Guiding Principles for Study Conduct, Analysis and Reporting

COVID-19 Impact to Trials

Cristina Sotto, Associate Director, QS-SDS SMM
BBS Virtual Seminar, 06 May 2020

Rhonda Fenwick, *Time is Now I*
Through her art, Rhonda has explored psoriasis, a chronic skin disorder she has lived with since the age of six.

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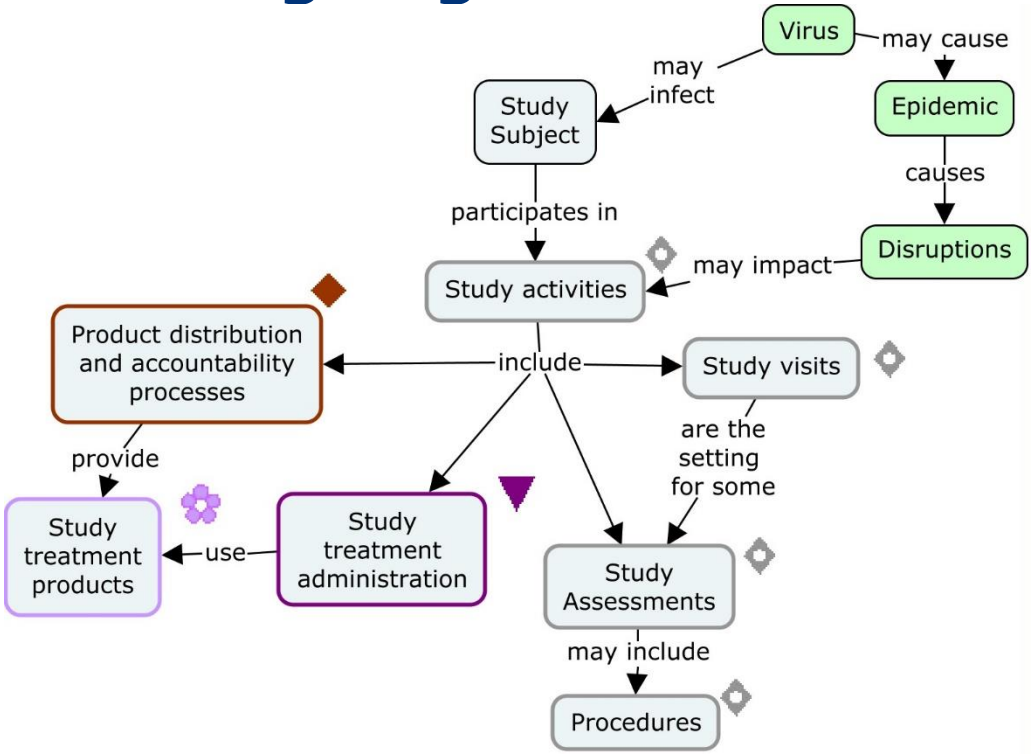
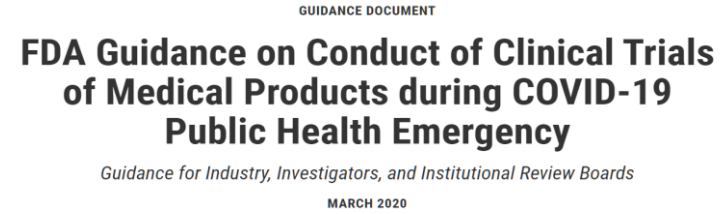
Impact of COVID-19 on Ongoing Trial

- **Trial participant(s)** become infected with COVID-19
- **Trial conduct** is affected due to lockdown
  - Study visits
  - Study assessments
  - Procedures
  - Study treatment administration
  - Product distribution and accountability processes
  - Study treatment products
  - …



https://wiki.cdisc.org/display/COVID19/Guidance+for+Ongoing+Studies

Regulatory Guidance


GUIDANCE DOCUMENT

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency

Guidance for Industry, Investigators, and Institutional Review Boards

MARCH 2020

(18 March 2020, updated 16 April 2020)

- Recognizes potential impact of COVID-19 on conduct of clinical trials
  - arising challenges due to pandemic measures can result in difficulties meeting protocol specified procedures
  - modifications may be required
- Outlines general considerations to assist sponsors in assuring safety, maintaining GCP, minimizing risks to integrity

Key Considerations: safety, documentation of modifications


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 March 2020
EMA/158330/2020
Committee for Human Medicinal Products (CHMP)

Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials

Draft

(25 March 2020, consultation closed 25 April 2020)

- Acknowledges impact of pandemic on trial participants and impact of measures taken on methodological aspects of ongoing trials
- Patient safety is paramount
- Encourages to integrate ethical, medical, methodological considerations, with advice from R&HA, into decision making
- Provides major points for consideration

Key Considerations: safety, systematic collection of relevant info, risk assessment

Janssen Working Group

Statistics and Decision Sciences (SDS)

Quantitative Sciences (QS) Consulting statistical experts

IDAR Statistical Programming and Analytics (SP&A)

- **Goal:** to provide general considerations, regarding COVID-19 related issues, for study conduct, analysis and reporting of ongoing studies
- **5 Workstreams**
  - to draft guiding principles incorporating recommendations from other functions, HA, cross-pharma WG

  - **Analyses/Assessments of Ongoing Clinical Trials**
  - **Data Collection**
  - **Protocol Deviations**
  - **Standardized Reporting**
  - **Statistical Principles**

- circulated 28 April

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BCP COVID-19: Guiding Principles for Study Conduct, Analysis and Reporting

Workstreams

Analyses/Assessments for Ongoing Trials

- How and What to monitor to assess study completeness, including use of Central Monitoring
- How to assess the impact of potential missingness on power/precision
- Strategies for improving completeness via changes in study conduct
- Strategies for modifying analysis plans to mitigate the impact of COVID-19
- How to plan the DMC activities– Interim Analysis meetings, addressing new questions, communicating conduct and analysis plan changes

Data Collection

- data collection guidance will address how sites should enter data and provide considerations for Data Management and Local teams related to COVID-19.
- This document will address data collection guidance specific to global forms.
- capture “specific” information in the case report form that explains the basis for missing data, impact to trial and treatment dispositions, etc., including the relationship to COVID-19.
- vital to ensure oneCTMS or DM CRO equivalent system align with EDC; where applicable

Protocol Deviations

- How to document and capture COVID-19 related protocol deviations
- How to incorporate minor and major COVID-19 related protocol deviations into SDTM DV Dataset for analysis and reporting
- What the relation is to CO (comments) dataset
- How to ensure quality and accuracy of protocol deviations
- How to generate analysis datasets for protocol deviations
- How to generate summary/analyses related to COVID-19.

Standard Reporting

The following guiding principles for Standard Reporting address COVID-19 impact to displays (Tables, Listings, Graphs) related to:

- Protocol Deviations
- Treatment /Exposure
- Subject Disposition & Discontinuation
- Efficacy Estimands/end points
- Visits
- Adverse Events & Deaths
- Laboratory Data
- Concomitant Medications

Statistical Principles

- Impact on the treatment effect evaluation
- Interim Analyses and DMC
- Adaptations to Study Design
- Estimands, Estimators and Handling Missing Information
- COVID-19 related Regional Differences

Analyses/Assessments for Ongoing Trials

- How and what to monitor to assess study completeness, including use of Central Monitoring
  - breakdown treatment deviations, protocol deviations, missed visits/assessments by COVID-19/non-COVID-19, possibly by region/country and/or extent per subject (e.g. PANDEM analysis data set can be created)
  - suggests projections of status of completeness
- How to assess the impact of potential missingness on power/precision
  - strategies ranging from simple sample size calculations (e.g. varying delta/SD) or more refined simulations to formal SSR
- Strategies for improving completeness via changes in study conduct
  - alternative collection strategies, e.g. virtual visits, alternative sites, modification of visit schedule
- Strategies for modifying analysis plans to mitigate the impact of COVID-19
  - modification of estimand, use of surrogate EP or early readouts, longitudinal modeling
- How to plan the DMC activities – Interim Analysis meetings, addressing new questions, communicating conduct and analysis plan changes
  - potentially, add a futility analysis, provide new tables for safety evaluation due to COVID-19
  - all changes to be communicated to DMC as soon as feasible

Data Collection

- Addresses data collection guidance specific to global forms
  - general guidance, guidance for oncology
- How sites should enter data and provide considerations to Data Management and local teams
  - screen failures, visits, missed ePRO, missed imaging, missed central labs, local labs, treatment disposition, trial disposition, AE, concomitant medications, study drug administration
- Emphasizes the importance of capturing "specific" information in the case report form
  - basis for missing data, impact to trial and treatment dispositions, etc., including the relationship to COVID-19
  - new/updated eCRF to capture direct COVID-19 impact on trial participant (e.g. exposure to COVID-19, tested and infected with COVID 19)
  - updated Date of Visit form (e.g. type of visit: onsite, via phone call, via televisit, etc.)
- Queries
  - recommends eliminating queries related to missing visits/assessments, unless the data is critical for safety, critical for milestone deliverable (e.g DBL), to minimize unnecessary burden on sites

Protocol Deviations

- How to document and capture COVID-19 related protocol deviations
  - regulatory (HA) guidance by country + internal guidance (3 SOPs)
    - *Guidelines for Documenting COVID-19 Protocol Deviations and Issues*
    - *Implementation Memo: Guidelines for Documenting Protocol Deviations and Issues related to COVID-19*
    - *Management of Minor Protocol Deviations related to COVID-19 Outbreak*

Protocol Deviations

- How to document and capture COVID-19 related protocol deviations
  - regulatory (HA) guidance by country + internal guidance (3 SOPs)
- How to incorporate minor and major COVID-19 related protocol deviations into SDTM DV Dataset for analysis and reporting
  - COVID-19 related PDs will be entered in CTMS and mapped to the SDTM DV dataset (DM/GCO guidance)
  - individual study team must work with GDM to ensure release of DV for planned analysis and reporting
- What the relation is to CO (comments) dataset
  - when applicable, use of specific eCRF form rather than rely on DV/CO datasets (Data Collection guidance)
- How to ensure quality and accuracy of protocol deviations
  - minor deviations are created/entered by the site managers
  - PDs need team review (including statisticians and programmers) to make sure all information entered is correct
- How to generate analysis datasets for protocol deviations
  - 2 options suggested
- How to generate summary/analyses related to COVID-19
  - Standardized Reporting GP

Standardized Reporting

To address COVID-19 impact to displays (Tables, Listings, Graphs) related to:

- Protocol Deviations
  - standard table for PDs to include extra entry for COVID-19 related PDs (TSIDEV-ST01-COV)
  - additional listings of PDs due to COVID-19 by subject, with reason
- Treatment /Exposure
  - listing of any deviation from planned treatment due to COVID-19 (e.g. DC, dose modification)
  - additional summary of incidence of dose not administered or modified
- Subject Disposition & Discontinuation
  - standard disposition table to include COVID-19 related study discontinuation, treatment discontinuation
- Visits
  - table/listing by subject of missed visits due to COVID-19, with reasons
- Efficacy Estimands/Endpoints
  - tables of compliance, both COVID-19 related and not
  - summary tables of missing data and intercurrent event summaries, with reasons, for primary EP
  - additional/supporting listings/displays, e.g. proportion or missing EPs imputed, subgroups (infected/not infected)
- Adverse Events & Deaths
  - additional row for all patients infected with COVID-19
  - separate summary table for COVID-19 related AEs/AEs leading to death
  - summary of deaths for reason of COVID-19
- Laboratory Data
  - summary of proportion of lab data location changes due to COVID-19
- Concomitant Medications
  - summary table/listing for concomitant medication taken for (S)AE of COVID-19

Standardized Reporting

To address COVID-19 impact to displays (Tables, Listings, Graphs)

Supplementary DPS template created (**DPS COVID-19 Part 1**)

TSFDTH-ST01-COV: Summary of Deaths During [Study/Treatment]; Safety Analysis Set (Study [Study ID])

		[Active Study Agent]		
	[Placebo]	[Treatment Group A]	[Treatment Group B]	Combined
Analysis set: Safety	###	###	###	###
Deaths during [study/treatment]	### (xx.x%)	### (xx.x%)	### (xx.x%)	### (xx.x%)
Cause term1	### (xx.x%)	### (xx.x%)	### (xx.x%)	### (xx.x%)
Cause term2	### (xx.x%)	### (xx.x%)	### (xx.x%)	### (xx.x%)
COVID-19 related	### (xx.x%)	### (xx.x%)	### (xx.x%)	### (xx.x%)
Cause unknown	### (xx.x%)	### (xx.x%)	### (xx.x%)	### (xx.x%)
Related to study agent	### (xx.x%)	### (xx.x%)	### (xx.x%)	### (xx.x%)
Relationship unknown	### (xx.x%)	### (xx.x%)	### (xx.x%)	### (xx.x%)

Note: Cause unknown includes unknown or missing cause of death. Related includes deaths that were [very likely, probably, or possibly] related to study agent.

[Output Identifier] [Program Location] [Date/Time of output]

Statistical Principles

- **Impact on Treatment Effect Evaluation:** consider
  - amending DM plans to capture new data
  - whether trial objectives are affected and if estimands need to be modified
  - design/analysis strategies to handle potentially altered endpoints, higher variability and missing visits
  - stratification by pre-, during- and post-COVID-19 pandemic
    - Challenge: different calendar times/intensities by regions/countries
    - Alternative: subgroup analyses by phase/country or region

- **Interim Analyses and DMC**
  - protocol (statistical analysis section) and SAP may need to be updated
    - ensure expert statistician(s) on DMC to advise on such
  - conduct trials as planned and implement changes only when there is a convincing scientific reason that it improves interpretability of results
  - unplanned (or early) analysis may be considered to minimize the effect of COVID-19 on the interpretability
    - e.g. trial is close to completion
  - benefits/risks (safety events) to participants in the trial who are affected by exposure to COVID-19 should be evaluated
    - e.g. efficacy impacted by co-medications or by confounding co-morbidities

Statistical Principles

- **Adaptations to Study Design**

> 2006 FDA Guidance on Establishment and Operation of Clinical Trial Data Monitoring Committees:
> *When a DMC is the only group reviewing unblinded interim data, trial organizers faced with compelling new information external to the trial may consider making changes in the ongoing trial without raising concerns that such changes might have been at least partly motivated by knowledge of the interim data and thereby endanger trial integrity. Sometimes accumulating data from within the trial (e.g., overall event rates) may suggest the need for modifications.*

  - an ongoing trial may be modified based on blinded data review triggered by an external event, such as the COVID-19 pandemic, without raising concerns
  - consider pause and restart strategy: two-stage adaptive design
    - maximum protection to participants
    - alleviates burden on healthcare workforce/clinical sites, allows focus on treating COVID-19 participants
    - allows ample time to assess how changes in healthcare workforce/clinical site operations affect the trial and develop appropriate modifications

- **COVID-19 Related Regional Differences**
  - engage regulatory authorities for alignment on how to handle possible regional differences on COVID-19 impact
  - evaluate from where regional differences arise
    - e.g. policy on hospital visits/enrollment, proportion of subjects per phase, COVID-19 related AE, treatment discontinuation/death due to COVID-19, missed visits/treatments, co-medications given to treat COVID-19
  - consider impact of regional differences of COVID-19 pandemic and restrictions
    - e.g. baseline characteristics/demographics, explore endpoints per phase, proportion of IEs due to COVID-19, rates of non-AE COVID-19 related discontinuation, proportion of missed visits/treatments, co-meds

Statistical Principles

- **Estimands, Estimators and Handling Missing Information**
  - for each trial,
    - examine whether trial objectives can still be evaluated
    - if not, modification may be needed (e.g. change of estimand) and discussed with health authorities
    - consider additional/supplementary estimands/analyses
  - potential impact of COVID-19 pandemic on *estimand attributes*
    - Treatment: would not have been planned to include additional COVID-19 treatments
    - Population: might be impacted by differences of participants in the phases
    - Variable/Endpoint: evaluate if adjustment is needed, if data can still be collected, impact of increased missing data on power, consider alternative endpoints
    - Intercurrent Events: which COVID-19 related events are to be considered as IEs or PDs and what strategies will be used
    - Summary Measure: consider alternatives that might better reflect treatment effect in presence of new IEs
  - potential impact of COVID-19 pandemic on *statistical analysis*, including handling missing data
    - develop procedures to capture additional COVID-19 info (e.g. new IEs, PDs, missing information)
    - consider alternative strategies to collect data
    - provide extra summaries (e.g. COVID-19 related or not)
    - characterize type and amount of missing data, perform sensitivity analyses
    - explore supplementary analyses


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