COVID-19 Pandemic and Clinical Data Management

- Presented by:

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Initial response from Industry to COVID-19

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SCDM COVID-19 Webinars

- ☑ **April 30th**, Overview of Changes in Regulatory Guidelines
  - Set the stage by simply summarizing COVID-19 related guidelines
  - 2 sessions (600+ Live participants)
- ▶ **May 14th**, Initial response from industry to COVID-19
- ▶ **TBD**, Peer-to-Peer Discussions
  - Panel discussion with industry leaders

Summary from April 30th Webinar

	Topics	US FDA	EMA PTC	EMA Guidance to sponsors	UK MHRA	Germany BfArM	India	China	Japan PMDA / MHLW
1	**Safety of clinical trial participants**	X	X	X	X	X	X	X	X
	Compliance with GCP	X						X	
	Clinical trial integrity	X	X	X				X	
	Clinical trial eligibility				X				
3	**Study Participant continuation/discontinuation**	X	X	X	-	X	X	X	-
	Safety assessments	X	-	X	X	X	-	X	X
	Access to IP - home delivery	X	-	X	X	X	-	-	X
	Access to IP - home health care administration	X	-	X	X	X	-	-	X
	New or modified processes	X		X		X		X	
	Protocol amendments	X	-	X	X	-	X	X	-
	Missing information/data	X		X				X	
	Efficacy endpoint assessment	X							
2	**Protocol deviations**	X	X	X	X	-	X	X	X
3	**Study monitoring**	X	-	X	X	X	-	X	X
	Data management plans	X							
	Statistical Analysis plans	X	X						
	COVID-19 screening	X							
	Consent process	X		X		X			X
	CSR- COVID-19 impact and study analyses	X		X					
	Patient privacy					X			
	Restart of clinical trials after suspension				X				
	Risk-assessment of the impact	X	X	X	X	-	X	-	-
1	**Interaction with Authorities**	X	X	X	X	X	X	X	X
	Communication with sites	X		X			X	X	
	Audits			X					
	Reimbursement			X					
	Trials to test treatments for COVID-19			X	X	X			

Initial response from Industry to COVID-19

- Share reactions of organizations to COVID-19 and related Guidelines
- 14 Organizations
- US and EMA Based
- Mainly Sponsors
- Small to Large
- Feedback collected around 8 areas:

1. Trials Conduct
2. Subject Management
3. Site Management
4. Data Management
5. Clinical Supplies (Incl. IP)
6. Protocol Deviation
7. Safety Reporting
8. Clinical Study Report

1 – Trial Conduct

Feedback from MOST companies on Protocol Amendment

- **NOT** requiring systematic Protocol Amendment due to COVID-19
- Protocols amended case by case:
  - Allow for Home Visits
  - Extend visit windows
  - Update Time & Events
  - Amend IC/EC
  - NOT for capturing additional information

- EMA: Changes should be proportionate, taking into account interest of trial sites in avoiding further burden during the COVID-19 pandemic as well as the subjects' well-being & best interests.
- EMA: Prospective protocol waivers remain unacceptable

1 – Trial Conduct

Feedback from MOST companies on Risk and Impact

- Complete a risk assessment

1) Patients/Study participants are unable to travel to the sites, resulting in-

  - Missed visits – need to flag visits due to COVID-19 and associated Protocol Deviations
  - Missed procedures – need to flag assessments missed due to COVID-19 and associated Protocol Deviations
  - Unable to use the central lab
  - Compliance with site-based Clinical Outcome Assessment (COA) measures
  - Use of Telehealth to perform parts of the patients visits
  - Needing to ship IP to the Patients' home
  - Overall enrollment and screening impacts – option to screen-fail now and rescreen later in the year an option?
  - Potentially higher number of discontinued patients

https://scdm.org/covid-19-risk-areas-and-potential-impact-to-clinical-data/

1 – Trial Conduct

Feedback from MOST companies on Risk and Impact

- Complete a **risk assessment**

2) Site staff unable to commute to work or need to go on leave, resulting in-

- Delays in data entry into EDC
- Delays in data queries resolution
- Delays in site initiations and enrollments
- Delays in processing of lab samples
- Unable to receive IP shipment – bulk dispensation an option?

https://scdm.org/covid-19-risk-areas-and-potential-impact-to-clinical-data/

1 – Trial Conduct

Feedback from MOST companies on Risk and Impact

- Complete a risk assessment

3) CRAs unable to perform site visits, resulting in-

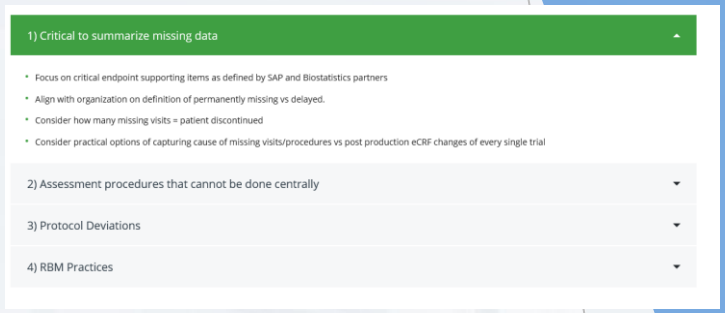
- Unable to perform traditional on-site SDV
- Delays in cohort-data reviews
- Impact on milestones such as DB Lock.

4) Vendors (Labs, eCOA, IxRS etc.) face staff shortage or facilities shutdowns, resulting in-

- Delays in sample analysis
- Delays in data transfers and reconciliations
- Delays in shipment of eCOA – paper and web-backup an option?

https://scdm.org/covid-19-risk-areas-and-potential-impact-to-clinical-data/

1 – Trial Conduct



Feedback from MOST companies on Risk and Impact

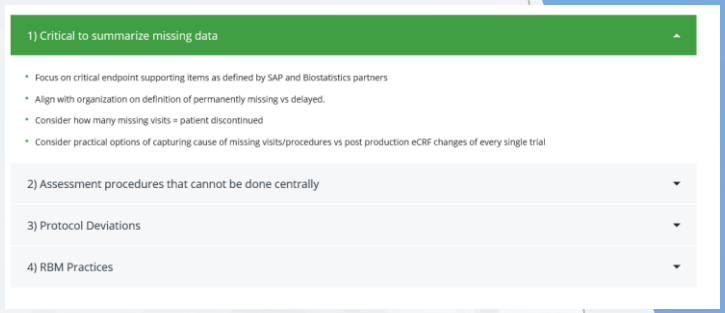
- Complete an impact assessment

1) Critical to summarize missing data

- Focus on critical endpoint supporting items as defined by SAP and Biostatistics partners
- Align with organization on definition of permanently missing vs delayed.
- Consider how many missing visits = patient discontinued
- Consider practical options of capturing cause of missing visits/procedures vs post production eCRF changes of every single trial.

https://scdm.org/covid-19-risk-areas-and-potential-impact-to-clinical-data/

1 – Trial Conduct



Feedback from MOST companies on Risk and Impact

- Complete an **impact assessment**

2) Assessment procedures that cannot be done centrally

- For non-specialty labs, local lab options may be more feasible or a local branch of a central lab
- Additional work for confirmation of local lab qualification, but may be necessary
- While same approach could apply for imaging, however in cases when Imaging is a primary endpoint, assess the scientific validity of the trial if the image is not captured, how many missed images would cause impact to the analysis.
- Study EDC designs need to be flexible to account for manual local lab data capture vs central lab collection

https://scdm.org/covid-19-risk-areas-and-potential-impact-to-clinical-data/

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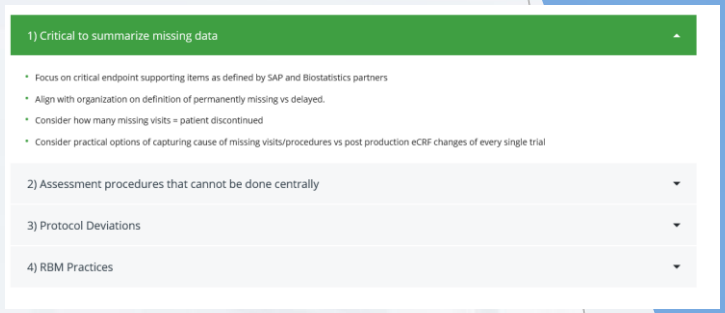
1 – Trial Conduct



Feedback from MOST companies on Risk and Impact

- Complete an impact assessment

3) Protocol Deviations

- Existing edit checks/derivations will report extremely high number
- Advisable to leave these in place to capture all, however more intelligent filtering as well as flagging of COVID-19 related PDs via reporting may be necessary

4) RBM Practices

- Consider increasing the frequency of the cross-functional data review
- Standard KRIs can remain in place and monitored but additional ones should be identified based on current risks
- Organizational-wide updates to KRI's can mitigate how many trial-specific ones may be necessary
- A decision tree to filter high volume of "false positives" and follow up actions needed

https://scdm.org/covid-19-risk-areas-and-potential-impact-to-clinical-data/

POLL Question #1

As a result of COVID-19, did you company?

Select all applicable answers:

A - Halt Enrollment (Globally or in impacted countries)

B – Delay new studies (Unless critical-e.g. study on COVID-19)

C – Leverage Telehealth Visits

D – Allow IP Shipment to Patient' Home

E - None of the above

1 – Trial Conduct

Feedback from MOST companies on Decentralized Clinical Trials (DCT)

- Assess DCT process and technologies that could be implemented on ongoing studies
- Consider scaling-up use of DCT processes and technologies on up-coming studies

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1 - Trial Conduct

Decentralized Clinical Trials (DCT)

- DCT is **NOT** a different study design category like Adaptive, Umbrella, Basket, etc.
- DCT is essentially decoupling clinical research activities from a physical site location

Example of a fully Patient Centric / Decentralized Clinical Trials

1 – Trial Conduct

Other feedback from SOME companies on Trial Conduct

- Consider to create a Business Continuity Plan for each trial
- Implement Telehealth and Home nursing when feasible
- Some companies halted study enrollment (Globally or most impacted countries)
- Some companies delayed start of new studies (unless critical / study COVID-19)
- Providing guidance on how to re-start study activities on halted studies post COVID-19
- Mandate documented training on COVID-19 related process changes

2 – Subject Management

Feedback from MOST companies on Subject Discontinuation

- Use standard Exit/Disposition form,
- If discontinued due to being infected by COVID-19,
  - Report infection as an AE
  - Reason for discontinuation is AE
- If discontinued due to other COVID-19 reason (e.g. Patient not able to go to sites, physician decision, etc.)
  - Reason for discontinuation is Other
  - Specify exact reason as Text and mention COVID-19

2 – Subject Management

Other feedback from SOME companies on Subject Discontinuation

- For Deaths in Long Term Follow Up trial phases (common in Oncology) which may not collect standard AE forms:
  - Leverage either Exit/disposition form or specific death form
  - Cause of death is either direct text or option of Other
  - Specify exact cause as text attributing COVID-19

2 – Subject Management

Other feedback from SOME companies on Subject Management

- Allow patient to use local labs for standard safety lab instead of central labs
- Consider alternative modalities for eCOA (i.e., phone interviews)
  - Generally recommended to not "mix" modalities
  - If team determines it is unavoidable there needs to be a method of differentiating (vis data or metadata) results generated via alternate method/modality
  - In site based ePRO scenarios, if completion is not tethered to a procedure it may be possible to modify system to allow completion at home, however supply chain of devices to patients is a challenge
  - **Do not take shortcuts:** Site users are **not** allowed to use a subject's credentials to enter data in the eCOA system. This would constitute a major breach of data attributability !
  - All vendors do not provide identical data collection platforms and each study has different constraints; therefore, understanding the limits of data collection for each assessment is key to determine alternatives

3 – Site Management

Feedback from MOST companies on Data Capture

- No change to the eCRF
- Update CRF Instructions (e.g. Missed Visits / Procedures, Patient disposition),
- Still use the eCRF for telehealth visits (i.e. Source data capture process changed)
- Update Source Management Guideline (e.g. Source management for telehealth/remote patient visits),

3 – Site Management

Feedback from MOST companies on Monitoring

- Onsite monitoring stopped or significantly reduced
  - Assess impact of stopped SDV on DB Lock Process
- Increase remote and Risk-Based monitoring
- Increase centralize data reviews
- **Some companies** considering remote SDV using Source copy / remote EMR Access
  - **EMA: Remote SDV in general is not allowed, but may be considered for trials on COVID-19 treatment, and for final data cleaning in pivotal trials on serious conditions with no satisfactory treatment options**
  - Many source document have personnel identifiers
  - Those are mainly in local languages
- Must document changes in Monitoring Plan
- Track impacted and non-impacted sites (Site closed due to lockdowns, etc.)
- Document/flag non-data driven COVID-19 related PDs in Monitoring Visit Report

POLL Question #2

As a result of COVID-19, did your Clinical Data Management function?

Select all applicable answers:

A – Increase risk-based approaches to focus on Critical Data

B – Increase surveillance of known risks (e.g. Missing Data)

C – Change SDV setting in EDC

D – Develop COVID-19 related checks, listings & dashboards

E – None of the above

4 – Data Management

Feedback from MOST companies on Data Handling

- No Change to eCRF (i.e. Use existing data capture tools)
- **Most companies** would primarily rely on site to flag missing data as COVID-19 related using existing EDC functionalities (e.g. Form & Item Level comments)
- Update CRF Completion Instructions for
  - Missed Visits and Procedures
  - Patient Disposition
  - Interruption of study treatment

4 – Data Management

Feedback from MOST companies on Data Reviews

- Focus on critical data for patient safety and clinical efficacy (rb-CDM)
- Increase frequency of data review
- Increase data surveillance of
  - Critical data
  - Missing data
  - Delayed data entry
  - Missed Visit Windows
  - Protocol Deviations
  - Compare data trends **before, during and after** Pandemic (Country and Site Level)

Edit Checks
Dashboards
Reports (incl. Exception reports)
rb-X like tools

- **Less than 50%** of companies would query for missing visits and critical procedures
- Add a COVID-19 section in DMP for impacted studies (i.e. Inspection ready DMP)

4 – Data Management

Other feedback from SOME companies on Data Management

- Add a code to code list on the “missed visit reason” for flagging missed visits for COVID-19 related reason
- Align SDV configuration in EDC with changes to the on-site monitoring process
- Provide guidance for handling studies and sites closed prematurely

POLL Question #3

As a result of COVID-19, did your company?

Select all applicable answers:

A - Change the AE reporting process

B - Change the SAE Reporting process

C - Change the Protocol Deviation (PD) Process

D - None of the above

5 – Clinical Supplies (incl. IP)

Feedback from MOST companies on Investigational Product

- Allowing sites to ship IP to patient case by case
  - Created an IP Direct to Patient shipment guidance
  - Authorize only when drug stability is not at risk and patient is able to self-administer
  - Site expected to have a documented process
  - **Same IP related requirements still expected by regulator (e.g. Temperature control, Drug Accountability)**
- Track temporary or permanent IP discontinuation due to COVID-19 in eCRF
- Consider impact on IP Management in IxRS

6 – Protocol Deviations

Feedback from MOST companies on Protocol Deviations (PDs)

- Provide guidance to enter a standard language (such as “COVID-19 pandemic circumstances”) when creating a new PD in CTMS
- Enable Biostatistician to report COVID-19 related PD in CSR
  - Add a new category / flag in PD Management tool
- Extract Missed Visits and Procedure comments from EDC with COVID-19 being mentioned to enable PD Creation

7 – Safety Reporting

Feedback from MOST companies on AE/SAE reporting

- Use standard AE and SAE form to report patients infected by COVID-19
- Applying new MSSO MedDRA version with updated codes for COVID-19

  A COVID-19 SMQ is anticipated to be included in MedDRA version 23.1 (Sep 2020)
- Provide additional guidance on capturing positive COVID-19 tests as well as COVID-19 like signs and symptoms.

NOTE: In the absence of a COVID-19 positive test, it may not be possible to 100% diagnose all COVID-19 cases. Some AEs may remain more generically coded as oppose to COVID-19.

Some Medical Physician may elect to query site to confirm diagnosis when the pattern of symptoms and time of event strongly suggest the potential of a COVID-19 infection.

7 – Safety Reporting

MedDRA SOC / Preferred Term (Version 23)

Infections and infestations	Asymptomatic COVID-19 Coronavirus infection COVID-19 COVID-19 pneumonia Middle East respiratory syndrome N/A SARS-CoV-2 carrier Severe acute respiratory syndrome Suspected COVID-19
Injury, poisoning and procedural complications	Exposure to SARS-CoV-2 Occupational exposure to communicable disease Occupational exposure to SARS-CoV-2
Investigations	Coronavirus test Coronavirus test negative Coronavirus test positive MERS-CoV test MERS-CoV test negative MERS-CoV test positive SARS-CoV-1 test SARS-CoV-1 test negative SARS-CoV-1 test positive SARS-CoV-2 test SARS-CoV-2 test false negative SARS-CoV-2 test negative SARS-CoV-2 test positive
Surgical and medical procedures	COVID-19 immunisation COVID-19 prophylaxis COVID-19 treatment Patient isolation Quarantine

8 – Clinical Study Report (CSR)

Feedback from MOST companies on CSR

- Documentation of COVID-19 Impact on Clinical Trial in CSR
  - List PD related to CODIV-19
  - List of patients impacted by CODIV-19
    - Describe how the individual's participation was altered (e.g. Discontinued due to any COVID-Reason)
  - Summarize COVID-19 missing data and missing visits
- For critical endpoints where method/modality of procedure or data capture was **purposely** altered or if missing data rules are applied
  - Team should consult their statistician to consider sensitivity analyses

8 – Clinical Study Report (CSR)

Other feedback from SOME companies on CSR

- Exclude safety local lab values from Statistical Analysis and CSR?
- Summarize AE reporting before and after Pandemic onset as well as specific AE reporting of Infections
- Develop a "boilerplate" CSR Template to be used by teams to document COVID-19 related mitigations and impact

POLL Question #4

As a result of the changes implemented to respond to COVID-19, do you anticipate your company to:

Select all applicable answers:

A – Scale-up DCT processes and systems (All or Partially)

B – Adjust business continuity strategies moving forward

C – Scale-up risk-based CDM Strategies

D – Scale-up Centralized Monitoring Strategies

E – None of the above

THANK YOU

Q&A