TAKEDA Guidance for Statisticians: Assessment of the Impact of the COVID-19 Pandemic on Clinical Trial Data Analysis and Interpretation

(Green text should be removed prior to finalizing this document.)

Due to the COVID-19 pandemic, governments and individuals around the world are acting to limit spread of the virus and to safeguard public health. These actions—including social distancing, testing, quarantines, travel restrictions, and treatment—as well as COVID-19 itself may impact ongoing clinical trials, in terms of subject accrual, treatment adherence and data collection, to name a few. To ensure the Takeda maintains the integrity of its trials, study teams need to assess the impact of COVID-19 and to propose necessary mitigative procedures.

The objective of this template is to assist the study statisticians in assessing the impact of COVID-19 on the statistical integrity of planned analyses, developing responsive actions to protect our ability to meet the study objectives (primary and key secondary), and documenting this work.

To address the full scope of this task, it is expected that the statistician will collaborate with and integrate input from across functional areas. This document should be considered a 'living' document, evolving to accommodate additional relevant information as it becomes available over time. Statisticians should adapt the content below to meet study needs. This is a tool for statisticians to use as they see fit.

Study:

TAU:

Protocol Title:

Protocol Number:

Document Version: 0.1 [First version for distribution to team should be 1.0]

Author: [Study Statistician]

Date:

I. Impact of COVID-19 on Trial Conduct

Summarize COVID-19 impacts on trial conduct that may impact the planned statistical analysis or interpretation of the results. For each factor, describe its current or potential impact. (Associated mitigation plans, including whether additional data collection is needed, should be listed in section V. Action Plan.) For example, quarantines and travel limitations may result in missed visits and overworked staff, leading to increased errors. Be aware of regional differences in impact.

Consider categorizing COVID-19 impacts into six groups: Subject enrollment, Treatment discontinuation, Compliance with study treatment/missed dose, Use of additional medication /change in background therapy, Data collection (including missing data), and Errors/protocol deviations.

Factors that may have an impact include, but are not limited to:

- *COVID-19 Testing*
- *COVID-19 Infection*
- *Quarantines and Travel limitations*
- *Site closures*
- *Temporary change in site healthcare practice*
- *Interruptions to supply chain of experimental drug and/or patients' other medications*
- *Paused enrollment*
- *Delayed visits/assessments*
- *Missed visits/assessments*
- *Stopping drug due to safety concerns*
- *Discontinuing patients due to infection*
- *Alternative administration of drug*
- *Alternative collection and analysis of specimens*
- *Alternative data collection*
- *Conmeds due to COVID-19 (eg, unproven remedies)*

Please see Appendix A for a list of their potential impacts.

Factor	Current Impact	Potential Impact
Enrollment	Is enrollment continuing, paused, or completed?	

II. Missing Data

The COVID-19 pandemic may cause missing data due to discontinuation of patients, missed visits, or missed assessments within a visit. Begin by evaluating the number of ongoing subjects and extent of missing data.

Consider how best to summarize missing data. For example, the table below could be used to highlight regional differences in a large multisite trial switching to remote assessments.

Summary of regional difference: sites and visits

Country	# of sites affected	# of subjects affected (ongoing + new)	# of visits achieved through on-site	# of remote visits	# of visits missed

Extent of missing data

Sources used	[Eg, recent SDTM transfer, information from other functions or CRO]
Number of ongoing subjects	
Number of subjects missing key endpoint data	
Current assessment of missing data	

To evaluate the impact of COVID-19 on missing data, list COVID-19 related intercurrent events (such as treatment discontinuation) that may cause large amounts of missing data or have substantial impact on analysis. Consider the different types of data that may be missing: efficacy assessments, safety assessments (eg, labs, AEs, vital signs, ECG, and concomitant medication), clinical outcomes assessments (COAs), dosing information, etc. If classifying missing data mechanism as MCAR, MAR, or MNAR, note that determining ways of appropriately addressing COVID-19-related intercurrent events first, taking into considerations the disease under study and the clinical context, will facilitate and validate the classification.

#	Cause of missing data	Impact	Missing Data Mechanism
1			[MCAR / MAR / MNAR]
2			
3			
4			

Note: The FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic states, “It will be important to capture specific information in the case report form that explains the basis of the missing data, including the relationship to COVID-19 for missing protocol-specified information (e.g., from missed study visits or study discontinuations due to COVID-19). This information, summarized in the clinical study report, will be helpful to the sponsor and FDA.”

Work with CDS and study team to determine whether changes in the CRF or CRF completion guidelines are absolutely necessary. If so, note this in the Action Plan section. Be aware that CRF modifications are burdensome to sites and may take months to deploy.

Below are examples of actions that might be taken to mitigate the effects of missing data. Be sure to include any proposed actions in the Action Plan section of the template. Note that modifications to the analysis need to be documented in the SAP (and possibly in a protocol amendment). Consultation with health authorities may also be needed.

- Explore strategies (with study team) to minimize the amount of missingness by collecting data via non-conventional channels, e.g., virtual visits, phone call follow-up.

- Work with study team to capture necessary COVID-19 -related information to understand the reason for the missing data (e.g., COVID19 infection, site closure, travel restriction, lockdown, COVID19-related constraints at site)
    - Knowing who was likely infected may improve properties of missing data (eg, MNAR to MAR) and allow for analyses assessing the impact of infection.
    - Collecting surrogate or other auxiliary variables may increase accuracy of imputation methods.

- Perform additional sensitivity analysis to evaluate the impact of missing data due to COVID-19 on efficacy analysis and check any assumptions made.
    - Eg, tipping point analysis to assess how severe departure from MAR must be to overturn conclusion from the primary analysis; additional subgroup analyses by country/city/age; exploration of imbalances observed for certain SAEs (eg, flu-like symptoms)

- Consider supplementary analyses using historical clinical trial data or real-world data to support assessment of the impact of missing data elements. Use of historical or real-world data may also enhance study power.

- Consider an unplanned interim analysis to evaluate whether the trial should be stopped early rather than modified or prolonged to avoid the impact of missing data.

- Communication with subjects from site staff will be likely to protect against dropout, missing data or nonadherence.

III. Impact on Ability to Achieve Main Objectives of Trial

Assess the risk of not achieving the main objectives of the trial.

List assumptions for sample size calculation and power

Start by making a comprehensive list of the assumptions underlying the original study design that may be impacted. Think beyond the ones commonly discussed. Assumptions that often go unstated may also be at risk due to COVID-19. (For example, the consistency of measurement of the primary endpoint may no longer be assumed due to virtual assessments. Visit windows may not remain fixed throughout the study.) Comment on which of the assumptions listed are at risk of no longer being valid.

Assumptions for sample size calculation and power

#	Assumption	Impact due to COVID-19 pandemic
1	*True variability of primary and key secondary endpoint(s) (if applicable or necessary)*	*Increased or decreased variability by switching to virtual assessments, noting that decreased variability may also be a liability*
2	*Dropout rate*	*Increased dropout rate*
3	*Sample size*	*Decreased sample size if the study is terminated early*
4	*Missing visit rate in time to event (TTE) study*	*Missed visits in TTE study result in decreased confidence in time of event*
5		

Consider impact on estimand(s)

Review how COVID-19 impacts affect the estimands of the primary and key secondary analyses. For example, COVID-19 impacts may affect enrollment, resulting in a study population that is less representative of the population of interest. Or they may directly affect the endpoint measurement or introduce new intercurrent events. Consider how site closures and lack of access to study drug affect the population analyzed.

Pay special attention to whether the default handling of COVID-19 pandemic related intercurrent events fit with the original question and generalizability of the study results. This may be particularly relevant when the estimand is "composite" or "treatment policy", where all dropouts are counted as failures. Additional supportive analysis may be required to show results are in line with the original estimand.

Primary estimand

	Planned	Modification
Population		
Variable (or endpoint)		
Strategy for addressing IEs	Choose an item.	
Population-level summary		

Secondary estimand

	Planned	**Modification**
Population		
Variable (or endpoint)		
Strategy for addressing IEs	Choose an item.	
Population-level summary		

Scenario planning

Having identified the potential impact of COVID-19 on trial conduct and missing data—and consequently the measurement, analysis, estimand, and assumptions underlying estimation/power of the primary and key secondary endpoints—the next step is to bring these pieces together and **provide an overall outlook of the trial under various scenarios**:

- Evaluate how modifying assumptions alters important operating characteristics, assuming no other mitigative action is taken (eg, impact of low to high rate of patient discontinuation on power).
- The study team may be considering additional changes to study design. Understanding the impact of these changes will help the study/leadership team to prioritize resources and energy, and to pro-actively maintain trial integrity. Examples of **changes to the study design** include:
    - Taking additional measures to limit missing data
    - Adopting statistical methodology to handle missing data or to handle possible measurement bias
    - Discontinuing patients
    - Introducing or redefining futility criteria
    - Changing analysis timing
    - Increasing sample size (eg, by adding or selecting sites)
    - Redefining the estimand

- Extension of study/follow-up period

It is recommended that 2-3 scenarios be presented for communication. Each scenario should include the assumptions made and the resulting operating characteristics. Important **operating characteristics** for consideration include, but are not limited to:

- Effective sample size (ESS)
- Statistical power
- Minimal detectable effect (MDE) or Least Significant Difference (LSD)
- Bias
- Go/No Go probabilities (for early phase studies)
- Probability of statistical success (for pivotal studies)

Potential impact on timeline, power, and other operating characteristics.

Scenario	**Modified Assumptions and/or Changes to Study Design** (conduct, missing data, estimand)	**Operating Characteristics** (timeline, ESS, power, MDE, bias, etc.)	
A		Timeline Primary Key second	 ESS= Power = MDE = ESS = Power = MDE =
B		Timeline Primary Key second	 ESS = Power = MDE = ESS = Power = MDE =

Impact on Statistical Aspects of the Clinical Trial

	Description of COVID19 Impact		**Mitigation (if applicable)**
	Current Impact	**Potential Impact**	
Primary Endpoint			
Key Secondary Endpoints			
Sample-size			

Power			
Probability of Success for program (if applicable)			
Primary Efficacy Analysis			
Key Secondary Analysis			
Primary Estimand			
Key Secondary Estimand			

Impact on Timeline [Add other key milestones to table as appropriate; consider pasting in a Gantt chart as well if available]

Milestone	Actual or Planned Date	Current Impact	Potential Impact
First Subject First Visit			
Last Subject Last Visit			
SAP Approval			
Planned IA			
Database Lock			

IV. Action Plan

Consider using a **decision tree** to clearly communicate and show documented evidence of the process of decision making to the study team.

The table below may be helpful in documenting modifications of planned decision criteria.

Changes to Decision Criteria

Pre-COVID-19 decision criteria	
Changes to decision criteria	
Impact/Risk/Comment	

Use the table below to list out proposed actions and track team approval.

#	Action	Purpose	Agreed to by team?	Colleague(s) or Function(s) Responsible	Timeframe
1					
2					
3					
4					

Other important considerations for the action list

- **Study Data Integrity**
  - The FDA asks that "robust efforts" be made to maintain study data integrity, and these efforts should be documented. Data integrity consists of data being attributable, legible, contemporaneous, original, and accurate (ALCOA). The FDA guidance makes some specific suggestions. This plan will influence and inform which of the FDA's suggestions are necessary. While such actions will be led by the data management function, statisticians should also be aware of them and help to safeguard data integrity, which is critical to study interpretation.
- **Preparing for next IA or for database lock**
  - In preparing for an interim analysis or database lock, a key step is to review and update the SAP as needed. The FDA guidance specifically notes, "Prior to locking the database, sponsors should address in the statistical analysis plan how protocol deviations related to COVID-19 will be handled for the prespecified analyses."
  - Go through each section of the SAP and see how it was impacted by changes to study procedures, whether or not there is an associated change in the protocol. Under the unique circumstances of COVID-19, some study changes that would normally be in a protocol amendment may not be.
  - Any SAP changes attributable to the COVID-19 pandemic, particularly if they aren't included in a protocol amendment, should be explained that way. It is important that such changes be correctly attributed to the true underlying cause: the pandemic. The relationship to COVID-19 may be somewhat indirect, eg, shipping of lab samples being slowed down by increased customs screening. When in doubt, err on the side of documenting circumstances related to the pandemic. Although there is an option of documenting this information in the CSR (see next section), these explanations may be more credible if they are documented in an approved SAP (or protocol amendment) before database lock and unblinding. Consult other functions as appropriate to collect the needed information.
  - The FDA guidance encourages sponsors to request the feedback from the appropriate review division changes to the SAP. If the FDA or other health authorities provided feedback specific to the product or study, make sure to cite it as appropriate. A future FDA reviewer may not otherwise be aware of it.

    - Also note the following points in regard to the SAP:
        - How will data on COVID-19 symptoms be captured and reported?
        - Make sure the CRO is provided with updated "stable SAP"
        - Make sure the appropriate functions review any SAP amendment (see applicable SOP)
        - As much as possible, methodologies should be harmonized across all studies for a compound, particularly across studies that could be used for registration.
    - In consultation with appropriate functions, consider how the database lock process will be affected by any COVID-19 related delays, eg, additional CRF pages on related to safety assessment or adjustments to monitoring plans.
- **CSR**
    - FDA guidance states that for all trials impacted, the CSR should include:
        - Contingency measures implemented
        - Listing of all participants affected by COVID-19 related study disruption (SUBJID, SITEID, description of how individual's participation was altered). Comment (not in FDA guidance): Some EU countries allow, or even encourage, subjects to switch to lower-risk sites.
        - Analyses and discussions addressing impact of contingency measures on safety and efficacy results. Comment (not in FDA guidance): When possible, any changes to the analysis should still be documented prior to database lock, in a SAP or protocol amendment. This is the best way to demonstrate that decisions were not driven by unblinded data.
    - In collaboration with study team, consider how the changes and additional analyses due to COVID-19 can be effectively emphasized in the text (eg, separate section or subsections) and what other tables (or figures) would be needed or desired.

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Anticipating and mitigating impact of COVID-19 on our trials will be a complex but worthy endeavor. Please work closely with your study team to brainstorm and identify challenges and solutions. Here are some final ***guiding principles when filling out the template****:*

- *Be sure to summarize all relevant findings regarding trial conduct and missing data.*
- *Brainstorm mitigation strategies with your study team. Ask questions such as "What trade-offs are acceptable?" and "What data need to be collected to make this happen?"*
- *Be ready to incorporate new information and input from your team. This is an iterative process. As such, the report is a living document that may change over time.*
- *Use the template to document new or modified decision criteria related to the trial.*
- *Use the Action Plan section to list out proposed actions and track team approval. (See Preparing for next IA or database lock and CSR sections below for ideas on additional actions needed.)*
- *Whether your calculations are made purely theoretically or supported by simulations, please document your calculations or code for reproducibility and for knowledge sharing across SQS.*

APPENDICES

A: Impacts of COVID-19
B: Resources

Appendix A: Impact of COVID-19

COVID-19-related factors that are likely to impact ongoing and future clinical trials.

Factor	Examples of Impact / Risk
COVID-19 Testing	• Inadequate or haphazard testing • Inability to use testing results in analysis • mITT and definition of statistical analysis data sets
COVID-19 Infection	• Dropout – voluntary versus mandatory • Symptoms or not • Potential effect on efficacy endpoints / estimand
Quarantines and Travel limitations	• Missed visits, • Overworked staff and increased errors
Site closures	• Loss to follow-up • Different investigator(s) • Different measurement modalities
Interruptions to supply chain of experimental drug and/or patients' other medications	• Missed dosing • Changes in conmeds
Stopped enrollment	• Termination or delay • Unplanned interim Analysis for futility
Delayed assessments	• Protocol visit window versus missed visit
Missed visits/assessments	• Partial data collection • Virtual assessment validation
Stopping drug due to safety concerns	• Informative censoring
Discontinuing patients due to infection	• Drop outs versus long term follow up
Alternative administration of drug	• Errors likely to increase
Alternative collection of specimens	• Reconciliation and verification
Alternative data collection	• Exchangeability of methods
Conmeds due to COVID-19	• IMP interaction

Other statistical considerations for on-going studies

Impact Factors	Considerations
Primary and Key Secondary endpoints	Modification of multiple testing method Modification to primary and key secondary endpoints (eg, PFS versus OS) Central versus Local assessments and site burden • Should include statistical determination of exchangeability
Enrollment suspension, delays or changes to inclusion/exclusion criteria	Continuation with delay and impact on study analysis (eg. Landmark) Discontinue enrollment and change of power

	Impact on estimand for any changes to enrollment/screening criteria Unplanned IA
Safety monitoring changes	Alternate processes to collect safety monitoring data Record COVID-19 related change
Missing or delayed assessments due to patient ability to travel	Virtual assessment feasibility Documentation of reason SAP modification Informative censoring possibility of IPW models
Missing or delayed assessment due to site-related ability	Missing assessment Alternate assessment method
Interruption to investigational drug supply chain	Dosing outside of window impact on efficacy and safety Missed scheduled dose and efficacy assessment Protocol and SAP changes and consultation with FDA
Site closures	Include sites or region analysis in SAP Data quality from site prior to closure RBM for future site closings and impact on data quality and analysis
Drug administration changes	Can current CRF capture changes?
Biomarker collections	Patient safety and burden Effect of COVID-19 on biomarkers of interest
Patient Safety	Immunosuppressants and increase in infection Regional patient safety in heavily affected regions

Appendix B: Resources

Select Regulatory Guidance on COVID-19

Document	Comment
FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic (March 2020) Link	This should be your first stop for US regulatory issues. May be superseded by advice on individual studies and/or programs.
Cytel comments on FDA Guidance Link	Apply your own judgment to their recommendations.
Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (EMA) Link	Corresponding EMA guidance, which focuses on trial logistics. Note the EU has strong data privacy laws which impact offsite data collection.
Points to consider on implications of Coronavirus disease 4 (COVID-19) on methodological aspects of ongoing clinical 5 trials (EMA) Link	Posted 25MAR. "It should be noted that due to the rapidly evolving situation further updates to this guidance are possible and likely." Notably, recommends ***independent DMC*** if looking at unblinded data.
Overview of Guidance from EU Countries Link	Mostly non-statistical. Some countries allow or encourage transfer of subjects between sites, which will impact our models.

Notes: This list is incomplete and does not include country-specific guidances. Also keep in mind that new guidances are being added all of the time: FDA link to latest updates.

Missing Data and Estimands

Document	Comment
ICH E9 (R1) Addendum and Estimand Link	This is the first document to read. It is up-to-date (2020) and authoritative.
Prevention and Treatment of Missing Data Link	Lengthy and somewhat historical (2010), this is where estimands came from.
Can Covariates Change the Estimand? (Permutt, 2020) Link	Deep thoughts from FDA estimand guru
Implementation of Pattern Mixture Models in SAS Link	How to implement one MNAR method

Colleagues with relevant expertise

a. Regulatory interpretation of unusual statistical issues – REDACTED
b. Missing data and estimands – REDACTED
c. RWD/RWE methodologies: REDACTED
d. Confirmatory Adaptive design, including sample size re-estimation and seamless design: REDACTED
e. Bayesian methodologies: REDACTED
f. Oncology dose finding: REDACTED
g. Survival analysis: REDACTED