



Takeda's COVID-19 response to aid Collection to Submission

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Abstract

When COVID-19 impacted the world, there was a quick move in the Pharma industry, regulatory authorities/Governments to mitigate the disease.

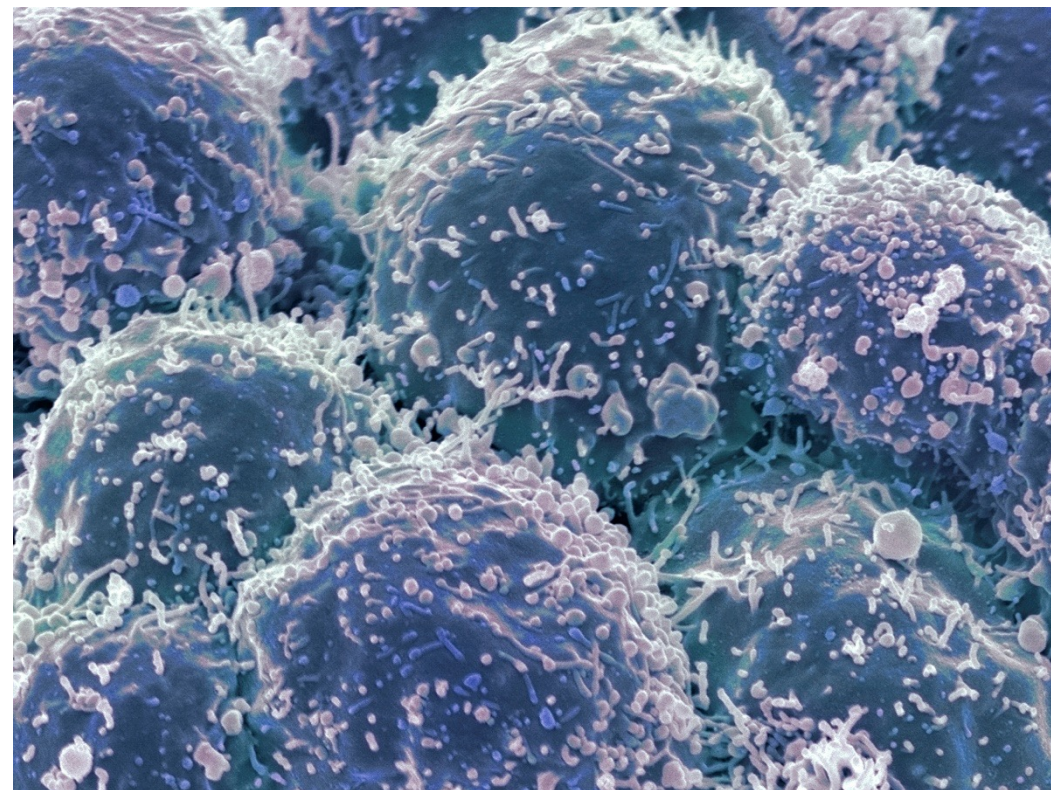
In March 2020 FDA released, “Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency” guidance in addition to other regulatory publications. All companies immediately started evaluating their products for a solution and methods to comply with this FDA guidance.

In April 2020, CDISC released “COVID-19 Interim Guide” to support the disease. Due to the pandemic, in March 2020, Takeda quickly took steps to adapt to the new Data Collection and reporting needs, to assess the impact of COVID-19. Takeda’s COVID-19 response implementation guidance and associated standards were developed for release before the CDISC’s publication of the COVID-19 Interim Guide.

This paper discusses the Takeda Standards content from collection, SDTM, analysis and how teams worked to cascade these company standards across the portfolio to support the needs.

Agenda

- Introduction
- Industry Guidances
 - FDA Guidance
 - EMEA Guidance
 - CDISC Interim COVID-19 Guidance
- Takeda's Response
 - COVID-19 Pandemic Timeline
 - Takeda Response to COVID-19 (March 2020)
 - Impact Assessment Framework for Takeda's ongoing studies
 - Takeda COVID-19 eCRF Standard eCRF
 - Standard eCRF Design Considerations
 - Designing COVID-19 studies
 - CDISC COVID-19 Response
 - Journey continues with COVID-19 Vaccines



Introduction

- Covid-19 is a pandemic affecting population around the world, there has been a quick move in the Pharma industry, regulatory authorities/Governments to mitigate the disease.
- Takeda's COVID-19 response implementation guidance and associated standards were developed for release before the CDISC's publication of the COVID-19 Interim Guide.
 - This included the Takeda Standards content from collection, SDTM, analysis and how teams worked to cascade these company standards across the portfolio to support the needs

Industry Guidances

COVID-19 Public Health
Emergency

Guidance for Industry,
Investigators, and Institutional
Review Boards

March 2020

Updated on January 27, 2021

For questions on clinical trial conduct during the COVID-19 pandemic, please email
Clinicaltrialconduct-COVID19@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)



20 March 2020
EMA/141885/2020
Media and Public Relations

Press release

Guidance to sponsors on how to manage clinical trials during the COVID-19 pandemic

The European Commission, the European Medicines Agency (EMA) and national Head of Medicines Agencies (HMA) have published [new](#) recommendations for sponsors on how to manage the conduct of clinical trials in the context of the coronavirus disease (COVID-19) pandemic. The impact of the pandemic on European health systems and more broadly on society, will make it necessary for sponsors to adjust how they manage clinical trials and the people who participate in these trials.

The guidance provides concrete information on changes and protocol deviations which may be needed in the conduct of clinical trials to deal with extraordinary situations, e.g. if trial participants need to be in self-isolation or quarantine, access to public places (including hospitals) is limited due to the risk of spreading infections, and healthcare professionals are being reallocated.

This guidance includes a harmonised set of recommendations, to ensure the utmost safety of trial participants across the European Union while preserving the quality of the data generated by the trials. It also advises how these changes should be communicated to authorities.

There is specific advice on the initiation of new clinical trials for treatments of COVID-19, and in particular on the need for large, multinational trial protocols. This is in line with the [call issued on Thursday](#) by EMA's human medicines committee (CHMP) for robust trial methodology in clinical trials for potential COVID-19 treatments or vaccines.

The guidance was agreed by the Clinical Trials Expert Group (CTEG) of the European Commission supported by EMA, the Clinical Trials Facilitation and Coordination Group (CTFG) of HMA and the GCP Inspectors' Working Group. It provides a harmonised approach in the conduct of trials, in order to mitigate the negative effects of the pandemic.

In the EU, clinical trials are authorised and supervised at national level. Sponsors are advised to also check whether there might be specific national legislation and guidance in place to complement or in some cases to take priority over this new guidance.



Interim User Guide
for COVID-19

Version 1.0

Notes to Readers

This document is based on SDTM v1.7 and SDTMIG v3.3.

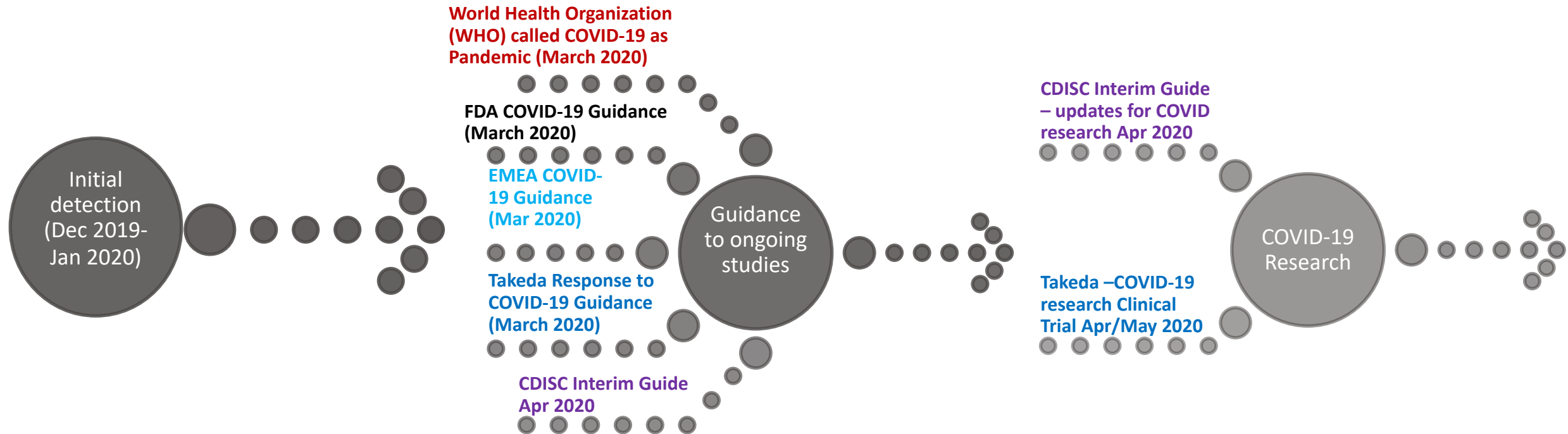
Revision History

Date	Version
2020-04-21	1.0

See [Appendix D](#) for Representations and Warranties, Limitations of Liability, and Disclaimers



Takeda's Response: COVID-19 Pandemic Timeline



Takeda Response to COVID-19 (March 2020)



- March 2020- Takeda responded by creating a Takeda COVID-19 Task force with cross-functional representations to evaluate and provide framework to ongoing studies
- Responsibilities included but were not limited to:
 - Providing Framework guidance to ongoing studies to scope and categorize the portfolio
 - Educate on the available guidances from regulatory agencies and other organizations
 - Collaborate externally with CRO and external vendors to discuss the changes and gain alignment
 - Determine impact on the visit schedule and monitoring visits

FDA Guidance (March 2020)

Here are the excerpts regarding the FDA Guidance:

- Changes in study visit schedules, missed visits, or patient discontinuations may lead to missing information (e.g., for protocol-specified procedures). 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.

- With respect to efficacy assessments, FDA recommends consultation with the appropriate review division regarding protocol modifications for the collection of efficacy endpoints, such as use of virtual assessments, delays in assessments, and alternative collection of research-specific specimens, if feasible. For individual

EMA Guidance (March 2020)

Some recommendations on statistical analyses

- Conduct analyses for 'affected' and 'unaffected' data
- Conduct subgroup analyses for exposed/non-exposed, infected/non-infected patients
- Conduct analyses to interpret the treatment effect in the pre-, during and post-pandemic phases
- Independent Data Monitoring Committee (DMC) to conduct analyses to preserve trial integrity as much as possible

Takeda's Impact of COVID-19 in ongoing clinical studies (March 2020)

- To assess the impact on Ongoing Clinical Studies:
 - Initial assessment should be performed by the joint study team, to understand
 - Possible impact of enrollment pauses
 - Missed visits/data
 - What can be done to mitigate adverse effects on trial integrity
- Considerations:
 - Final subject status may not yet be understood
 - Not all sites are able to accommodate on-site or remote monitoring visits
 - All data has to be considered - EDC, third-party vendors as well as protocol deviations reported in CTMS
 - It may not be clear if data is truly missing or simply not yet entered in EDC or submitted to a vendor (e.g., central lab samples, submission of digital images, etc.)
 - Teams should consider predicted delay, enrollment pause that may impact studies once situation stabilizes

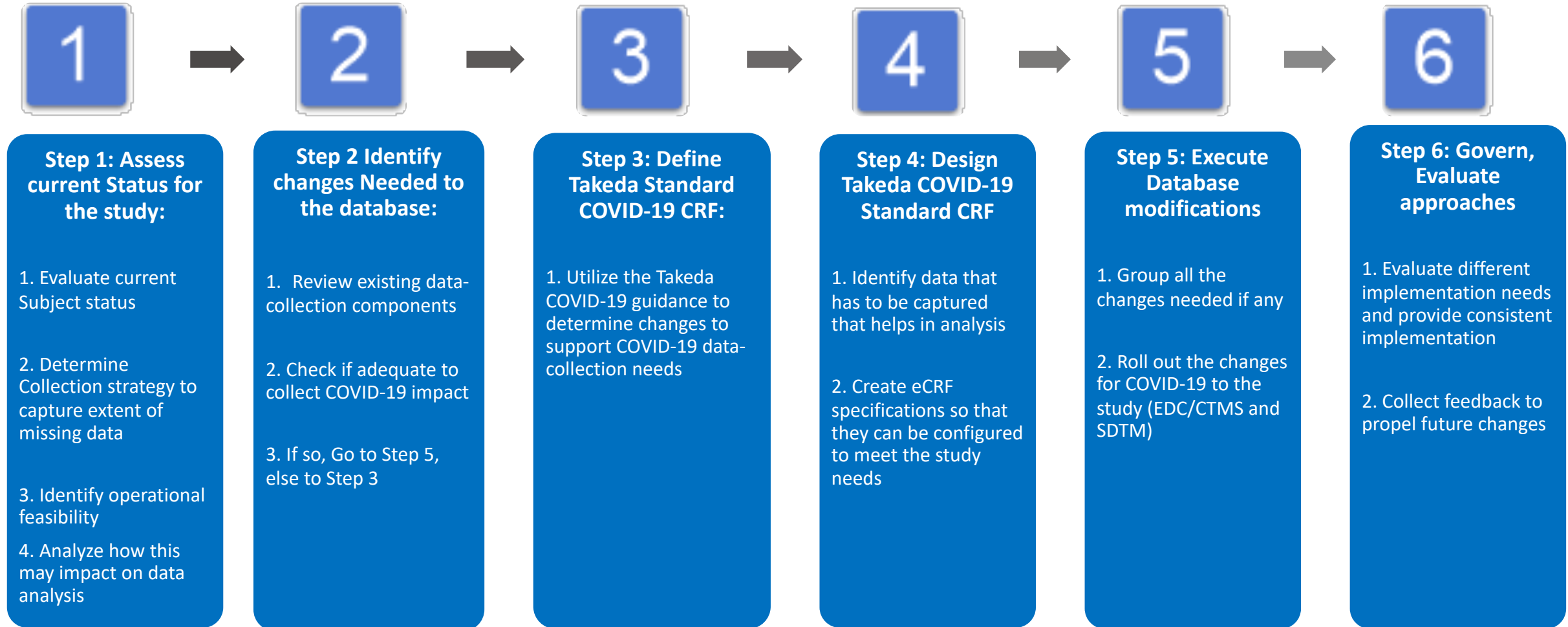
Hence cross-functional study team with external vendors and CROs should fully assess the operational risk for ongoing studies

Takeda's Impact of COVID-19 in ongoing clinical studies (March 2020) (contd.)

Additional data points to consider:

- Number of reported COVID-19 protocol deviations
- Number of sites in impacted countries
- Number of expected patients from impacted sites or countries
- Duration (to date) of pandemic in affected regions
- Current study subject status prior to pandemic (enrolling, enrollment complete, all patients complete)
- Upcoming milestones (LSI, LSLV, DBL, IA Data Cut-off, etc.)

Impact Assessment Framework for Takeda's ongoing studies



Takeda COVID-19 eCRF Standard eCRF

- New data needs to be collected as a result to COVID-19's impact
 - to ensure subject safety, compliance with regulatory expectations, and data integrity
- New Standard COVID-19 CRF was to be launched to collect critical information focused on impact to planned visits and assessments
 - Method of contact (e.g., phone, home visits, Telehealth)
 - Other optional questions are available based on study design (e.g., at home drug administrations)

Collection Principles:

- There is no single way to collect the impacts of COVID-19 that will fit the needs of all studies
- Each study must determine the appropriate implementation to meet their needs.
- Exhaust standards approaches before customizing
 - First use existing EDC system and third-party databases
 - Then make a concerted effort to use Takeda library standards



Standard eCRF design considerations

- The COVID-19 diagnosis should be entered as the AE or as the Medical History verbatim term. These terms can be coded and available using MedDRA release v23.0 [March 2020] or later versions).
- When subject was discontinued due to COVID-19, guidance had to be provided (AE due to COVID, other with “COVID-19” prefix)

Standard eCRF Design Considerations

- Added as adhoc CRF for impacted visits
- Capture visit name, adjusted method of contact, and impacted assessments
 - E.g., Day 15, Telehealth visit with video, eCOA
- If relevant to mitigation strategy, capture details on drug administration
 - E.g., Home administration by Nurse/Health Care Professional
- If protocol amends to permit intervals between assessments (i.e., “optional” visits) related to COVID-19 pandemic, capture reason for missed visit rationale
 - E.g., Travel Restrictions due to COVID-19
- Other new concepts such as “Visit Delayed” had to be considered for studies in specific Therapeutic Areas

Standard eCRF Design Considerations

- As the standards concepts were communicated, we quickly found that there are different scenarios that had to be taken into consideration. Different versions had to be made available for different use case scenarios and expedited deployment
- Scenarios listed but not limited to the following:
 - No visit occurred
 - Visit occurred with some assessments missed
 - Visit occurred with alternative methods utilized
 - Any important visit such as Drug Administration
 - Any combination of the last three scenarios
- If a single visit event is impacted by the COVID-19 pandemic in multiple ways, Takeda COVID-19 eCRF may be completed multiple times referring to the same visit

Standard SDTM Mapping considerations

- The Takeda COVID Standard eCRF data are mapped to SV/SUPPSV
- These were developed before the release of CDISC COVID-19 Interim Guide
- Current mappings are the best representation as opposed to creating a custom domain (VE as mentioned in the CDISC Interim Guide)
- FDA had announced that their preference is to have all visit related data represented in a single domain (i.e., SV)

Following will have to explained in the cSDRG:

- The Takeda Standard COVID-19 eCRF can be completed multiple times for same visit, “Duplicate VISITNUM (SD1060)”
- Alternative method when mapped to SV domain (SVMETHOD) causes “Variable appears in Dataset and not in SDTM Model (SD0058)”

CDISC Controlled Terminology (CT) Updates

- NCI CDISC CT recently re-aligned several immunology panel tests from the LB domain to MB domain
 - Appropriate guidance was provided if studies used immunology tests
- Specimen Type (IMSPEC) and Specimen Location (IMLOC) are required during collection

CODE	Microbiology Test Code MBTESTCD	Microbiology Test Name MBTEST	DEFINITION
C171456	CRONAVIR	Coronaviridae	A measurement of the coronaviridae in a biological specimen.
C171515	MERSRNA	MERS-CoV RNA	A measurement of the MERS-CoV RNA in a biological specimen.
C171527	SAR2IGA	SARS-CoV-2 IgA Antibody	A measurement of the SARS-CoV-2 IgA antibody in a biological specimen.
C171528	SAR2IGG	SARS-CoV-2 IgG Antibody	A measurement of the SARS-CoV-2 IgG antibody in a biological specimen.
C171529	SAR2IGGM	SARS-CoV-2 IgG/IgM Antibody	A measurement of the SARS-CoV-2 IgG and/or IgM antibody in a biological specimen.
C171530	SAR2IGM	SARS-CoV-2 IgM Antibody	A measurement of the SARS-CoV-2 IgM antibody in a biological specimen.
C171531	SAR2RNA	SARS-CoV-2 RNA	A measurement of the SARS-CoV-2 RNA in a biological specimen.
C171532	SARSCOV2	Severe Acute Resp Syndrome Coronavirus 2	A measurement of the severe acute respiratory syndrome Coronavirus 2 in a biological specimen.

Rapid Response in time of Pandemic

- Due to the Pandemic, nature of all workforce being remote, it was very important to communicate and train teams and set expectations
- Several training materials were available
 - Data Principles Documents
 - CRF Completion Documents
 - Study specific configurations (e.g., Scheduled visits or Assessments) allowed study teams to deploy changes faster
 - Specifications for collection, SDTM Mappings with Controlled Terminology
 - Information sessions to train and familiarize the framework and approach



Designing COVID-19 Studies

- All companies in the Pharma industry started to find cure or mitigate severity of the COVID-19 pandemic. Takeda started designing COVID-19 studies.
 - New clinical concepts are needed for COVID-19 studies:
 - Specific COVID-19 Symptoms (Cough, Fever, Myalgia, Diarrhea, Dyspnoea)
 - COVID-19 testing with Diagnostic Swab – Track the location and testing method is useful in addition to the result collection and type of testing (Real time PCR) along with specimen type and condition
 - Hospitalization Encounters, Hospital Discharge
 - Immunology and Inflammatory Markers tracked to decide treatment and disease progressions
 - Supplemental Oxygen, Oxygenation Index provides an overall track on the oxygen levels
 - Clinical Classification used for COVID-19:
 - Sequential Organ Failure Assessment Score (SOFA): used to track a person's status during the stay in an intensive care unit (ICU) to determine the extent of a person's organ function or rate of failure.
 - National Early Warning Score (NEWS), National Early Warning Score 2 (NEWS2): to detect deteriorating patients in hospital wards, specifically those at increased risk due to COVID-19
 - Hospitalization Severity Rating Scale



CDISC COVID-19 Response

- COVID-19 Interim Guide Available and Released (Apr 2020)
- CDISC NCI Controlled Terminology for COVID-19 Released - June 2020

CDISC Interim User Guide for COVID-19 Version 1.0

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Glossary and Controlled Terminology Off-cycle Releases in Response to COVID-19

CDISC published two off-cycle releases for **Glossary** and **Controlled Terminology** in response to the COVID-19 pandemic. There are approximately 37 new QRS terms and 65 new terms across SDTM, SEND, CDASH, and CDISC Glossary. Additionally, there are updates to four published codetable mapping files (RACEC_ETHNICC, SC, TS, and VS) and an update to the Unit-UCUM Mapping file.

Home / Standards / Foundational / Controlled Terminology Release Update 26 June 2020

Controlled Terminology Release - Update 26 June 2020

Release Information Files & Links

Published Date: 26 June 2020

Journey continues with COVID-19 Vaccines

- The data collection needs has changed with recent enhancement for COVID-19 vaccinations
 - These administrations may impact ongoing clinical trials
 - Vaccine-related AEs are quite common
 - Impact on AEs, treatment adherence, procedures, data collection, statistical analysis, interpretation of results, protocol endpoints, study objectives etc.
- New Standard Vaccination eCRF is being launched to collect vaccine information
 - Enter name of vaccine as verbatim term with as much precision as possible, preferably with manufacturer product name:
 - E.g., Moderna COVID-19 vaccine
 - E.g., Pfizer BioNTech COVID-19 vaccine
 - E.g., AstraZeneca COVID-19 vaccine
 - Date of administration (each dose is entered as separate entry)
 - Coding of new Vaccines at the lowest level, e.g. Trade (Product Name). – Use latest WHO Drug to code CMDECOD to “COVID-19 VACCINE”. When using older version of WHO Drug, then use “VIRAL VACCINES”
- When Vaccine information is being collected, AEs associated with the Vaccine Reaction must be collected

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Questions?



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