Statistical Analysis Plan Checklist for Addressing COVID-19 Impacts

Since early 2020, the COVID-19 public health emergency has compelled clinical research teams to postpone recruitment, alter methods of participant engagement, and modify tools for research assessment and intervention delivery. The NIH Health Care Systems Research Collaboratory has sought to navigate the impacts of study disruption on pragmatic clinical trials embedded in healthcare systems and to identify strategies for maintaining patient and staff safety while ensuring rigorous research design and conduct.

The checklist below links major elements of study conduct to the specification or modification of statistical analysis plans to address unique challenges associated with data collection, research measurement, and analysis in pragmatic clinical trials. The checklist uses the Population, Intervention, Comparison, Outcome, Timing, Setting (PICOTS) framework for summarizing research questions to identify impacts on study conduct that should be documented, measured, analyzed, and reported.

<table>
<thead>
<tr>
<th>PICOTS Element</th>
<th>Document and Measure</th>
<th>Analyze and Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>□ Measure changes to participants’ demographic and clinical characteristics</td>
<td>□ Compare participants’ baseline characteristics over time (for example, before and after March 2020)</td>
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<tr>
<td></td>
<td>□ Measure changes to participants’ access</td>
<td>□ Compare participants’ characteristics over and attitudes (for example, see time periods defined by local COVID-19 Coronavirus Impact Scale) status or impacts on research conduct</td>
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<td></td>
<td>□ Evaluate COVID-19-related methods for electronic phenotyping</td>
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<tr>
<td>Intervention</td>
<td>□ Document modifications to the intervention to ensure the safety of patients and providers</td>
<td>□ Compare engagement in intervention components over time periods</td>
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<td></td>
<td>□ Document and measure changes to methods to communicate and deliver the intervention</td>
<td>□ Consider modifying the primary analysis to adjust (stratify) for COVID-19 phases</td>
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</tbody>
</table>
### COVID-19 SAP Checklist

- [ ] Document and measure changes to any components or mechanisms associated with the intervention
- [ ] Consider sensitivity analyses that restrict to periods of time based on COVID-19 status
- [ ] Consider subgroup (interaction) analysis of heterogeneity of treatment effect across COVID-19 time periods due to changes in the intervention (or other factors)
- [ ] Consider time-specific mediation analysis to evaluate putative mechanisms across COVID-19 time periods

#### Comparison

- [ ] Document modifications to the comparison to ensure the safety of patients and providers
- [ ] Compare engagement in the comparison (such as usual care) over time periods
- [ ] Measure trends in concomitant care over time
- [ ] Clarify the estimand of interest, typically the average treatment effect that averages over explicit participant and time characteristics while potentially controlling certain factors
- [ ] Consider subgroup (interaction) analysis of heterogeneity of treatment effect across COVID-19 time periods due to changes in usual care (or other factors)
- [ ] Report the consequence of COVID-19 impacts that are specific to the study design (for example, parallel randomized trials will be affected differently than crossover or stepped-wedge designs)

#### Outcome

- [ ] Document and measure changes in how clinical assessments and patient-reported outcomes are obtained
- [ ] Report psychometric properties of any modified measures
- [ ] Measure impacts of COVID-related distress on patient-reported outcomes
- [ ] Consider subgroup analyses based on patient-reported characteristics at baseline that are predictive of outcomes or COVID-19 susceptibility
- [ ] Describe temporal trends in patient reported outcomes
- [ ] Evaluate patterns and correlates of missing data over time to assess differential nonresponse

#### Timing

- [ ] Document COVID-19 status at the regional level over time
- [ ] Consider effect modification with proximal measures of COVID-19 impact (patient level, clinical level)
| Document COVID status at the clinic level | Describe longitudinal trajectories in participant outcomes across treatment groups and COVID-19 time periods |
| Measure participant-level impacts of COVID-19 over time | Describe differences in the intervention, the comparison, and concomitant care across research settings |
| Consider evaluating participant outcomes at longer (or shorter) lags to determine potential impacts on response trajectories | Describe differences in outcomes across research settings |

**Setting**
- Document changes to the research setting (or modality) for both intervention delivery and participant assessment
- Describe differences in the intervention, the comparison, and concomitant care across research settings
- Describe differences in outcomes across research settings