RESPONSE TO FDA COMMENTS ON CLINICAL DATED OCTOBER 28, 2021

The Sponsor acknowledges FDA Comments on CLINICAL (in **BOLD**)

COVID-19 Vaccine, mRNA (SPIKEVAX)
Subject: Responses to Information Request #5 (Datasets)

The Sponsor has provided responses to a few of the discussion points for CBER to facilitate discussion during the planned TC:

ITEM 1:

The SDTM define file stylesheet has an incorrect filename ('define1-0-0.xsl').
Please change the file name to 'define2-0-0.xsl' and resubmit the file.

Sponsor Response
The Sponsor would like to apologize for any inconvenience this brings to review. The file name of the SDTM define file stylesheet was automatically renamed by the publishing tool, renamed the file name from 'define2-0-0.xsl' to 'define1-0-0.xsl' in tabulation \sdtm location. Please rename the file name back to 'define2-0-0.xsl'. This would be a more straightforward approach.

CBER Discussion Point:
Unfortunately, this is not a straightforward approach as we are unable to change names in the system. Please resubmit with the correct file name.

Sponsor Response
Moderna will resubmit the file. No further discussion is needed.

ITEM #4:
Regarding ongoing solicited events:

b. 'Ongoing' was not flagged in CE as requested. Instead you flagged an event in SUPPAE with Y for 'solicited adverse reaction' and N for 'AR remove flag' (please notify us if this is incorrect), which impacts our analysis of this data. Please update the CE dataset by including 'ongoing' in CENRTPT with CEENTPT of 'Day 7.'

Response to b:
We first would like to explain SUPPAE.REMOVEFL=Y. In this study, participants reported SAR using eDiary after each injection. If an AR is collected on AE eCRF but not satisfies criteria of SAE or last beyond 7 days after injection, such AR would be mapped to CE and FACE domains and flagged as removed in SUPPAE (SUPPAE.REMOVEFL=Y). This mapping logic was implemented after a series of IR correspondence of SDTM mapping (Reference: IND 19745 SN0052 provided on 06-Oct-2020) as well as a teleconference held on 23-Oct-2020 between Moderna and CBER to discuss this topic.
Ongoing flag is not utilized in CE domain as there is no clear definition of 'ongoing', i.e.

whether 'ongoing' refers to an SAR ongoing on Day 7 or an SAR ongoing at the time of data snapshot. Per Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review Guidance for Industry Technical Specifications Document, the ongoing information is suggested to be collected; however, in study P301, such information is not collected. In study P301, an ongoing SAR meant a SAR was reported on both D7 and D8. In eDiary data, there could be cases where SAR was reported by a study participant,
• on D7 and D9 (but not reported on D8 or no event on D8), or
• on D6 and D8 (but not reported on D7).
Due to this fact, there was no robust logic to assign "ongoing" in CEENRTPT.

CBER Discussion Points:
Please add the flag to CE and resubmit the dataset.

Sponsor Response: We accept CBER's comment and agree to update CE domain adding CENRTPT="Day 7" and CEENTPT="ONGOING" for all last beyond Day 7 events.
We have assessed, such update would have no impact on analysis. Thus, the Sponsor would like to propose to implement CBER's suggestion in the future sBLA submission.

c. Events are listed in AE that were neither an ongoing solicited event nor an SAE, but which were categorized as 'reactogenicity' in AECAT. We acknowledge that you may have categorized events that were reported by the investigator which were synonymous with solicited events and which occurred during the 7-day evaluation period and which may have been merged into the CE dataset as such, but this negatively impacts out ability to analyze the data. These events should have been reported in CE from the start of the study. Please note that we requested reporting of this data in this way in our September 28, 2020 advice under your IND submission, but since this was not implemented in your November 2020 EUA submission, we agreed that you could flag these events in SUPPAE as 'removed' from AE analysis and instead were included in the CE dataset and ultimately the reactogenicity analysis. As these events are already flagged, please revise the category for these events back to 'Adverse Event' so that they are not confused with ongoing events.

Response to c:
a. AECAT="reactogenicity" is based on answer to the SAR question on AE eCRF form (please refer to response to Item 5 too);
b. Independently, remove flag = "Yes" in SUPPAE if the AE preferred term is pre-identified solicited AR symptom terms but the event not satisfying either lasting beyond 7 days nor SAE criteria.
a) and b) above are assessed independently. Would you please disregard AECAT?

CBER Discussion Points:
□ By reporting it in AE and then categorizing it as "reactogenicity" you have now indicated it is either ongoing or an SAE (as per the Vaccine guidance).
□ Please correct and resubmit.

Sponsor Response: The Sponsor would like to clarify that, as this topic was discussed previously with CBER, the Sponsor did not realize that CBER expected us to update the mapping logics for BLA submission from what were used for EUA submissions.

We would like further clarification from CBER on the request to ensure we are aligned on the updates to be made:
Is the request to merge events unreported in eDiary for SAR but collected on AE eCRF form and did not satisfy serious criteria, back to CE domain with EVAL="INVESTIGETOR"?

We would like to use two examples for discussion purpose (Pain):
Example 1. A subject reported No Pain on Day 1 and Day 2, missed reporting Symptom Pain on Day 3 and Day 4 after Dose 1 (Not Done) during the window opening for eDiary reporting. The Investigator captured this event (Pain for 2 days – Day 3 and 4) in AE eCRF form.

Example 2. A subject reported Symptom Pain on Day 1 and 2 after Dose 1 using eDiary; missed reporting Symptom Pain at Day 3 and Day 4 during the window opening for eDiary reporting (not done). The Investigator captured this event in AE eCRF form.

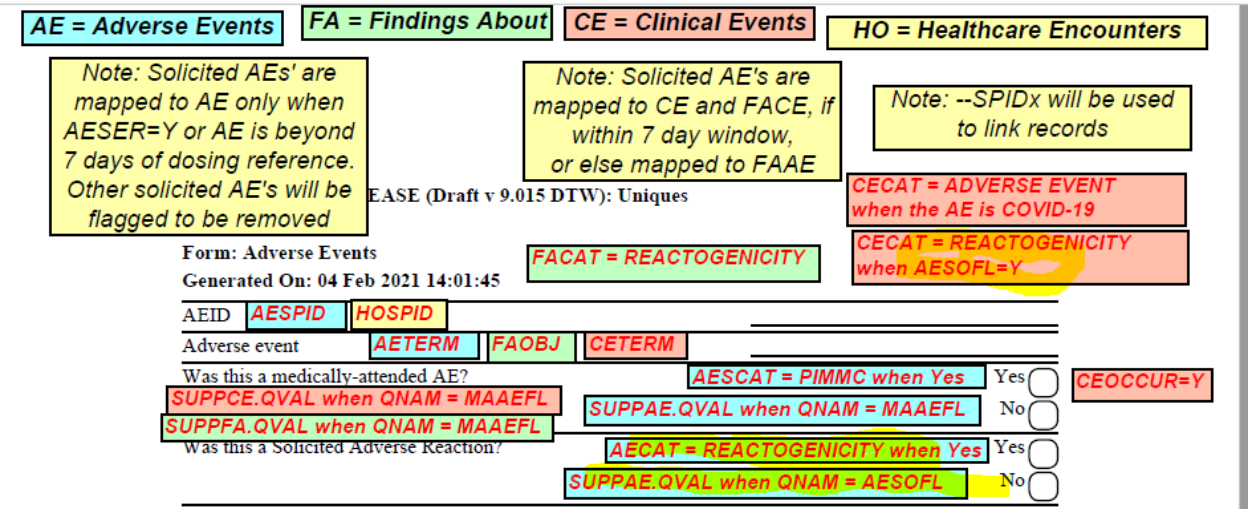
With our current mapping logic, this event is mapped to FACE, as well as kept in AE domain with AECAT=REACTOGENICITY and REMOVEFL=Y. Currently, Pain on Day 3 and 4 are not in topline CE records. For analysis, which is based on FACE, such events are included. No update in FACE is needed.

Below table lists our understanding of your suggestion, could you please clarify/confirm?

SYMPTON	Current mapping logic for CE (CURRENT) - Based on e-DIARY Only	CBER's suggestion (to discuss)
Example 1		
	DAY 1, 2 with No EVENT DAY 3, 4 with NOT DONE DAY 5, 6, 7 with No EVENT	
PAIN	CEOCCUR=NULL	CEOCCUR=Y
	CETOXGR = NULL	CETOXGR=2
	CEDTC = Date of DAY 7	CEDTC = Date of DAY 7
Example 2		
EVAL	STUDY SUBJECT	INVESTIGATOR
	DAY 1, 2 with EVENT DAY 3, 4 with NOT DONE DAY 5, 6, 7 with No EVENT	Day 3, Day 4 captured in AE
	CEOCCUR=Y	CEOCCUR=Y
	CETOXGR = EVENT Grade	CETOXGR = EVENT Grade
	CESTDTC = Date of Day 1	CESTDTC = Date of Day 1
	CEENDTC= Null	CEENDTC= Date of Day 4

	CEDTC = Date of DAY 7	CEDTC = Date of DAY 7
EVAL	STUDY SUBJECT	? *as this is a mix of* INVESTIGATOR and STUDY SUBJECT Our proposal: "STUDY SUBJECT/INVESTIGATOR"?

Regarding your request:
As these events are already flagged, please revise the category for these events back to 'Adverse Event' so that they are not confused with ongoing events.
Let's discuss the reactogenicity events as in the above two examples, which based on current logic, would have records in AE domain with AEACT=" REACTOGENICITY" and REMOVEFL="Y". These events are considered SAR and included in analysis of SAR; such events are not included in analysis of unsolicited AE.
We would like to seek further clarification:
Our understanding of your request is to keep this record in AE domain but to change AECAT from "REACTOGENICITY" (current) to "ADVERSE EVENT". Per CDISC guideline, we prefer to follow the annotation CRF mapping as shown below:



Please note these events are considered SAR and included in analysis of SAR; such events are not included in analysis of unsolicited AE.

Response to d:
In Study P301, SAR event captured on AE eCRF was identified through clinical review of AE preferred terms in correspondence of AR symptoms as collected on eDiary. For subject 300-2215, Lymphadenopathy was reported on Days 7-9 (AEDECOD="Lymphadenopathy"), but such preferred term was not identified in correspondence of the pre-defined SAR symptoms.

CBER Discussion Points:
□ The solicited term "underarm gland swelling or tenderness" should = axillary lymphadenopathy (and potentially other closely associated terms). We have provided a file for your reference showing the events that are reported in AE that may potentially be a SAR (see also item 6).
□ Please revise the datasets and resubmit.

Sponsor response: We agree with the comment that AEDECOD=”Lymphadenopathy” should be included in the pre-defined SAR symptoms. No further discussion is required.

ITEM #5
We have identified several instances where events reported in AE were erroneously categorized as ‘Reactogenicity’. For example, subject 305-2061 had a left knee torn meniscus with AECAT= Reactogenicity. Please ensure that all events in AE are characterized correctly and resubmit the AE dataset. Please note that none of the events correctly categorized as ‘reactogenicity’ should be included in ADAE.

Sponsor Response
The value “reactogenicity” in AECAT was assigned based on the following question on the AE eCRF page (screenshot below) if the answer to the question is ‘Yes’:

Part of the data review and cleaning was to identify if an event should be mapped to the CE when it was marked as SAR on the AE eCRF page. If there wasn’t enough detail provided to support the mapping to CE domain, sites were queried to provide more details or to make updates. At the time of the database lock and analyses, if queries were not fully resolved, the corresponding events were left in AE domain.

CBER Discussion Points:
□ Since this is an error in categorization in this example, please indicate the steps taken to ensure the datasets are correct and useable.
□ Please correct and resubmit AE.

Sponsor Response: We understand the request, however, as Per CDISC implementation standard, we should not change collected data. Data captured on AE eCRF form reflects investigator assessment. We propose, at analysis dataset level (ADaM), we drop AECAT from ADAE and add AAECAT=”ADVERSE EVENT”.
Please note that such event has been included in ADAE and the analysis of unsolicited AE. The proposed update would not have any impact in terms of analysis.

ITEM #8:
The duration of solicited adverse reactions appear to be calculated based on the number of unique days in which the event is reported. We are concerned that this underestimates the event duration (e.g. an event reported on Day 1 and Days 3 and 5 likely had lasted 5 days as opposed to 3). Please provide an analysis of solicited adverse reaction duration (as presented in Tables 14.3.1.4.1.1 and 14.3.1.4.1.2 of the CSR) where duration is calculated assuming that the event occurred continuously from the first day to the last day the event was reported (i.e. duration = last day – first day + 1), regardless of how many days the event was documented in between.

Sponsor Response

The duration of solicited adverse reaction (SAR) was calculated as the cumulative number of days that the solicited AR was reported, including the day of injection. We would like to use this opportunity to further explain/clarify the data derivation on duration of SAR. In this study, participants reported SAR using eDiary after each injection started within 7 days until the end of the SAR. If an AR is collected on AE eCRF but does not satisfies criteria of SAE or last beyond 7 days after injection, such AR would be mapped to CE and FACE domains, and flagged as removed in SUPPAE (SUPPAE.REMOVEFL=Y), correspondingly in ADAR and ADARP7D (section 5.2.3 and 5.2.4 of ADRG). If an AR is collected on AE eCRF and either satisfies criteria of SAE or last beyond 7 days after injection, such AR would be included in AE, CE, FAAE and FACE domains, and correspondingly in ADAE, ADAR and ADARP7D. These mapping logics have been implemented after a series of IR correspondence of SDTM mapping (Reference: IND 19745 SN0052 provided on 06-Oct-2020) as well as a teleconference held on 23-Oct-2020 between Moderna and CBER to discuss this topic. ADaM dataset ADARSUM includes summary data of ADAR and ADARP7D, contains total number of days with symptom grade > 0 that are derived from both ADAR andADARP7D. ADARSUM is one record per subject (SUBJID), per symptom (PARAMCD), and per vaccine/injection (ATPTREF), please refer to Section 4.2 Data Dependencies and Section 5.2.5 ADARSUM of ADRG). ADARSUM is the ADaM dataset that supports Summary of number of days of solicited adverse reaction after each injection provided in the CSR (Tables 14.3.1.4.1.1 and 14.3.1.4.1.2). We believe the provided summary of number of days (duration) of SAR in CSR presents the reported duration of SAR in this study. In this response, we are providing the requested analysis of summary of duration of SAR using the suggestion of the reviewer which represent a conservative approach of calculating the duration of SAR, in which duration = last date – first date +1 (tables 8-1 and 8-2). The results are summarized in Table 8-1 below with the source tables provided in in Module 5.3.5.1. Using this conservative approach, the results are consistent with the duration of SAR reported in CSR section 7.1.3: The solicited ARs in participants who received mRNA-1273 persisted for a median of 1 to 3 days after the first and second injection, with no apparent difference noted between the first and second injection.

CBER Discussion Points:

 We appreciate that you performed the sensitivity analysis, in the future please report duration as = last day – first day + 1.

Sponsor Response

No further discussion required at this TC.

ITEM #10:

We have identified instances where the start date or end date of an event is missing in CE even though FACE and FAAE had each day reported. For example, 301-2053 had underarm gland swelling on Day 2, 5, 6, and 7 in FACE and on Days 9-15 in FAAE. The event for this subject was also reported in AE from Days 6-16. This event is also inappropriately reported in ADAE (note that in addition to this event not being appropriate for reporting in ADAE, it is also reported from the subject's diary as indicated in FAAE). Please update the CE dataset with the appropriate dates/days.

Sponsor Response
Per CDISC VXUG1-1, CE START Date/END Date should be set to missing if they cannot be determined due to missing event report date. For subject 301-2053, we cannot determine the end date for this event. There were 2 records in FAAE on Day 16 and 17 with missing report. Therefore, the Sponsor couldn't tell which date is the end date.

CBER Discussion Points:
• While CBER agrees that the start date/end date can be null in CE if it cannot be determined, it was unclear if that was the case for this example.
• Why was the ongoing SAR reported in ADAE?
• Please correct all of these inconsistencies and resubmit the datasets.

Sponsor Response

Thank you for the follow-up comments. We have looked up this example (Subject 301-2053).
1. We would like to confirm that, for this example, the reason CEENDTC is null because last two records are 'Not Done", please see below for displays from FAAE last 2 records.
CE

USUBJID	CETERM	CETOXGR	CEDTC	CESTDTC	CEENDTC	CESER	CEDY	CESTDY	CEENDY	CEDUR	CETPT
mRNA-1273-P301-US301-2053	Underarm Gland Swelling or Tenderness	3	2020-08-12T17:27	2020-08-07T17:28				7	2	P4D	DAY 7

FAAE

USUBJID	FAOBJ	FAORRES	FASTAT	FAEVAL	FADTC	FATPT
mRNA-1273-P301-US301-2053	Underarm Gland Swelling or Tenderness	ANY USE OF PRESCRIPTION PAIN RELIEVER OR PREVENTS DAILY ACTIVITY		STUDY SUBJECT	2020-08-13T12:02	DAY 8
mRNA-1273-P301-US301-2053	Underarm Gland Swelling or Tenderness	ANY USE OF PRESCRIPTION PAIN RELIEVER OR PREVENTS DAILY ACTIVITY		STUDY SUBJECT	2020-08-14T12:01	DAY 9
mRNA-1273-P301-US301-2053	Underarm Gland Swelling or Tenderness	ANY USE OF PRESCRIPTION PAIN RELIEVER OR PREVENTS DAILY ACTIVITY		STUDY SUBJECT	2020-08-15T16:15	DAY 10
mRNA-1273-P301-US301-2053	Underarm Gland Swelling or Tenderness	ANY USE OF PRESCRIPTION PAIN RELIEVER OR PREVENTS DAILY ACTIVITY		STUDY SUBJECT	2020-08-16T23:08	DAY 11
mRNA-1273-P301-US301-2053	Underarm Gland Swelling or Tenderness	ANY USE OF PRESCRIPTION PAIN RELIEVER OR PREVENTS DAILY ACTIVITY		STUDY SUBJECT	2020-08-17T12:02	DAY 12
mRNA-1273-P301-US301-2053	Underarm Gland Swelling or Tenderness	ANY USE OF PRESCRIPTION PAIN RELIEVER OR PREVENTS DAILY ACTIVITY		STUDY SUBJECT	2020-08-18T14:20	DAY 13
mRNA-1273-P301-US301-2053	Underarm Gland Swelling or Tenderness	ANY USE OF PRESCRIPTION PAIN RELIEVER OR PREVENTS DAILY ACTIVITY		STUDY SUBJECT	2020-08-19T19:28	DAY 14
mRNA-1273-P301-US301-2053	Underarm Gland Swelling or Tenderness	ANY USE OF PRESCRIPTION PAIN RELIEVER OR PREVENTS DAILY ACTIVITY		STUDY SUBJECT	2020-08-20T13:26	DAY 15
mRNA-1273-P301-US301-2053	Underarm Gland Swelling or Tenderness		NOT DONE			DAY 16
mRNA-1273-P301-US301-2053	Underarm Gland Swelling or Tenderness		NOT DONE			DAY 17

2. The SPONSOR would like to clarify, in ADAE, "UNDERARM GLAND SWELLING" is not an ongoing SAR (row 1 below). The ongoing AE event for this subject is listed in row 3.

USUBJID	AECAT	AETERM	AEDECOD	AESTDTC	AEENDTC	AESTDY	AEENDY	AEENRF	AEREL
mRNA-1273-P301-US301-2053	REACTOGENICIT	UNDERARM GLAND SWELLING, LEFT ARM (VACCINATION ARM)	Lymphadenopathy	2020-08-11	2020-08-21	6	16		RELATED
mRNA-1273-P301-US301-2053	REACTOGENICIT	PAIN AT INJECTION SITE, LEFT ARM	Injection site pain	2020-08-06T16:00	2020-08-26	1	21		RELATED
mRNA-1273-P301-US301-2053	ADVERSE EVENT	LEFT ANTECUBITAL SPACE PAIN FROM VENIPUNCTURE	Vessel puncture site pain	2020-08-06T04:00		1		ONGOING	NOT RELATED