

Mapping COVID-19 related data into SDTM

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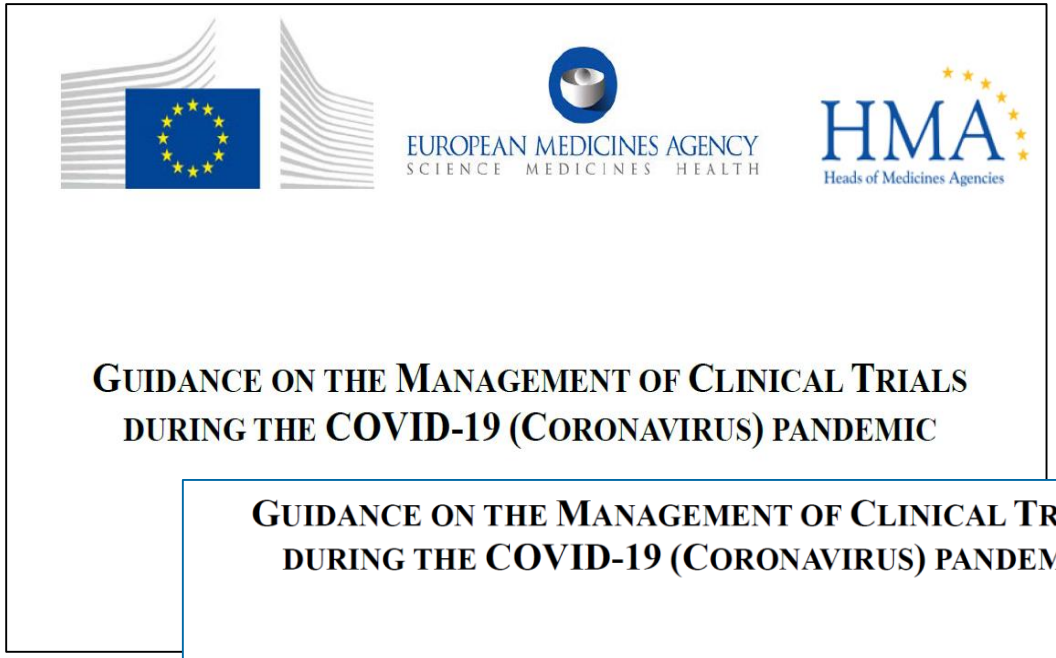
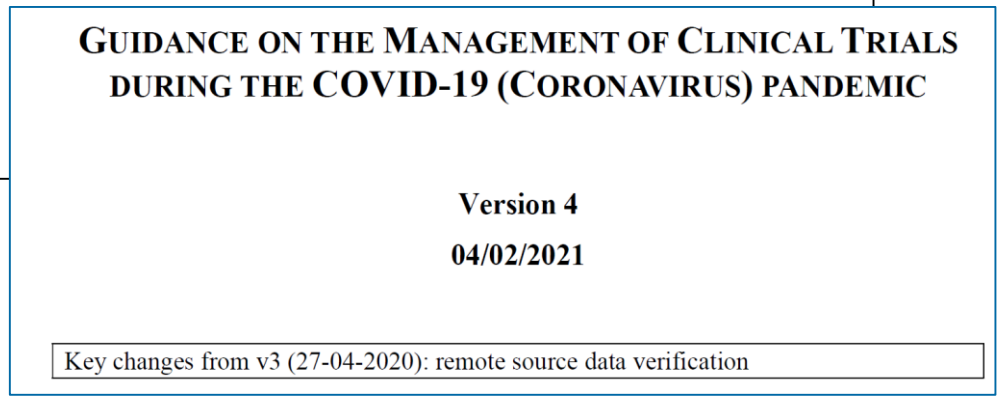
Agenda

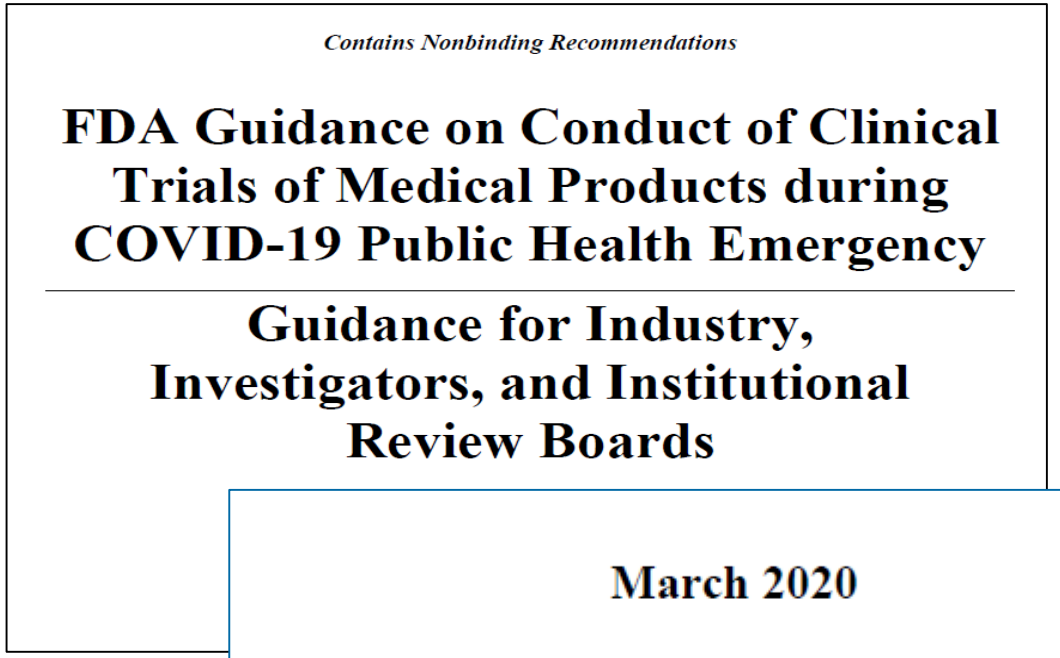
- Regulator Position
- CDISC response
- Overview Chiesi actions
- Data Collection and SDTM impact analysis
- Impacted documentation

Regulators Position

- Regulators require information about disturbances to ongoing studies caused by the COVID-19 pandemic, state the need to document the changes, their duration and which trial participants were affected.

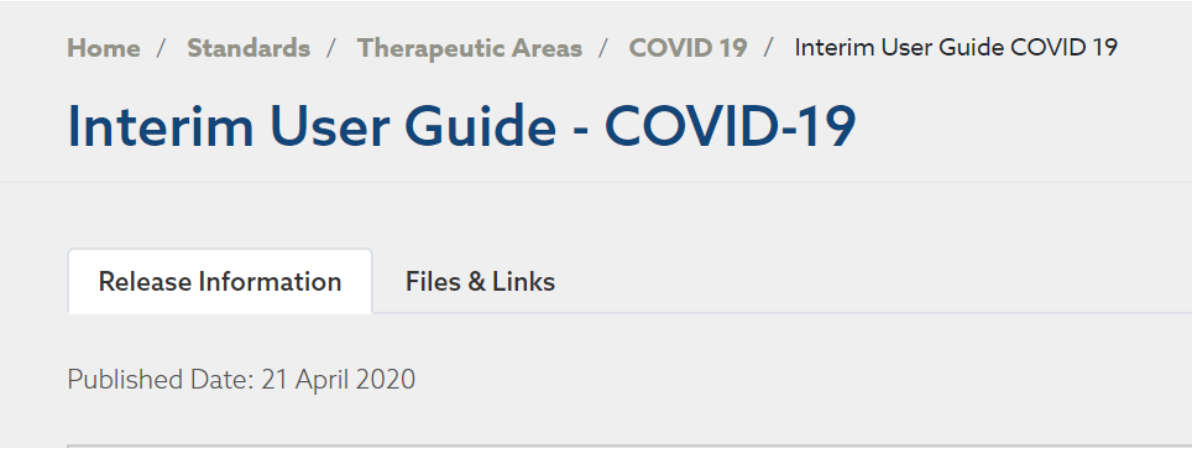






CDISC response to COVID-19 (1/2)

- **CDISC Task Force** launched in Late March 2020 to support CDISC members and research community to treat COVID, with the goal of developing Interim User Guide and related materials.

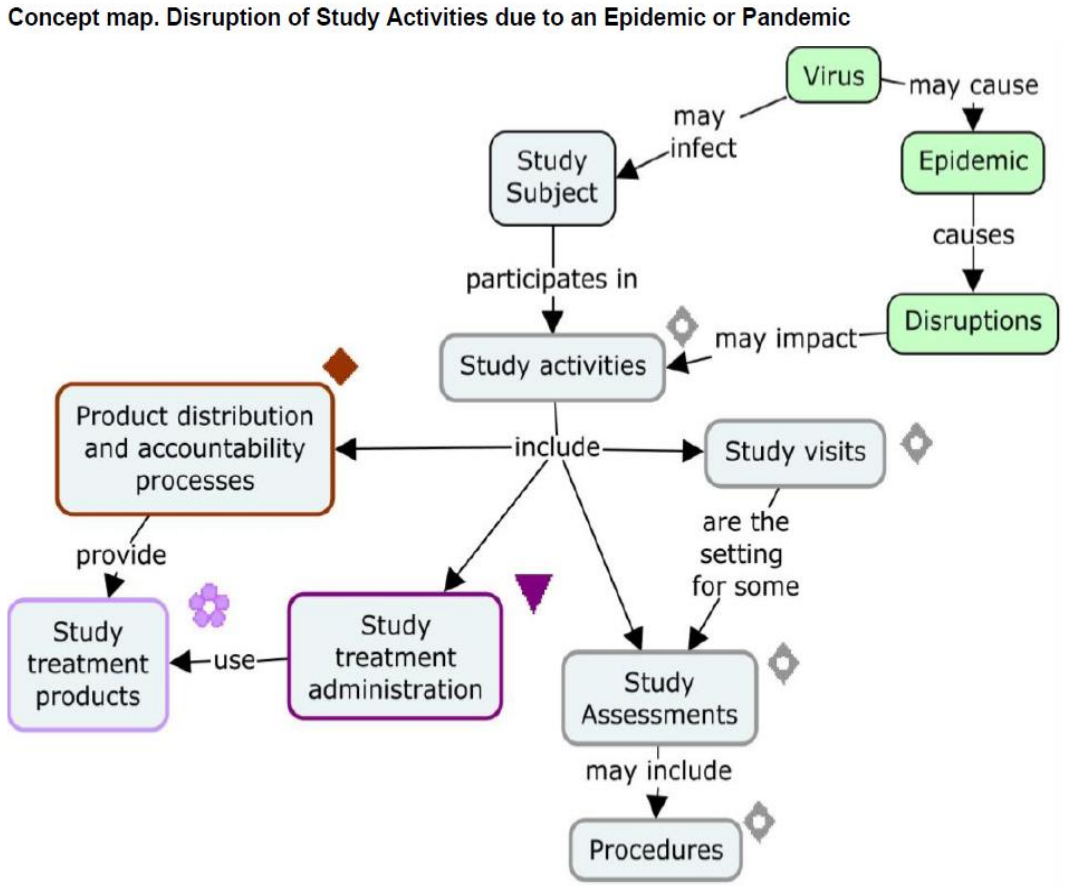


Task force members:
- Industry stakeholders
- Regulatory
- Academia
- Key CDISC data standards staff

- On April 21, 2020 the Task Force released 2 guidelines:
  - ✓ **Guidance for Ongoing Studies Disrupted by COVID-19**
  - ✓ **CDISC Interim User Guide for COVID-19**

CDISC response to COVID-19 (2/2)

- **Guidance for Ongoing Studies Disrupted by COVID-19**



Reference: *Guidance for Ongoing Studies Disrupted by COVID-19 Pandemic*

FDA Guidance	CDISC COVID-19 Interim User Guide	Associated Domains
The Introduction of the guidance discusses how restrictions related to COVID-19 may lead to changes in study conduct, and states the need to document the changes, their durations, and which trial participants were affected.	The Introduction to the guidance does not provide specifics on how or where the documentation should happen (e.g., documentation could reside in the site's files and not necessarily appear in collected data).	n/a
The Discussion section provides an overview of process, data, and analysis changes that may be needed for ongoing studies. Per Section III.B, when data are missing due to COVID-19-related reasons, both the data that was missed and the pandemic-associated reason must be clearly noted on the CRF. Section III.B provides context for the specifics listed in Section III.C.	For missing protocol-specified information, the preference is to capture subject-level data on a CRF. If this is not possible, data can be captured systematically across sites in a way that allows the regulatory body to analyze its impact. See the Protocol Deviations, Missed Visits, and Missed Assessments sections for direction. The domain-specific information on missing data will primarily appear in the domains, using standard variables such as --STAT and --REASND, and non-standard variables such as --REASOC and others proposed in this guide (see Appendix A, Non-standard Variables (NSVs)). When visits are missed, a different solution is needed. Advantages and disadvantages of these approaches are discussed in Missed Visits. How data are acquired to populate each of these depends upon how the sponsor's data capture is set up. Extending the Subject Visits (SV) domain was considered, but this approach was rejected because the model does not allow additional standard or NSVs in that domain. If data on site-level reasons for missing information are captured in such a way that individual subjects affected could be identified, the effects of site-level disruptions on individual subjects can be represented in SDTM-based datasets.	VE (Visit Events; interim custom) DV (Protocol Deviations)
Section III.C describes specific information to be included in the CSR, including • the contingency measures implemented during study disruption, • a listing of all participants affected by COVID-19-related study disruptions and specifics about how participation was disrupted, • analyses and discussions addressing the impact of implemented contingency measures on safety and efficacy, and • protocol deviations and specific reasons for them.	For the information required in Section III.C: • Contingency measures would be derived from protocol amendments, addenda to monitoring guidelines, data management plans, and documentation in the trial master file. Because some of this may come from the sponsor's administrative database content, it is probably not related to CDISC standards. • The listing of participants affected by COVID-19-related disruptions will probably be a highly derived compilation of data from many different domains, the specific content of which will depend on the data in the study. The domains that are most likely to be impacted by the COVID-19 pandemic are addressed in this interim guide. • A significant concern when processes or data are changed during a study is the potential impact on the primary outcome. Impacts will vary greatly from study to study, and	DV (Protocol Deviations) DS (Disposition) DA (Product Accountability) PR (Procedures) AE (Adverse Events) EC/EX (Exposure as Collected/ Exposure) ST (Site Transfer; custom domain) Any/all domains holding data which may be missed due to the pandemic

Overview Chiesi actions

- In the context of COVID-19, Chiesi undertaken a number of measures to ensure **patients' safety** and **data validity** creating a cross-functional **Task Force** inside the Global Clinical Development Group (QA, GCP Compliance unit, CPM and DM/STAT).

  Outcomes:

  - ✓ **Risks assessment** for each individual ongoing Clinical Trials
  - ✓ **DM/STAT analysis** of impacts on ongoing studies on data collection, SDTM domains, DM/STAT documents

Basic rules & Risk assessment

- **Basic rules** during the outbreak periods:

✓ No new trial should be initiated unless the risk/benefit for patient was clearly undisputable. Studies where FPFV has not been achieved yet were put on hold.

✓ Trials set up activities (design, feasibility on DB etc…) may carry on. Sites' feasibility shall never increase the burden to sites staff.

- **Risks assessment** for each individual **ongoing** Clinical Trials

✓ Investigate with the CRO the impact of the emergency on the study conduction and how any changes could be implemented;

✓ Request CRO to update on regular basis, the regulatory guidance that the National Competent Authority issued at national level about the management of clinical trials they have authorized;

✓ CRO to start writing a detailed story board for trial;

✓ Tracking any risk analysis/identification related to the outbreak of COVID-19 performed for any clinical trial related to activities such as recruitment, drug administration and monitoring strategies.

DM/STAT analysis on data collection & SDTM

How to satisfy the regulators requests from DM/STAT perspective and harmonize the solutions between studies and the CROs?

- Recommendation from ‘CDISC Guidance for Ongoing Studies Disrupted by COVID-19’
- Status of Chiesi studies & chance to update or not existing eCRFs

ONGOING studies

eCRF update (preferred option) to add COVID related indicators (e.g. discontinuation due to COVID)

OR

workaround (when eCRF update is not possible): instructions to sites to include key words such as "COVID-19" in existing text fields (e.g. CRF Comment page)

NEW studies

Standard CRF forms to be amended or custom forms to be designed to collect COVID related information

Chiesi standards

- **Background:**

Chiesi Libraries: based on latest version of CDISC SDTMIG guideline and Therapeutic Area Data Standards, we prepare guidelines for CRF, aCRF and SDTM for internal and CROs usage.
The aim is to collect data and to generate SDTM in a standardized way within programs and across CROs.

- ✓ **CRF guideline:** to guide the CRF designer/Data Manager in the design of the Case Report Form (CRF) for Chiesi Group clinical studies;
- ✓ **aCRF guideline**: this guideline contains the general rules for annotating the CRF with the corresponding SDTM variables in the database and the templates of the standard annotated CRF;
- ✓ **SDTM guideline:** aim of this document is to describe the Chiesi requirements for the SDTM dataset design and preparation of the define.xml. This guideline defines which datasets and which variables for each dataset should be produced.

Data: Disposition (1/2)

- **Case**: **Subject discontinue due to AE, DEATH, WITHDRAWAL of CONSENT linked to COVID-19.**

Data collection: 2 options

Option 1. **eCRF update**

STUDY TERMINATION FORM – EARLY WITHDRAWAL

Date of discontinuation |__|__|___|__|__|___|__|__|__|__| (DD / MMM / YYYY)

Primary Reason for discontinuation

Withdrawal of consent	❑	
Adverse Event	❑	Please specify/select the AE no/term. as reported in the Adverse Event Form: .....
<Disease> Exacerbation	❑	Please specify/select the Exacerbation no/term. as reported in the Exacerbation Form: .....
Lack of efficacy	❑	
Lost to follow-up	❑	
Occurrence of Pregnancy	❑	
Protocol violation	❑	Please specify: .....
Randomised by Mistake	❑	
Death	❑	
Other	❑	Please specify: .....

Did the subject discontinue due to COVID? ❑ YES ❑ NO

SDTM impact

NEW

ds.xpt

Row	STUDYID	DOMAIN	USUBJID	DSSEQ	DSTERM	DSDECOD	DSCAT	DSSCAT	EPOCH	DSDTC	DSSTDTC	DSSTDY	DSEPRELI
1	ABC123	DS	101	1	Died due to COVID-19	DEATH	DISPOSITION EVENT	STUDY PARTICIPATION	TREATMENT	2020-03-21	2020-03-21	46	Y
2	ABC123	DS	102	1	Treatment withdrawn due to COVID-19	ADVERSE EVENT	DISPOSITION EVENT	STUDY TREATMENT	TREATMENT	2020-03-24	2020-03-24	57	Y
3	ABC123	DS	103	1	Subject withdrew due to fears related to COVID-19	WITHDRAWAL BY SUBJECT	DISPOSITION EVENT	STUDY PARTICIPATION	TREATMENT	2020-03-24	2020-03-24	42	Y
4	ABC123	DS	104	1	Subject unable to participate due to COVID-19 quarantine	WITHDRAWAL BY SUBJECT	DISPOSITION EVENT	STUDY PARTICIPATION	TREATMENT	2020-03-24	2020-03-24	42	Y
5	ABC123	DS	105	1	Study terminated due to impacts of COVID-19	STUDY TERMINATED BY SPONSOR	DISPOSITION EVENT	STUDY PARTICIPATION	TREATMENT	2020-03-29	2020-03-29	65	Y

DS NSV Metadata In **SUPPDS** domain

Variable	Label	Type	Codelist	Role	Origin
DSEPRELI	Epi/Pandemic Related Indicator	text	NY	Non-standard Record Qualifier	CRF

Data: Disposition (2/2)

- **Case**: Subject discontinue due to AE, DEATH, WITHDRAWAL of CONSENT linked to COVID-19.

Option 2. **Study Disposition form AS IS + Workaround**

STUDY TERMINATION FORM – EARLY WITHDRAWAL

Date of discontinuation |___|___| |___|___|___||___|___|___|___|
DD MMM YYYY

Primary Reason for discontinuation

Withdrawal of consent	❑	
Adverse Event	❑	Please specify/select the AE no/term. as reported in the Adverse Event Form: .....
<Disease> Exacerbation	❑	Please specify/select the Exacerbation no/term. as reported in the Exacerbation Form: .....
Lack of efficacy	❑	
Lost to follow-up	❑	
Occurrence of Pregnancy	❑	
Protocol violation	❑	Please specify: .....
Randomised by Mistake	❑	
Death	❑	
Other	❑	Please specify: .....

Workaround:

- If reason = **AE**, the COVID relatedness will be derived from the AE page.
- If reason = **DEATH**, the COVID relatedness will be derived from the AE page (fatal event).
- If reason = **WITHDRAWAL OF CONSENT**, a comment referring to COVID-19 will be added in the *Comments* form.
- If the subject discontinues due to Sponsor/site decision related to COVID:

  Reason = '**Other**' → Please specify: 'restricted due to Coronavirus outbreak'

Sites will be instructed by detailed information in the eCRF Completion Guideline

DS NSV Metadata

Variable	Label	Type	Codelist	Role	Origin
DSEPRELI	Epi/Pandemic Related Indicator	text	NY	Non-standard Record Qualifier	CRF

Data: Adverse Events

- **Case**: **the need to identify adverse events related to COVID-19**

Data collection: no need to update AE form; we instructed the sites on using key text (e.g. COVID-19) in the verbatim (AETERM).

ADVERSE EVENTS

Has the Subject experienced any Adverse Event? Yes ☐ No ☐

[Specific reference to the AE collection period should be included]

If yes, complete the section below.

	Event(s) (one event per line)	Is the AE serious? (***)	Seriousness criteria	Onset date (DD-MMM-YYYY)	End date (DD-MMM-YYYY)	Outcome	Intensity	Is the AE Related to Study Drug?	Action taken with Study Drug	Other action taken
			1. Results in death 2. Life-threatening 3. (Prolonged) Hospitalization 4. Persistent or significant disability/ incapacity 5. Congenital anomaly or birth defect 6. Medically significant			1. Recovered/Resolved 2. Recovering/Resolving 3. Not recovered/Not resolved 4. Recovered with sequelae/Resolved with sequelae 5. Fatal 6. Unknown	1.Mild 2.Moderate 3.Severe		1. Dose not changed 2. Drug permanently withdrawn 3. Drug temporarily interrupted 4. Dose reduced 5. Dose increased 6. Unknown 7. Not applicable	1. Specific therapy/ Medication 2. Concomitant Procedure 3. NA
1.		Yes ☐ No ☐	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐			1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐	1 ☐ 2 ☐ 3 ☐	Yes ☐ No ☐	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐	1 ☐ 2 ☐ 3 ☐

SDTM impact

ae.xpt

Row	STUDYID	DOMAIN	USUBJID	AESEQ	AETERM	AELLT	AEDECOD	AESTDTC	AEENDTC	AESTDY	AEENDY	AEEPRELI
1	COV-4	AE	200	1	COVID-19	Coronavirus infection	Corona virus infection	2020-03-31	2020-04-26	23	49	Y
2	COV-4	AE	200	2	COVID-19 pneumonia	Pneumonia viral	Pneumonia viral	2020-04-05	2020-04-26	28	49	Y

AEEPRELI to be populated programmatically using PT codes COVID-19 related (*reference MedDRA v23.0; https://www.meddra.org/COVID-19-terms-and-MedDRA COVID-19 related New terms MedDRa 23.0 and MedDRa 23.1 spreadsheet'*)

AE NSV Metadata In SUPPAE domain

Variable	Label	Type	Codelist	Role	Origin
AEEPRELI	Epi/Pandemic Related Indicator	text	NY	Non-Standard Record Qualifier	CRF

NEW

Data: Procedures (1/3)

- **<u>Case</u>: COVID-19 test/any other diagnostic procedure COVID related need to be captured during the course of the study in case of <u>suspected infection</u>**

Data collection:

✓ Records (i.e. COVID-19 test results, CT scan) collected in Concomitant Procedures form;

✓ The procedures will be coded by the MedDRA dictionary.

CONCOMITANT PROCEDURES

Has the Patient any relevant (Medical/Surgical) Procedure(s)? **Yes ❑** **No ❑**

If yes, complete the section below.

Procedures	Start Date (DD MM YYYY)	End Date (DD MM YYYY)	Ongoing	Any conc. medication been taken?
1.	__|__| __|__|__|__|__|__|__|__| DD MMM YYYY	__|__| __|__|__|__|__|__|__|__| DD MMM YYYY	❑	❑ No ❑ Yes

SDTM impact: no impact on SDTM domain (PR).

Data: Procedures (2/3)

- **Case**: COVID-19 test/any other diagnostic procedure COVID related to be captured during the course of the study in case of suspected infection

Instructions for the sites reported in eCRF Completion Guideline: the Covid-19 test will be recorded in the Concomitant Procedure form with its result, unless differently agreed depending from country regulation.

SYMPTOMATIC SUBJECT

Form	Symptomatic subject	Test done: POSITIVE	FALSE POSITIVE
Adverse Event	Record symptoms	Update symptoms with COVID-19 diagnosis	Symptoms kept until final diagnosis is known
Concomitant Procedures		Record test result (*i.e. COVID-19 test positive*)	Update record *(i.e. COVID-19 test false positive)*

Form	Symptomatic subject	Test done: NEGATIVE	FALSE NEGATIVE	RETEST
Adverse Event	Record symptoms	Symptoms kept	Update symptoms with COVID-19 diagnosis	
Concomitant Procedures		Record test result (*i.e. COVID-19 test negative*)	Update record *(i.e. COVID-19 test false negative)*	Additional record for test result (*i.e. COVID-19 test positive*)

Data: Procedures (3/3)

- **Case**: COVID-19 test/any other diagnostic procedure COVID related to be captured during the course of the study in case of suspected infection

Instructions for the sites reported in eCRF Completion Guideline: the Covid-19 test will be recorded in the Concomitant Procedure form with its result, unless differently agreed depending from country regulation.

ASYMPTOMATIC SUBJECT

Form	Asymptomatic subject	Test done: POSITIVE
Adverse Event	No record	No record
Concomitant Procedures		Record test result (*i.e. COVID-19 test positive*)

Form	Asymptomatic subject	Test done: NEGATIVE
Adverse Event	No record	No record
Concomitant Procedures		Record test result (*i.e. COVID-19 test negative*)

Data: Medical terms (1/2)

- **MedDRA v. 23.0 updated to include COVID related terms** (released on 19-April-2020)
  - ✓ exceptional change to the standard release schedule;
  - ✓ needed to ensure that any scientific and medical information from COVID-19 outbreak can be captured, shared and analyzed appropriately.

ONGOING STUDIES

Dictionary upgrade to be evaluated at study level

STUDIES IN THE SET-UP PHASE

MedDRA extended version (v. 23.0) to be used

- In **define.xml,** version used to be clarified as following:

Reference Name	External Dictionary	Dictionary Version
MedDRA (external)	MedDRA	23 - with COVID 19 terms

Data: Medical terms (2/2)

- **Main updates (~70 new COVID-19 related terms)**
  - HLT *Coronavirus infections* added to group these infections (e.g. COVID-19, COVID-19 Pneumonia)
  - Investigation terms (e.g. Coronavirus test positive, Coronavirus test negative)
  - Immunisation, quarantine terms under SOC *Surgical and medical procedures*

LLT	Currency	PT	HLT	HLGT	Primary SOC
Corona virus infection	Y	Coronavirus infection	Coronavirus infections	Viral infectious disorders	Infections and infestations
Coronavirus infection	Y	Coronavirus infection	Coronavirus infections	Viral infectious disorders	Infections and infestations
Coronavirus disease 2019	Y	COVID-19	Coronavirus infections	Viral infectious disorders	Infections and infestations
COVID-19	Y	COVID-19	Coronavirus infections	Viral infectious disorders	Infections and infestations
COVID-19 respiratory infection	Y	COVID-19	Coronavirus infections	Viral infectious disorders	Infections and infestations
SARS-CoV-2 acute respiratory disease	Y	COVID-19	Coronavirus infections	Viral infectious disorders	Infections and infestations
SARS-CoV-2 infection	Y	COVID-19	Coronavirus infections	Viral infectious disorders	Infections and infestations
Coronavirus pneumonia	Y	COVID-19 pneumonia	Coronavirus infections	Viral infectious disorders	Infections and infestations
COVID-19 pneumonia	Y	COVID-19 pneumonia	Coronavirus infections	Viral infectious disorders	Infections and infestations
Novel COVID-19-infected pneumonia	Y	COVID-19 pneumonia	Coronavirus infections	Viral infectious disorders	Infections and infestations

LLT	Currency	PT	HLT	HLGT	Primary SOC
Coronavirus test	Y	Coronavirus test	Virus identification and serology	Microbiology and serology investigations	Investigations
Coronavirus test negative	Y	Coronavirus test negative	Virus identification and serology	Microbiology and serology investigations	Investigations
Coronavirus test positive	Y	Coronavirus test positive	Virus identification and serology	Microbiology and serology investigations	Investigations

LLT	Currency	PT	HLT	HLGT	Primary SOC
COVID-19 prophylaxis	Y	COVID-19 prophylaxis	Antiinfective therapies	Therapeutic procedures and supportive care NEC	Surgical and medical procedures
COVID-19 immunisation	Y	COVID-19 immunisation	Immunisations	Therapeutic procedures and supportive care NEC	Surgical and medical procedures
COVID-19 vaccination	Y	COVID-19 immunisation	Immunisations	Therapeutic procedures and supportive care NEC	Surgical and medical procedures
Home isolation	Y	Patient isolation	Therapeutic procedures NEC	Therapeutic procedures and supportive care NEC	Surgical and medical procedures
Quarantine	Y	Quarantine	Therapeutic procedures NEC	Therapeutic procedures and supportive care NEC	Surgical and medical procedures

Reference: covid-19_related_terms_meddra_23_0_update_0_5

Data: Concomitant Medications

- **<u>Case</u>: Medication used as prophylaxis or treatment of COVID-19**

Data collection:

- ✓ the actual trade or generic name under “Trade or generic name” of Prior and Concomitant medications form;
- ✓ the relationship to COVID-19 should be captured within the “Indication” field for these medications. E.g., “Prophylaxis: COVID-19” or “AE nr <number of corresponding AE>.

PRIOR AND CONCOMITANT MEDICATIONS

Has the Subject taken any Medication? **Yes ❑** **No ❑**

If yes, please list in the table below: Any previous (*<X weeks>* before visit 1) and/or new Concomitant Medication taken during the Study.
Any change (dose, formulation …) in Concomitant Medication.

Trade or Generic Name	Route	Dosage			Medication Started	Medication Stopped	On going	Indication
		Dose per administration	Dose Unit	Frequency				
1.					__|__|___|____| DD MMM YYYY	__|__|___|____| DD MMM YYYY	❑	❑ *<Disease under study>* ❑ *<Disease exacerbation>* ❑ AE nr __ __ __ ❑ MH nr __ __ __ ❑ Proced. nr ❑ Prophylaxis _____ ❑ Other, specify

Instructions for the sites reported in eCRF Completion Guideline

SDTM impact:

- ✓ no impact on SDTM domain (CM).

Data: Drug Intake (1/2)

- **Case: during the pandemic, subjects may not be able to come to the study site in person to receive or return study product**

Data collection: 2 options

Option 1. **Study Drug Administration** form to be amended to record reasons

STUDY DRUG ADMINISTRATION

Date of administration

X Tick if the same as visit date or complete: |___|___| |___|___|___| |___|___|___|___|
DD MMM YYYY

Has the study drug dispended as per protocol? ❑ Yes X No

If NO, please specify ……*Drug not available at the site*……

SDTM impact

- **DA** domain: DAREASND to be used to collect the reason for missing dispensation.
- **EC** domain: No action; if the intake is skipped, no record will be available in the dataset

Option 2. Note recorded in the **Comment** page for dispensation not according to the protocol.

INVESTIGATOR'S COMMENTS

	Visit number	Form/Assessment (if applicable)	Comment
1	*Visit 4*	*Study Drug Administration*	*The medication was delivered directly to the patient at home*

SDTM impact

- The information will be available in **CO** domain.
- **EC** domain: No action; if the intake is skipped, no record will be available in the dataset

Data: Drug Intake (2/2)

- **Case**: during the pandemic, subjects may not be able to come to the study site in person to receive or return study product

da.xpt

Row	STUDYID	DOMAIN	USUBJID	DASEQ	DAREFID	DATESTCD	DATEST	DACAT	DAORRES	DAORRESU	DASTRESC	DASTRESN	DASTRESU	DASTAT	DAREASND	VISITNUM	DADTC	DADY	DACNTMOD	DAEPCHGI
1	COV1901	DA	101	1	ABC-2345	DISPAMT	Dispensed Amount	Study Treatment	30	TABLET	30	30	TABLET			1	2020-01-06	1		
2	COV1901	DA	101	2	ABC-2345	RETAMT	Returned Amount	Study Treatment	3	TABLET	3	3	TABLET			3	2020-02-03	29		
3	COV1901	DA	101	3	ABC-7838	DISPAMT	Dispensed Amount	Study Treatment	30	TABLET	30	30	TABLET			3	2020-02-03	29		
4	COV1901	DA	101	4	ABC-7838	RETAMT	Returned Amount	Study Treatment	1	TABLET	1	1	TABLET			5	2020-03-02	57		
5	COV1901	DA	101	5	ABC-8308	DISPAMT	Dispensed Amount	Study Treatment	30	TABLET	30	30	TABLET			5	2020-03-02	57		
6	COV1901	DA	101	6		UNUSAMT	Unused Amount	Study Treatment	0	TABLET	0	0	TABLET				2020-04-01	87	TELEPHONE CALL	Y
7	COV1901	DA	101	7	ABC-7239	DISPAMT	Dispensed Amount	Study Treatment	30	TABLET	30	30	TABLET				2020-04-08	95	SHIPMENT CONFIRMED BY SIGNATURE	Y
8	COV1901	DA	101	8	ABC-7239	UNUSAMT	Unused Amount	Study Treatment	2	TABLET	2	2	TABLET				2020-05-06	123	TELEPHONE CALL	Y
9	COV1901	DA	101	9	ABC-7203	DISPAMT	Dispensed Amount	Study Treatment	30	TABLET	30	30	TABLET				2020-05-06	123	SHIPMENT CONFIRMED BY SIGNATURE	Y
10	COV1901	DA	101	10		UNUSAMT	Unused Amount	Study Treatment		TABLET			TABLET	NOT DONE	Subject died of COVID-19, unable to obtain information about remaining study drug.		2020-05-20	137		Y

OPTION 1

DA NSV Metadata **In SUPPDA domain**

Variable	Label	Type	Codelist	Role	Origin	
DACNTMOD	Contact Mode	text	CNTMODE	Non-standard Record Qualifier	CRF	CNTMODE is a sponsor-defined codelist
DAEPCHGI	Epi/Pandemic Related Change Indicator	text	NY	Non-standard Record Qualifier	CRF	

NEW

Data: Missed Visits (1/3)

- **Case**: **COVID-19 pandemic may cause missed visits, and in same cases may result in remote visits rather than clinic visits**.

CDISC proposals:

- ✓ Track missed visits as protocol deviations (**DV** domain)
- ✓ New custom domain (**VE** domain)

Background:

- ✓ The Subject Visits (SV) domain is a standard domain that includes data about visits that occurred and there is no way within the SDTM model to add variables to the SV domain as either standard variables or supplemental qualifiers.
- ✓ As per CDISC Guidance for Ongoing Studies Disrupted by COVID-19, the **custom Visit Events (VE)** could be used as interim solution. In the future, it is possible that the solution for recording data about visits that did and did not occur may mean using a modified SV domain or using a new domain (e.g., the VE domain).

Data: Missed Visits (2/3)

- **Case: COVID-19 pandemic may cause missed visits, and in same cases may result in remote visits rather than clinic visits.**

Data collection: 2 options

Option 1. **eCRF update**

Visit Date |__|__| DD |__|__|__| MMM |__|__|__|__| YYYY

Onsite ☐

Remote ☐ *<include methods: video, telephone contact>*

Not done ❑ Please specify .....

In SUPPVE domain

VE NSV Metadata

Variable	Label	Type	Codelist	Role	Origin	Comment
VEREASOC	Reason for Occur Value	text		Non-Standard Record Qualifier	CRF	
VEEPCHGI	Epi/Pandemic Related Change Indicator	text	NY	Non-Standard Record Qualifier	CRF	
VECNTMOD	Contact Mode	text	CNTMODE	Non-Standard Record Qualifier	CRF	CNTMODE is a sponsor-defined codelist.

ve.xpt

Row	STUDYID	DOMAIN	USUBJID	VESEQ	VETERM	VEDECOD	VEPRESP	VEOCCUR	VISITNUM	VISIT	VISTDY	VEDTC	VESTDTC	VEDY	VESTDY	VEREASOC	VEEPCHGI	VECNTMOD
1	CVD-3	VE	301	1	ONSITE VISIT	PLANNED VISIT	Y	Y	1	BASELINE	1	2020-03-04	2020-03-04	1	1			
2	CVD-3	VE	301	2	ONSITE VISIT	PLANNED VISIT	Y	Y	2	WEEK 1	8	2020-03-11	2020-03-11	8	8			
3	CVD-3	VE	301	3	REPEAT VISIT FOR ABNORMAL LAB	UNSCHEDULED VISIT			2.5			2020-03-13	2020-03-13	10	10			
4	CVD-3	VE	301	4	ONSITE VISIT	PLANNED VISIT	Y	Y	3	WEEK 2	15	2020-03-19	2020-03-19	16	16			
5	CVD-3	VE	301	5	ONSITE VISIT	PLANNED VISIT	Y	N	4	WEEK 3	22	2020-03-25		22		Subject lacked transportation		
6	CVD-3	VE	301	6	ONSITE VISIT	PLANNED VISIT	Y	N	5	WEEK 4	29	2020-04-01		29		Subject refused due to fear of epidemic	Y	
7	CVD-3	VE	301	7	ONSITE VISIT	PLANNED VISIT	Y	N	6	WEEK 5	26	2020-04-08		36		Hospital restricted access to clinic	Y	
8	CVD-3	VE	301	8	VIRTUAL VISIT	PLANNED VISIT	Y	Y	7	WEEK 6	43	2020-04-15	2020-04-15	43	43		Y	REMOTE AUDIO
9	CVD-3	VE	301	9	VIRTUAL VISIT	PLANNED VISIT	Y	Y	8	WEEK 7	50	2020-04-22	2020-04-22	50	50		Y	REMOTE AUDIO VIDEO
10	CVD-3	VE	301	10	HOSPITAL RESTRICTED ACCESS TO RADIOLOGY DUE TO COVID-19	INCOMPLETE PLANNED VISIT	Y	Y	9	WEEK 8	57	2020-04-30	2020-04-30	59	59		Y	

NEW

Data: Missed Visits (2/3)

- **Case: COVID-19 pandemic may cause missed visits, and in same cases may result in remote visits rather than clinic visits.**

Point of discussion for SDTM implementation: Chiesi approach

SV: we continue to use this domain for visits occurred on site;

VE/SUPPVE: used for visits did not occurred (missed visits) and for visits performed remotely

Option 2. **Workaround** with data collected on the CRF Comments page

INVESTIGATOR'S COMMENTS			
	Visit number	Form/Assessment (if applicable)	Comment
1	*Visit 5*	*Visit not done*	*Restrictions due to COVID outbreak*

SDTM impact

The **CO** domain will collect information about missed visits or visits performed remotely.

Data: Missed Assessments

- **Case**: **due to pandemic some scheduled assessments cannot be performed**

Data collection: 2 options

Option 1. **eCRF update**

<ASSESSMENT>		
Was the <assessment> performed?	Yes ❑	No ❑
If No, please specify		

Option 2. Note recorded in the **Comment** page

INVESTIGATOR'S COMMENTS			
	Visit number	Form/Assessment (if applicable)	Comment
1	*Visit 5*	*ECG not done*	*Visit performed remotely due to COVID restrictions*

SDTM impact

- Non-performance of a test:
  --STAT = "NOT DONE".
- Non-performance of all the tests:
  --ALL convention (e.g., "LBALL" in the LB domain)
- --REASND = *reason for not performing*

Data: Protocol Deviation

- **<u>Case</u>: COVID-19 disruptions may lead to protocol deviations**

If no chance to amend the protocol, missed visits, visits performed remotely, assessments not performed etc… will be captured as protocol deviations in according to Sponsor procedures (manual PDs and programmatic PDs).

dv.xpt

Row	STUDYID	DOMAIN	USUBJID	DVSEQ	DVREFID	DVSPID	DVTERM	DVDECOD	DVCAT	DVSCAT	EPOCH	DVSTDTC	DVENDTC	DVREAS	DVEPRELI
1	CVD-3	DV	300	1			Site shut down		SITE DEVIATION		TREATMENT	2020-02-17	2020-02-20	Flooded basement	
2	CVD-3	DV	301	1			Site shut down		SITE DEVIATION		TREATMENT	2020-02-17	2020-02-20	Flooded basement	
3	CVD-3	DV	301	2			Site shut down		SITE DEVIATION		TREATMENT	2020-04-06	2020-04-18	All transportation in country down due to COVID-19.	Y
4	CVD-3	DV	303	1			Site shut down		SITE DEVIATION		TREATMENT	2020-02-17	2020-02-20	Flooded basement	
5	CVD-3	DV	306	1			Site shut down		SITE DEVIATION		TREATMENT	2020-04-06	2020-04-18	All transportation in country down due to COVID-19.	Y
6	CVD-3	DV	307	1			Site shut down		SITE DEVIATION		TREATMENT	2020-04-06	2020-04-18	All transportation in country down due to COVID-19.	Y
7	CVD-3	DV	309	1			Site shut down		SITE DEVIATION		TREATMENT	2020-04-06	2020-04-18	All transportation in country down due to COVID-19.	Y
8	CVD-3	DV	312	1			Site shut down		SITE DEVIATION		TREATMENT	2020-02-17	2020-02-20	Flooded basement	
9	CVD-3	DV	312	2			Site shut down		SITE DEVIATION		TREATMENT	2020-04-06	2020-04-18	All transportation in country down due to COVID-19.	Y

DV NSV Metadata **In SUPPDV domain**

Variable	Label	Type	Codelist	Role	Origin	Comment
DVREAS	Reason for Deviation	text	DVCODES	Non-standard Record Qualifier	CRF	DVCODES is a sponsor-defined codelist.
DVEPRELI	Epi/Pandemic Related Indicator	text	NY	Non-standard Record Qualifier	CRF	

Data: Trial Summary

- **Case**: **TS domain used to indicate if a study was distrupted by a pandemic and the pandemic name**

ts.xpt

Row	STUDYID	DOMAIN	TSSEQ	TSGRPID	TSPARMCD	TSPARM	TSVAL	TSVALNF	TSVALCD	TSVCDREF	TSVCDVER
1	ABC123	TS	1	COVID-19	EPDISIND	Epi/Pandemic Related Disruption Ind	Y		C49488	CDISC CT	2020-03-27
2	ABC123	TS	1	COVID-19	EPDEMIC	Name of Epi/Pandemic	COVID-19 PANDEMIC				

EPIDEMIC in according to CDISC CT

CDISC CT: 2020-09-25

Under internal discussion the usage of TSPARM 'Data Cutoff Description/Date to capture the date of Chiesi starts actions in term of containment measure.

DCUTDESC	Data Cutoff Description	Text that describes the cutoff date.
DCUTDTC	Data Cutoff Date	A date which indicates any data collected by this date will be used for analysis.

*This to answer to EMA requirement… Additional analyses (to be included in the SAP) to investigate the impact of the **three phases (pre, during, and post COVID-19)** to understand the treatment effect as estimated in the trial"*

Impacted documentation

Data Management

- **eCRF guidelines**: update needed to include specific instructions to the sites
- **DMP**: amendment needed in case the approach to data collection changes (affected sections to be updated, document history to clarify that the DMP amendment is due to COVID)
- **Data Handling Report/DM Report/ad hoc document**: update needed to document issues that remain open at study closure
- **Define.xml**: to include new domains and new variables

Other documents

- **Data Quality Report**: to monitor the impact of COVID-19 during the course of the study
- **Data Review Report**: to include deviations due to COVID-19
- **Statistical Analysis Plan**: to include additional analysis to evaluate the impact of the COVID-19

Next steps

- **Development of new custom CRF forms**: i.e. COVID-19 History?

SARS-COV-19 ARDS HISTORY

Date of Positive SARS-Cov-19 rtPCR |__|__| |__|__|__| |__|__|__|__| (DD MMM YYYY)

ICU admission date: |__|__| |__|__|__| |__|__|__|__| (DD MMM YYYY)

Intubation date/time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__| (DD MMM YYYY hh mm)

Please record ventilatory details in the Ventilatory support form.

SARS-COV-19 ARDS MEDICATIONS

Treated by:

- ❑ antiviral drugs
- ❑ monoclonal antibodies
- ❑ antibiotics
- ❑ systemic corticosteroids
- ❑ heparin
- ❑ plasma from immunized patients
- ❑ other Please specify: _____

Please record the medication category here below and add full details in the Concomitant Medications form

- **Improvement of current CRF forms**: based on feedback from stat analysis or from the occurrences of other scenarios

References

- **EMA** Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf
- **FDA** guidance on conduct of clinical trials of medical products during COVID-19 pandemic. Guidance for industry, investigators, and institutional review boards. https://www.fda.gov/media/136238/download
- **CDISC** Guidance for Ongoing Studies Disrupted by COVID-19. https://www.cdisc.org/standards/therapeutic-areas/covid-19
- **MedDRA** COVID term webinar, April 2020. https://www.meddra.org/COVID-19-terms-and-MedDRA


THANK
YOU