA.
- Consider intermittent re-assessment of other uses of ZIP code of residence, including distance from transplant center for significance in the risk adjustment model. Consider collecting ZIP+4 for greater refinement in use of ZIP code.
- Evaluate completeness of current data collection, and potential contribution to CSA of marital status, occupation, work status, highest education level, and health insurance using cohort of US HCT recipients who have these data. Significant variables should be considered for data collection on all US recipients for future inclusion in the risk adjustment model. Prioritize testing of health insurance coverage as potentially having the greatest impact.
- No new variables were recommended for data collection at this time.
- Consider a pilot study to evaluate the feasibility of capturing socio-demographic factors directly from patients using patient-reported outcomes (PRO) data collection tools.

Recommendations from the SARS-CoV-2 Working Group regarding risk adjustment

- CIBMTR should expedite data collection efforts for allogeneic HCT recipients from 2019 to facilitate preliminary modeling to understand the impact of the COVID-19 pandemic on outcomes of allogeneic HCT.
- Develop a modeling approach to test the impact of COVID-19 on outcomes for recipients of HCT in 2019 and implement that approach in early 2021.
    - Communicate with center directors and escalate relevant data collection efforts with centers to support earlier timelines for data submission to support these analyses.
    - The preliminary modeling approach is likely to employ Cox modeling to handle time-dependent covariates.
- Use the results of the preliminary modeling for impact of COVID 19 to design, if possible, a modified pseudo-value modeling approach for the CSA for the cohort of patients transplanted in 2017-2019.
    - It is important to use a consistent CSA model, if possible, to achieve results that are consistent with previous years and with known performance characteristics to allow year-over-year comparisons and maintain confidence in the modeling process.
    - Include sections in the CSA Report outlining the methodology and limitations of the risk adjustment for COVID-19 pandemic.
- Develop communications for use across all relevant stakeholder groups regarding plans for CSA in 2021 and subsequent years to address COVID-19.
- Continue to collaborate with the Scientific Registry of Transplant Recipients (SRTR) and other organizations involved in public outcomes reporting to explore if other organizations are making assessments of the impact of COVID-19 on general acute care for geographic areas to inform this effort.
- Using results from the analysis conducted in 2021, begin to develop an approach to subsequent analyses that address all relevant COVID-19 impacts for recipients of HCT in 2020.

Introduction

To increase transparency and understanding of center outcomes reporting in HCT, CIBMTR began in 2008 to hold biannual Center Outcomes Forums. CIBMTR invites representatives of the HCT community, including transplant physicians and center directors, the ASTCT, FACT, governmental funding agencies, patients, private payers, and statisticians. The purpose is to review the current approach to center-specific outcomes reporting and to provide meaningful recommendations for future reports. Summaries of these meetings are available at http://www.cibmtr.org/Meetings/Materials/CSOAForum.

The 2020 Center Outcomes Forum was held on November 20, 2020, and included a broad range of invited stakeholder participants (Appendix A). A summary of the group discussion and recommendations from this meeting follows.

Working groups were formed to present recommendations about three key questions related to the CSA:

1. Is MRD for acute leukemia (AML, ALL) ready for use as a risk adjustment factor in the CSA?
2. Are there new approaches to account for social determinants of health in the CSA risk adjustment model?
3. Can CIBMTR adequately adjust for the impact of the COVID-19 pandemic in the CSA?

Membership of the working groups is shown in Appendix B.

Overview of 2020 Center-Specific Survival Report

An important function of the Center Outcomes Forum is to review the CSA and provide recommendations for improvement. It is essential that CIBMTR continue to collect relevant and updated patient, disease and transplant characteristics for use in the risk-adjustment models. Additionally, because this publicly available report has high impact for the HCT community, it is important to review the statistical modeling methodology to maintain accountability and transparency. Details about the report methodology can be found on the CIBMTR website. The 2020 CSA Report was reviewed, as was progress on accomplishing the main recommendations from the 2018 Center Outcomes Forum.

The 2020 analysis and report, which included patients who received a first allogeneic HCT between January 1, 2016, and December 31, 2018, was reviewed. More than 24,600 patients at 172 US centers met inclusion criteria. The 2020 model is similar to 2019, except for the following:

- Recipient ethnicity and ALL T-cell lineage were not included in the model due to lack of statistical significance,
- Therapy related MDS was included in the model this year due to meeting the significance requirement,
- Donor age was broken down into 5-year increments rather than decades, and
- Separate variables for adult and pediatric BMI groups were added. These identified those underweight to test as a factor in the model; it was significant among the adult group only.

The risk adjustment model was enhanced with the following factors in 2018 and 2019 [* <0.01; ** <0.001]:

- Patient factors:
    - Median household income by ZIP **
    - History of mechanical ventilation**
    - History of invasive fungal infection**
    - Recipient ethnicity*

- Disease factors:
    - AML transformed from MDS/MPN **
    - AML ELN risk – cytogenetic and molecular**
    - Greater refinement of AML and ALL in CR3+/REL/PIF*
        - CR1, CR2, CR3+, REL1, REL2, PIF
    - Addition of interval dx to tx for CR3+ and REL*
    - ALL Ph+ *
    - MDS IPSS-R at HCT**
    - Plasma cell disorders disease status at HCT**

Recommendations from 2018 Center Outcomes Forum have been addressed:

- The impact of "enhanced" risk adjustment model implemented in 2018 has been thoroughly evaluated and continues to be used, including further refinement of categorization of significant variables.
- Recommended variables to improve risk adjustment for pediatric non-malignant diseases have been added to the revised data collection forms and will be appropriately incorporated in future analyses.
- Modeling techniques to handle center effects were evaluated, several machine learning approaches were tested and did not improve the model, and CIBMTR continues to use variability indices to test new variables in the risk adjustment model.
- CIBMTR, FACT and ASTCT collaborated to develop a streamlined process and timelines for FACT Corrective Action Plans as a tool for communication between payers and centers about quality improvement to assist with managing consequences of below expected center performance; and educating stakeholders about relevant limitations of the analysis. Further information was provided in the 2020 Forum.
- CIBMTR has begun working with groups of interested investigators to develop a research agenda regarding impacts of the CSA on the practice of HCT.

Is minimal residual disease/measurable residual disease (MRD) for acute leukemia (AML, ALL) ready for use as a risk adjustment factor in the CSA?

- *If not, what criteria need to be met in the future (e.g., consistent/standardized measures, etc.)?*
- *What changes in data collection should CIBMTR make to support future use of MRD?*

Current CIBMTR data collection for MRD on Disease Classification Form (F2402):

- Molecular /cytogenetic data are collected for ALL, AML, and MDS/MPN at three time points: diagnosis, between diagnosis and HCT, and at HCT.
- Flow cytometry to test for MRD is collected at HCT only (if complete remission (CR) is achieved) for ALL and AML.
- No sensitivity threshold is requested for MRD status.
- In AML, molecular panel currently includes: FLT3-ITD, FLT3-TKD, IDH1/2, CEBPA, KIT, NPM1, Others.
- In ALL, molecular panel includes: BCR/ABL, TEL-AML/AML1, Others.

Background:

- High and low volume centers report to CIBMTR using MRD testing methods in similar frequency and proportions.
- A summary of the current state of the science and studies evaluating MRD in ALL and AML were presented by Drs. Davies, Scott, and Hourigan.

- Molecular testing types include flow cytometry, quantitative polymerase chain reaction (qPCR), digital PCR, diagnostic next-generation sequencing (NGS) and NGS MRD depth.
    - Flow cytometry is the most used.
    - qPCR is the recommended molecular technique for AML based on ELN consensus recommendations.
    - Diagnostic NGS "myeloid panels" are insufficient to test for MRD negativity.
    - NGS MRD depth is externally validated, but not yet available clinically.
    - Interpretation of testing for MRD requires caution, as not all mutations represent cancer.
- Many studies have been completed evaluating MRD impact on HCT outcomes in ALL and AML.
    - Meta-analyses/systematic reviews of outcomes in ALL demonstrate substantially worse outcomes (overall survival (OS), relapse-free survival (RFS)) when MRD is present for adult and pediatric patients who undergo allogeneic HCT in CR1 and CR2. There is less data available to support recommendations in CR3+.
    - Several studies also demonstrate worse outcomes (OS, RFS) in patients who underwent allogeneic HCT for AML in MRD positive remission compared to MRD negative remission, regardless of CR#.
    - One study suggests AML patients with MRD positive remission have allogeneic HCT outcomes similar to patients with active disease at HCT.
    - There is some suggestion in studies that myeloablative conditioning can overcome adversity of MRD positivity in AML patients transplanted in CR.
- Generally speaking, regardless of whether PCR or flow cytometry-based testing is used as the method to detect MRD, presence of MRD pre-HCT for patients with AML is associated with worse OS after HCT.
  Summary:
    - Knowledge of MRD status in patients with ALL and AML is essential for appropriate risk adjustment in HCT outcomes analyses.
    - Although there is variability in testing techniques employed by US centers, a positive MRD provides meaningful information, whereas a negative MRD test result is only meaningful if a sensitive test is used.
    - Patients in CR1 or CR2 with MRD+ have similar survival as those patients with evident morphologic disease pre-transplant for AML and ALL.
- Centers not using high sensitivity MRD testing for patients with AML or ALL in remission at HCT are likely including patients with higher risk of relapse in their categorization of CR1 and CR2.

Working group initial recommendations:

- Revise pre-transplant questions for ALL/AML (and possibly MDS, CLL and MM):
    1. In Morphologic CR, was MRD assessed? y/n
    2. If Flow was tested
       Was an original leukemia immunophenotype used for detection? y/n
       Was an aberrant phenotype used for detection? y/n
       What is the lower limit of detection?
    3. Was molecular assay (PCR or NGS) used for MRD detection? y/n
       Was MRD detected? y/n
    4. Were cytogenetic assays (Metaphase or FISH) used for MRD detection? y/n
       Was MRD detected? y/n
- For future survival analyses, test new disease status categories for AML and ALL in CR1/2/3+ without MRD, CR with MRD, and CR with no high-sensitivity testing for MRD.

Discussion:

Testing and analysis:

- ALL is easier to report than AML due to widely adopted use of flow cytometry in ALL and significant heterogeneity in testing and disease markers in AML.
- To add new variables to the risk adjustment model, they should add precision to categories and be associated with one-year survival.
- CIBMTR will need to use the "pre-HCT" timepoint for testing new disease categories in ALL and AML as these are the currently available data that are most complete. Giving centers the opportunity to report test sensitivity may provide incentive for centers not already doing high-sensitivity testing to begin doing it. About half of transplant centers are not consistently doing MRD testing in ALL and AML patients pre-HCT; this is a good opportunity to influence this practice.
    - High sensitivity testing is important; lower levels of sensitivity may fail to detect MRD. Minimum testing that may be considered "high" sensitivity is multi-color flow cytometry. PCR-based methods may have greater sensitivity, at least for some mutations and are increasingly available in many centers.
- Molecular testing results often require a few weeks to be completed. Consequently, more planning is needed by transplant centers to receive results in time to affect pre-HCT decision making. Use of high-sensitivity MRD testing may also influence decision-making regarding which patients proceed to HCT.
- There was agreement that MRD testing is important in acute leukemia patients in morphologic CR at time of HCT; both positive and negative with high sensitivity are relevant to the CSA risk adjustment model.
- In the future, it may be possible to move data from lab systems more quickly and with automation, streamline reporting and comparative standardization of these important data. However, interpretation is important as not all positive results are relevant.

Education:

- CIBMTR should develop consensus on how the results should be reported and instructions for data managers who enter the data. Education sessions for data managers, which will describe and simplify the reporting, will be launched. One challenge is that the initial diagnostic information may not have been performed at the transplant center reporting the data. It would be beneficial to run a pilot of the training to obtain feedback before launching. Key things to include in the training are:
    - Why reporting of MRD status matters,
    - How to find the results,
    - Understanding reporting based on level of sensitivity, and
    - How to report the results.
- Plans to implement MRD testing in the CSA risk adjustment model and other CIBMTR studies should be discussed with center directors to raise awareness of the plans.
- A white paper summarizing assays, targets deployed, etc., would be helpful so the community understands that this work is in progress.
- ASTCT can help in educational efforts, working within their existing mechanisms.

Final Recommendations:

- CIBMTR should revise the data collection forms used to support the CSA to collect additional information relevant to define MRD status in AML, ALL at the pre-HCT time point.
    - Revised data collection should specifically request whether MRD was assessed for patients in remission, the technique used, the level of sensitivity, and whether MRD was detected.

    - CIBMTR should actively consider revising data collection forms to incorporate pre-HCT MRD status in MDS, CLL and MM as more evidence becomes available.
- CIBMTR should begin education efforts for data professionals and others regarding reporting of MRD status and importance of complete data reporting.
- Using currently collected data, for patients with AML or ALL transplanted in CR, CIBMTR should apply and test the following disease categories in the risk adjustment model:
    - CR (1, 2 or 3+) without MRD tested by high sensitivity method
    - CR (1, 2, or 3+) with MRD
    - CR with no high sensitivity testing for MRD

Are there new approaches to account for social determinants of health in the CSA risk adjustment model?

Current status of social determinants of health variables:

- Socio-demographic data collected on all US HCT recipients and currently considered In CSA:
    - Recipient ethnicity/race (self-reported)
    - Socioeconomic status (median annual household income based on ZIP code of residence)
        - Included as variable starting with 2018 analysis
        - Categorized as deciles (<10th percentile [$37K] to ≥90th percentile [>$100K])
        - Well captured overall (2019 analysis: unknown in 2% patients)
- Additional variables collected on Comprehensive Report Form (CRF)
    - Marital status
    - Occupation
    - Work status
    - Highest education
    - Health insurance
    - Gross household income (six categories)

Background:

- This topic was last addressed at the 2014 Center Outcomes Forum. Sociodemographic/socioeconomic status (SES) factors recommended for data collection and use in future risk adjustment for US HCT recipients included insurance status, ZIP code of residence, race/ethnicity, level of education and marital status.
- CIBMTR currently collects self-reported (by center) race/ethnicity, and ZIP code of residence for all US recipients and data have a high degree of completeness.
- CIBMTR additionally collects marital status, occupation, work status, highest education level, and health insurance for some recipients on the CRF.
- Median household derived from ZIP code of residence, and race/ethnicity have been included in the CSA for US recipients since 2018. Income has been a statistically significant factor, whereas race and ethnicity have not been statistically significant once income was included in the model.

Recent CIBMTR studies:

- Sociodemographic data has been used in other recently published studies, including community health status and its association with HCT outcomes (Hong, S et al Cancer 2020) and marital status (Tay J, et al Current Oncology 2020).

- Community health status: A risk score—based on health behaviors, clinical care, social/economic environment, and physical environment of a community—is assigned to each patient and center; a higher patient community risk score is associated with lower survival and higher non-relapse mortality (NRM). Center Community risk scores were not associated with survival, relapse or NRM.
- Marital status and HCT outcomes: Married people had lower risk of aGVHD compared to non-married; there is no clear association between marital status and survival.
- Neighborhood poverty level:
    - For non-malignant disease, there was no association with neighborhood poverty.
    - For malignant disease, there was no association with survival and a positive association with NRM with lower neighborhood poverty level.

Working group initial recommendations:

- Evaluate if any high-quality socio-demographic variables currently collected on the CRF are independently associated with center survival and should be captured on TED for use in risk adjustment
    - Evaluate completeness of existing CRF data
    - Evaluate contribution of these variables to risk adjustment model (beyond race/ethnicity and ZIP code defined SES) in the subset for which the data are complete.
    - Priority of variables to test: health insurance coverage is anticipated to have greater impact than other variables
    - Add categories and/or allow variables to capture pediatric-specific data (i.e., information on parent/guardian occupation, education, and work status).
- No new variables were recommended to be added to CRF.
- Prioritize evaluation of feasibility and contribution of existing socio-demographic variables in refining the risk adjustment model rather than adding additional variables to the CRF forms.
- Consider pilot studies evaluating feasibility of capturing socio-demographic information directly from patients:
    - Explore the possibility of using the CIBMTR PRO data collection platform to capture current and new variables that may inform the risk adjustment model in the future.
    - Explore the possibility of capturing data via the CIBMTR consent form/process (e.g., add key questions on consent form for patients to complete).

Discussion:

- The working group outlined several relevant framework considerations regarding inclusion of additional variables in the risk adjustment model. These include feasibility of collecting complete and reliable data, the need to balance center effort vs. benefit of collecting the data, demonstrating candidate factors have proven contribution to survival risk adjustment before collecting on all patients, and considering whether variables to be collected may inform interventions that improve outcomes.
- Income/poverty:
    - ZIP code (area level), ZIP+4 (neighborhood level), household
        - Area and neighborhood income are not a substitute for household income.
        - ZIP+4 may allow for more refined estimation of household income and other socio-demographic factors.
        - Consider collecting income as a PRO for better determination of household income; a limitation is the need to have the information on all patients for inclusion in the risk adjustment model.

    - Distance to TC: more rural areas generally represent higher poverty.
    - Having or being eligible for Medicaid could serve as a surrogate for income. Medicaid eligibility criteria are subject to heterogeneity, including by state.
- New variables to be considered in the context of socio-demographic status:
    - Distance to transplant center (interaction with urban/rural status and SES)
    - Caregiver support
    - Health literacy
    - Poverty (PRO: Food Insecurity Screen)
    - Need for interpreter
    - Use of NMDP grants (e.g., donor search, patient financial assistance)
- Consider future research on patients that do not get an HCT and the relationship to SES factors.
    - CIBMTR does not collect data on patients that do not go to HCT. A cohort of centers could aid in understanding of factors for those that do not go to HCT and evaluation of how much this impacts CSA and patients.
    - There is currently one study following patients; only about half go to HCT which implies they were already in the early stages of being considered for HCT.
    - It may be possible to use payer databases to better understand this issue. Partnerships between centers and payers would be beneficial to better understand the best way to treat patients.
    - In the future, CIBMTR may be able to allow transplant centers to share data regarding a larger cohort of patients using automation of data collection from electronic medical records and other sources.

Final Recommendations:

- Continue inclusion of household income derived from ZIP code of residence and race/ethnicity in the CSA.
- Consider intermittent re-assessment of other uses of ZIP code of residence, including distance from transplant center for significance in the risk adjustment model. Consider collecting ZIP+4 for greater refinement in use of ZIP code.
- Evaluate completeness of current data collection, and potential contribution to CSA of marital status, occupation, work status, highest education level, and health insurance using cohort of US HCT recipients who have these data. Significant variables should be considered for data collection on all US recipients for future inclusion in the risk adjustment model. Prioritize testing of health insurance coverage as potentially having the greatest impact.
- No new variables were recommended for data collection at this time.
- Consider a pilot study to evaluate the feasibility of capturing socio-demographic factors directly from patients using PRO data collection tools.

Can CIBMTR adequately adjust for the impact of the COVID-19 pandemic in the CSA?

- *What factors are most essential and how can they be incorporated in the risk adjustment?*

Background:

HCT recipients infected with SARS-CoV-2 have been reported to have higher mortality rates than the general population (Shah et al, JCI 2020; Altuna et al BMT 2020; Sharma, AK et al submitted (CIBMTR)). The COVID-19 pandemic has therefore had direct negative effects on outcomes of HCT recipients. In addition, changes in HCT and centers' standard practices and procedures in response to the pandemic may have indirect effects on HCT outcomes and may not be equally distributed across all US HCT centers. CIBMTR must carefully consider the

ways these direct and indirect factors largely beyond the control of HCT centers, may influence HCT outcomes, and whether they can be adequately incorporated into the CSA to create a fair and unbiased representation of center outcomes.

- COVID-19 has direct effects on outcomes in HCT recipients; impact could vary by:
    - Timing of pandemic onset and intensity over time
    - Types and distribution of patients/disease indications treated at center
        - Age
        - Disease indications (underlying immunosuppression)
        - Risk factors and exposures for COVID-19
        - High vs. low socio-economic status
        - Family donor vs. matched unrelated donor
    - Geographic location of the center
- COVID-19 likely has had indirect effects on outcomes – quality processes/programs put in place to support patients could be severely disrupted by forces outside a center's control.
    - Pre-HCT: delays in performing HCT, abridged risk assessment, changes in center's patient selection based on risk, reduced availability of optimal donor/graft choices, increased use of donor graft cryopreservation.
    - Peri-HCT: blood product shortages, reduced access to housing options near the HCT center, early return of patients to local community, truncated or modified follow-up by transplant team, constraints on health care resources (bed availability, ICU access) especially at HCT center.
    - Post-HCT: shifting to virtual or telehealth with fewer visits or examinations, less oversight of ongoing care, monitoring of immunosuppressive regimen and infectious complications, potential delays in identifying and managing GVHD or other complications, less ability to conduct education, encourage health promoting behaviors, and screen for complications, less availability of social networks to assist in care needs.
- Centers have been affected unevenly, by time, location, and COVID-19 burden.
- Questions to consider regarding data to include in analysis
    - Did COVID-19 affect center mortality rate?
    - What is the best marker of COVID-19 burden? Infection, hospitalization, or mortality?
    - What is the best way to account for geographic variation in the impact of COVID-19?
    - What is the best proxy for the indirect effects of COVID-19 burden on a center?
    - What additional data should CIBMTR to collect to better define the impact of COVID-19?
- Potential approaches to the analysis to determine whether COVID-19 and associated factors affected HCT outcomes and how they can be incorporated in risk adjustment:
    - At least two distinct time scenarios need to be accounted for:
        - *Patients who received allogeneic HCT in 2019* may have been exposed to COVID-19 during their first-year follow-up interval, or to changes in centers' surveillance and post-HCT management practices during 2020. Pre-HCT center practices were not altered; post-HCT practices and patient care and exposures may have been affected.
        - *Patients who received an allogeneic HCT in 2020 or later* may be at risk for all the indirect and direct effects of the pandemic outlined above during all phases of HCT, pre- and post.
        - Potential impacts for patients receiving HCT in 2021 and later are yet to be determined.
    - A pseudo-value approach (the traditional method used for HCT outcomes) makes it difficult to test time-dependent covariates. An alternative model should be used to better determine whether the pandemic impacted HCT outcomes and which factors should be considered for risk adjustment.

    - A Cox regression model is designed to test time-dependent effects with the following advantages:
        - A continuous function of time can be fit to determine potential breakpoints.
        - Interactions among the time-dependent variables can be tested.
        - Cox model can use all available follow-up time, even if less than one year (important for HCTs completed in the second half of 2019).
        - Modeling will use *patients* as the unit of analysis (to establish the impact of the pandemic), rather than *centers* (to determine performance) giving considerable power to statistical testing.
    - Time-dependent effects to be addressed in the analysis:
        - Calendar time: to adjust center experience with COVID-19. Experience and adaptation vary by time and center since the beginning of the pandemic.
        - Time varying geographic incidence/exposure rates of COVID-19. This effect can be divided into geographic incidence/exposure at the center, or at the patient's area of residence. For the analysis that includes patients who had HCT in 2019, the patient may be censored at time of COVID-19 infection to reduce the need to adjust for the geographic effect at the patient's area of residence.
        - Time after HCT, susceptibility to infection or its complications may vary with time since HCT: 100 days, 3-6 months, 6-12 months.
        - Time-dependent complications: aGVHD/cGVHD or similar HCT complications may modify risk of COVID-19 infection or infectious complications.
        - Time to COVID-19 infection at the level of patient.
- The purpose of the initial analysis using the Cox regression model will be to determine whether COVID-19 affected survival outcomes for HCT recipients during 2019 in the first year after HCT, and if so, which time dependent covariates may be best utilized for risk adjustment.
    - If the analysis does not suggest an impact from the pandemic, CIBMTR may 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 and potential interactions.
    - If the analysis confirms impact and the pseudo-value regression model cannot be adapted or too many time variable effects exist, CIBMTR may recommend to the Health Resources & Services Administration (HRSA) to defer specific cohorts from inclusion in the model.
    - Regardless of the modeling results, CIBMTR should include a statement regarding the limitations to fully adjust for potential effects of the pandemic on the analysis and results.
    - If modeling does not suggest an impact for HCTs performed during 2019, it will need to be retested in subsequent years when all phases of transplant were affected.

Working group initial recommendations:

- CIBMTR should review data being collected to assess the impact of COVID-19 on outcomes to determine whether these data will be sufficient for risk adjustment while bearing consideration of the burdens of data collection.
- Current COVID-specific data being collected by CIBMTR in addition to existing data to assess impact include:
    - Pre HCT: History of SARS-CoV-2 infection, hospitalization for SARS-CoV-2 infection, history of mechanical ventilation for SARS-CoV-2 infection.

    - Post HCT: SARS-CoV-2 infection and date, SARS-CoV-2 infection as a cause of death, intended HCT date, intended donor and product type, use of cryopreservation, and changes in preparative regimen or GVHD prophylaxis related to COVID-19.
- Develop a modeling approach to test the impact of COVID-19 on outcomes for recipients of HCT in 2019 and implement that approach in early 2021.
    - Communicate with center directors and escalate relevant data collection efforts with centers to support earlier timelines for data submission to support these analyses.
- Use the results of the preliminary modeling for impact of COVID 19 to design, if possible, a modified pseudo-value modeling approach for the CSA.
    - It is important to attempt to use a consistent CSA model to achieve results that are consistent with previous years and with known performance characteristics
- Modeling will need to be retested for recipients of HCT in 2020, and potentially subsequent years, since the pandemic's effects on pre-HCT/peri-HCT care may be greater than post-HCT care alone.

Discussion:

- The pandemic has exacerbated access to follow-up care, caused changes to graft source selection and increased use of frozen products. It is unclear how to adjust for these patient-related issues. Center/region activity should be considered as it will impact these intangibles.
- Other organizations involved in public outcomes reporting may also be considering how best to address the impact of COVID-19 on their analytic processes that could inform CIBMTR's effort.
    - The SRTR has delayed reporting of their risk-adjusted metrics beginning with the cohort of organ transplants at March 14, 2020. CIBMTR and the SRTR contractor have been sharing information about planned approaches.
- Several payers discussed their organization's views regarding the impact of COVID-19:
    - Several are not intending to make any changes in their "centers of excellence" networks pending better understanding of the potential impacts of COVID-19.
    - The payer community is closely following CIBMTR plans to address COVID-19 risk adjustment as payers consider modifications to their center assessments.
    - FACT can review directly at the individual centers, something that may not be available to the payer groups.

Final Recommendations:

- CIBMTR should expedite data collection efforts for allogeneic HCT recipients from 2019 to facilitate preliminary modeling to understand the impact of the COVID-19 pandemic on outcomes of allogeneic HCT.
- Develop a modeling approach to test the impact of COVID-19 on outcomes for recipients of HCT in 2019 and implement that approach in early 2021.
    - Communicate with center directors and escalate relevant data collection efforts with centers to support earlier timelines for data submission to support these analyses.
    - The preliminary modeling approach is likely to employ Cox modeling to handle time-dependent covariates.
- Use the results of the preliminary modeling for impact of COVID 19 to design, if possible, a modified pseudo-value modeling approach for the CSA for the cohort of patients transplanted in 2017-2019.
    - It is important to use a consistent CSA model, if possible, to achieve results that are consistent with previous years and with known performance characteristics to allow year-over-year comparisons and maintain confidence in the modeling process.

    - Include sections in the CSA Report outlining the methodology and limitations of the risk adjustment for COVID-19 pandemic.
- Develop communications for use across all relevant stakeholder groups regarding plans for CSA in 2021 and subsequent years to address COVID-19.
- Continue to collaborate with SRTR and other organizations involved in public outcomes reporting to explore if other organizations are making assessments of the impact of COVID-19 on general acute care for geographic areas to inform this effort.
- Using results from the analysis conducted in 2021, begin to develop an approach to subsequent analyses that address all relevant COVID-19 impacts for recipients of HCT in 2020.

CSA research project proposals summary and plans

In response to discussion during the 2018 Center Outcomes Forum, CIBMTR solicited ideas for research projects to address the impacts of public reporting of center-specific survival on the field of HCT. Several groups of investigators have developed research proposals and these proposals are in the process of refinement. They were presented to inform the stakeholders groups and to provide an opportunity to collect feedback for the proposals.

Impact of CSA on HCT volumes

- Hypothesis: Public reporting of outcomes for US HCT centers through CSA could have important implications at patient, center, and payer-level and thus may impact HCT centers' patient selection process, transplant volumes, and HCT outcomes. A change in center performance for one-year survival is associated with a change in patient volume at the index center in the same direction (negative score decreases volume, positive score increases volume or has no change), while changing voolumes at surrounding centers in the opposite direction.
- Specific Aims are to evaluate whether center performance change impacts patient volume at the index center; whether center performance reporting impacts patient numbers at large-volume centers to the same extent as it impacts small volume centers; and whether a negative center performance at an index center affects patient volumes at neighboring centers.
- Rationale:
    - The change in volume may occur, in part, due to reluctance of low performance centers to take high-risk patients to HCT under the assumption that this change in patient selection may influence and improve future center performance.
    - Patients may be driven away from underperforming centers due to changes in insurance carrier's designated "preferred status" and/or patient preferences or perceptions. These patients may have to travel longer distances for treatment at other centers, compromising care and access to HCT.
    - Some centers may be more significantly affected by changes in center performance than others, which may result in some centers losing their clinical expertise and incurring financial losses due to lower patient volumes.
- Two separate analyses will be conducted to evaluate the patient volumes following decrease (e.g., 1 or 0 to -1) or increase (-1 to 0 or 1) in the center performance using a combined dataset inclusive of allogeneic HCT performed between 2010 and 2019.

Impact of CSA on HCT outcomes

- Hypothesis: A transplant center's center performance, based on one-year OS, is associated with changes in other transplant-specific outcomes for the center.

- Aim: To determine if an improvement in a center's performance is associated with improvement in three-year OS, one-year Event-Free Survival, one-year Relapse Probability and one-year Treatment-Related Mortality.
- The impact of public reporting on center performance is not clear. While it facilitates transparency and stimulates quality improvement initiatives, there is no compelling data that it impacts outcomes and it may increase health care disparities.
- The study will compare outcome measures between US centers with center performance increase (-1 to 0 and -1 to 1) and center performance decrease (0 to -1 and 1 to -1) for allogeneic HCT performed between 2010 and 2018.

Impact of CSA on access/patient selection

- Hypothesis: Physicians in HCT centers that receive an "underperforming" (–1) rating will change their behavior regarding patient selection to exclude those perceived to be at a higher risk of death at one year thus limiting access to a potentially curative procedure. Patients subsequently selected for transplantation at underperforming centers will be younger, with a lower comorbidity index and an improved performance status; a lower proportion of patients with advanced disease and under-represented minorities will be selected.
- FACT guidelines note that eliminating high-risk patients is not an appropriate solution to under-performing. Results of this study may provide a better understanding of the impact of public reporting on access to HCT and inform centers quality improvement initiatives by improving understanding of risk adjustment on HCT outcomes.
- "Newly underperforming centers," defined as having two years of "as predicted" (0) or "better than predicted" (+1) followed by "less than predicted" (-1), will be compared to centers with "as predicted" outcomes for allogeneic HCT performed between 2010 and 2019 using time matched cohorts of centers.

Consequences of CSA public reporting—update

- A task force representing FACT, CIBMTR and ASTCT was formed to address recommendations from the 2018 Center Outcomes Forum regarding consequences of CSA public reporting. The task force's objectives were to make recommendations for stakeholders to manage the consequences of CSA reporting and for responses to be taken by various stakeholder groups in relation to the consequences of the CSA.
- Educational initiatives for stakeholders occurred to clarify the statistical methodology and limitations of the analysis to improve understanding of appropriate usage of the CSA Report. Future education efforts are planned.
- A process and timeline was developed to leverage FACT's established mechanism of reviewing corrective action plans (CAPs) for underperforming centers to provide assurance to payers that centers are actively using the CSA Report for quality improvement, and to better inform payer's decisions regarding centers' inclusion in their "centers of excellence" networks. FACT will provide response to centers for their CAP in a timely manner; centers are encouraged to share their FACT letter and CAP with payers (as applicable) as part of a dialog about the center's quality improvement efforts.
- Some payers have begun to implement changes based on the recommendations from the task force. Assessment from FACT, CIBMTR and ASTCT is helpful for payers for defining objective approaches to center assessment, CAP development and enhancing communication.

Appendix A: Attendees of 2020 Center Outcomes Forum

Name	Organization	Representation
Kwang Woo Ahn, PhD	CIBMTR	CIBMTR PhD
Jack Aiello, EE, MS	Consumer Advocacy Committee	Patient Advocate
Jenni Bloomquist, BA, MS	CIBMTR	MSP Staff
Kira Bona, MD, MPH	Dana-Farber Cancer Institute	HCT Center-Peds
Anthony Bonagura, MD	Optum Health Services	Payer
James Bowman, MD	Health Resources & Services Administration	Gov't staff (HRSA)
Luciano Costa, MD, PhD	University of Alabama	HCT Center-Adult
Sharniece Covill, BS	CIBMTR	MKE Staff
Tonya Cox	Sarah Cannon	Center Admin
Christopher Dandoy, MD	Cincinnati Children's Hospital	ASTCT QOC/Adult
Stella Davies, MBBS, PhD, MD, BS	Cincinnati Children's Hospital	HCT Center-Peds
Steven Devine, MD	NMDP/Be The Match	CIBMTR Scientific Director
Clint Divine, MBA, MSM	University of Kansas	Center Admin
Carol Doleysh	CIBMTR	MKE Staff
Caitrin Fretham, MPH	CIBMTR	MSP Staff
Dennis Gastineau, MD	Mayo Clinic Rochester	ASTCT/FACT
Keith Goldstein, MD	Barnes Jewish Hospital	HCT Center-Adult
Shelley Grant, MHSA	Health Resources & Services Administration	Gov't staff (HRSA)
Theresa Hahn, PhD	Roswell Park Cancer Institute	HCT Center-Adult
Mary Hengen, MBA	NMDP/Be The Match	MSP Staff
Mary Horowitz, MD, MS	CIBMTR	CIBMTR Scientific Director
Christopher Hourigan, MD, D Phil	National Heart Lung & Blood Institute	Gov't staff (NIH)
Dianna Howard, MD	Wake Forest Baptist Health	HCT Center-Adult
Samantha Jaglowski, MD, MPH	Ohio State Medical Center	ASTCT QOC/Adult
Mark Juckett, MD	University of Wisconsin	CSA Research TF
Michelle Kuxhausen, MS	CIBMTR	MSP Staff
Leslie Lehmann, MD	Dana-Farber Cancer Institute	CSA Research TF
Charles LeMaistre, MD	Sarah Cannon	HCT Center-Adult
Marilyn Levi, MD	Health Resources & Services Administration	Gov't staff (HRSA)
Mark Litzow, MD	Mayo Clinic Rochester	HCT Center-Adult
Brent Logan, PhD	CIBMTR	CIBMTR PhD
Sue Logan, BS	CIBMTR	MSP Staff
Selina Luger, MD	University of Pennsylvania	HCT Center-Adult
Navneet Majhail, MD, MS	Cleveland Clinic	ASTCT QOC/Adult
Wendy Marinkovich, MPH	BCBSA	Payer
Lin-Wen Mau, PhD, MPH	NMDP/Be The Match	MSP Staff
Richard Maziarz, MD	Oregon Health & Science University	HCT Center-Adult
Meggan McCann, MPH	NMDP/Be The Match	MSP Staff
Joseph McGuirk, DO	University of Kansas	HCT Center-Adult
Tatenda Mupfudze, PhD	CIBMTR	MSP Staff

Name	Organization	Representation
Christine Nishiguchi, MS, MPH	Health Resources & Services Administration	Gov't staff (HRSA)
Kristin Page, MD	Duke University	HCT Center-Peds
Miguel-Angel Perales, MD	Memorial Sloan Kettering	HCT Center-Adult
Waleska Perez, MPH	CIBMTR	MKE Staff
Ronald Potts, MD	Interlink Health Services	Payer
Matt Prestegaard, BA	CIBMTR	MSP Staff
Jaime Preussler, MS	CIBMTR	MSP Staff
Marcie Riches, MD, MS	University of North Carolina	CIBMTR Scientific Director
J. Douglas Rizzo, MD, MS	CIBMTR	CIBMTR Scientific Director
Wael Saber, MD, MS	CIBMTR	CIBMTR Scientific Director
Bart Scott, MD	Fred Hutchinson	HCT Center-Adult
Mary Senneka	NMDP/Be The Match	MSP Staff
Akshay Sharma, MD	St. Jude Children's Research Hospital	CSA Research TF
Bronwen Shaw, MD, PhD	CIBMTR	CIBMTR Scientific Director
Nawraz Shawir, MBBS	Health Resources & Services Administration	Gov't staff (HRSA)
Stephen Spellman, MBS	CIBMTR	MSP Staff
Patricia Steinert, PhD, MBA	CIBMTR	MKE staff
Christopher Strouse, MD	Medical College of Wisconsin	HCT Center-Adult
Jesse Troy, PhD, MPH	Duke University	PhD Stat
Bryce Waldman	Consumer Advocacy Committee	Patient Advocate
Julie Walz	Humana	Payer
Daniel Weisdorf, MD	University of Minnesota	HCT Center-Adult
Andre Williams	ASTCT	ASTCT
Michelle Williams, RN	BCBSA	Payer
John Wingard, MD	University of Florida	HCT Center-Adult
William Wood, MD, MPH	University of North Carolina	HCT Center-Adult
Mei-Jie Zhang, PhD	CIBMTR	CIBMTR PhD

Appendix B: Working Group Members

Minimal Residual Disease Working Group

Name	Organization	Representation
Daniel Weisdorf, MD (moderator)	University of Minnesota	HCT Center-Adult
Stella Davies, MBBS, PhD, MD, BS	Cincinnati Children's Hospital	HCT Center-Peds
Christopher Hourigan, MD, D Phil	National Heart Lung & Blood Institute	Gov't staff (NIH)
Selina Luger, MD	University of Pennsylvania	HCT Center-Adult
Wael Saber, MD, MS	CIBMTR	CIBMTR Scientific Director
Bart Scott, MD	Fred Hutchinson	HCT Center-Adult

SARS-CoV-2 Working Group

Name	Organization	Representation
John Wingard, MD (moderator)	University of Florida	HCT Center-Adult
Kwang Woo Ahn, PhD	CIBMTR	CIBMTR PhD
Christopher Dandoy, MD	Cincinnati Children's Hospital	ASTCT QOC/Adult
Miguel-Angel Perales, MD	Memorial Sloan Kettering	HCT Center-Adult
J. Douglas Rizzo, MD, MS (ex officio)	CIBMTR	CIBMTR Scientific Director
William Wood, MD, MPH	University of North Carolina	HCT Center-Adult

Social Determinants Working Group

Name	Organization	Representation
Navneet Majhail, MD, MS (moderator)	Cleveland Clinic	ASTCT QOC/Adult
Kira Bona, MD, MPH	Dana-Farber Cancer Institute	HCT Center-Peds
Luciano Costa, MD, PhD	University of Alabama	HCT Center-Adult
Theresa Hahn, PhD	Roswell Park Cancer Institute	HCT Center-Adult
Richard Maziarz, MD	Oregon Health & Science University	HCT Center-Adult
Tatenda Mupfudze, PhD	CIBMTR	MSP Staff
Ronald Potts, MD	Interlink Health Services	Payer