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)

Dear Dr. Olsen,
Below, please find the discussion points (related to your responses for the Items listed in Information Request # 5 communicated to you on September 24, 2021) for the teleconference scheduled on October 29, 2021, at 1:00 PM EST.
Please comment on the impact each item has on the solicited and/or unsolicited safety results.
Please update and resubmit the CBER Requested Tables (Batches #1 and #2) after addressing the items that impact the safety results (with particular attention to items 4a, 4d, 5, 6 and 10 [highlighted in yellow]), if applicable.

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 2:
In study P301, 25 subjects had AEs with an AEOUT= RECOVERED/RESOLVED or RECOVERED/RESOLVED WITH SEQUELAE, but an end date or collected duration is not provided. Please clarify if AEOUT is correctly reported (in which case an end date should be provided) or if AEOUT is incorrectly reported. Please correct the dataset accordingly.

Sponsor Response
The Sponsor would like to thank the reviewers' thorough review. The Sponsor has examined the 25 AE records with an AEOUT=RECOVERED/RESOLVED but an end date not provided. Out of these 25 AE records, 3 have been removed by the site personnel; 1 record has been updated with an end date provided; 1 record has been updated with AEOUT=NOT RECOVERED/NOT RESOLVED; sites have responded/provided comments for 4 records but were not able to update either AEOUT or provide end date; data queries are open for 2 records. The rest 14 AE records had issues on raw data handling, such partial dates were populated inconsistently. We will discuss how to fix this specific raw data issue.

CBER Discussion Points:
Please see discussion points listed under Item #3

Sponsor Response
In addition to the Sponsor's previous response regarding these 25 Subjects AEs, the Sponsor would like to clarify the documented and pre-defined BLA DBL scope that was put in place to enable the interim lock whilst the study was ongoing and data, including safety events, were being continually being collected and updated.

As previously communicated, the data cut-off (DCO) for the BLA DBL was the 26th March 2021, primarily driven by the 6-month median safety follow-up post dose 2 in Part A for both study cohorts.

For standard visits and safety calls, defined in the protocol schedule of events tables included in the protocol, this translated as any visit or safety call that had occurred up to and including the date of the DCO were in scope for full lock. Full lock of these data included as a pre-requisite: complete eCRFs, all queries resolved and closed, SDV (if sampled) and PI signed.

For safety data, in this interim lock context, a more nuanced approach was required, in order to define what could be fully clean and locked vs what could not, as data collection was ongoing. The process implemented for safety data, is outlined below:

- **AEs:**
  - Only AEs that are resolved at the time of the DCO will be locked
  - Coding review will be complete for all
  - Some AEs in scope may not be locked for the following reason:
    - If AE is a COVID AE and external lab/hospital records are not available at the time of DBL to answer queries and/or complete SDV
    - If an AE is the last log line in the log form and therefore needs to stay unlocked to allow for further data to be added

- If an AE is unable to be signed by the investigator because other log lines on the page (out of scope) are not clean and therefore the form is not available for signing
- If AE for other reasons other than the above cannot be locked as they are not fully cleaned in time for DBL with an acceptable rate of <1% not clean/locked

- **SAEs:**
  - SAEs (regardless of resolution status) will not be locked
  - SAEs that are resolved at the time of the DCO will have SDV* complete and will be PI signed. *Note SDV will only be possible for data fields present and supported by relevant records. As source records for SAEs will quite often come from third party hospitals it is understood that delays in receiving records may result in not all SDV being complete at the time of DBL.
  - Early terminated subjects that have SAEs will potentially fall under the same caveat as outlined above if external records are not present at the time of DBL to ensure that SAEs are only locked as complete reconciled data
  - SAE reconciliation as specified in the Data Validation Manual
  - Coding review will be complete for all

- **SAEs, MAAEs and COVID-19 cases ongoing at time of DCO or newly occurring between DCO and DBL**:
  - Data relating to these events will continue to be prioritized for cleaning and PI signature up to the DBL but will not be locked. All will be coded.

Of the 25 Subjects AEs, none were in scope for lock. 20 of the AEs were non-Serious and had no resolution date, without which they could not fall into the category for resolution by the DCO. The remaining 5 were serious, however also did not have resolution dates, hence were not in scope for full SDV, and no SAEs were in scope for lock, as are significant safety events and considered subject to change until study completion and the final DBL.

In summary, all 25 Subject's AEs were out of scope for data to be included in the BLA DBL that was not subject to change at a later date due to the ongoing context of the clinical trial.

We do not expect this to have an impact on the safety analyses.

TC Discussion:

In the initial response by Moderna, it was noted that out of these 25 AE records, 3 have been removed by the site personnel. CBER asked for further details on why these 3 were removed. Moderna will provide this information.

Post-Meeting Follow-up:

Please see below summary of the 3 AEs that have been removed from the live database since the BLA DBL and related datasets:

Record #	**1**	**2**	**3**
Subject ID	**US3262234**	**US3252516**	**US3252516**
AE Category	Reactogenicity	AE	AE
Reported Term for AE	Fatigue	Irregular heart beat	Irregular heart beat
Dictionary-Derived Term	Fatigue	Heart rate irregular	Heart rate irregular
Start Date/Time of AE	2020-09-23	N/A (none present at DBL)	T00:00
End Date	N/A (none present at DBL)	N/A (none present at DBL)	N/A (none present at DBL)
Serious	N	Y	Y
Causality	Related	Not Related	Not Related
Severity	Mild	Severe	Severe
Outcome	Recovered/Resolved	Recovered/Resolved	Recovered/Resolved
Sponsor Comments	This record has been deleted from the live database since the BLA DBL. It was deleted because it was already recorded in the Subject diary and no SAR reporting criteria was met and therefore should not have been recorded as an AE.	This record has been deleted from the live database since the BLA DBL. Record deleted because it was a symptom of another SAE.	This record has been deleted from the live database and was a duplicate of record #2. See comments for record #2.

ITEM 3:

In study P301, 6 subjects had AEs with an AEOUT= NOT RECOVERED/NOT RESOLVED, but an end date is provided. Please explain and correct where appropriate.

Sponsor Response
Data queries have been sent to the sites, one record has been updated to RECOVERED after data extraction for BLA.

CBER Discussion Points pertaining to Items #2 and #3:
• Please submit the revised datasets (SDTM and ADaM) pertaining to Items #2 and #3
• In addition to the revised AE datasets, CBER will need a separate document indicating which subjects were impacted by the revision. This can be provided before the resubmission of the datasets.

Sponsor Response
For these 6 events, 4 were in scope for DBL, i.e. AEs with resolution dates that were before DCO. These events cannot be fixed now that they are locked, but we do not think they have a significant impact on the assessment of the safety profile. For the remaining 2 events, they were not locked and have been queried and corrected for the next DBL. One event was an SAE so not in scope for lock and the other was an AE out of scope as resolution date was past the DCO.

TC Discussion:

CBER requested details on the 6 events. Moderna will provide.

Post-Meeting Follow-up:

Record #	**1**	**2**	**3**	**4**	**5**	**6**
Subject ID	**US3172322**	**US3192081**	**US3232048**	**US3292158**	**US3532212**	**US3692148**
AE Category	AE	AE	AE	AE	AE	AE
Reported Term for AE	Chronic obstructive pulmonary disease acute exacerbation	2 and 4 sternal border murmur	Increased salivary secretions	Exacerbation of COPD	Worsening back pain	Hypothyroidism
Dictionary-Derived Term	Chronic obstructive pulmonary disease	Cardiac murmur	Salivary hypersecretion	Chronic obstructive pulmonary disease	Back pain	Hypothyroidism
Start Date	2020-10-07	2021-01-15	2020-09-23	2021-04-07	2020-09-25	2021-02-08
End Date	2020-10-10	2021-03-11	2020-12-12	2021-04-09	2020-11-17	2021-04-12

Record #	1	2	3	4	5	6
Subject ID	**US3172322**	**US3192081**	**US3232048**	**US3292158**	**US3532212**	**US3692148**
Serious	N	N	N	Y	N	N
Causality	Not Related	Not Related	Not Related	Not Related	Not Related	Not Related
Severity	Mild	Mild	Moderate	Severe	Moderate	Moderate
Outcome	Not Recovered/ Not Resolved	Not Recovered/ Not Resolved	Not Recovered/ Not Resolved	Not Recovered/ Not Resolved	Not Recovered/ Not Resolved	Not Recovered/ Not Resolved
Sponsor Comments	Pending Query on AE to update outcome to resolved.	AE was in scope for lock and was locked with discordant data, which cannot be changed or queried now.	AE was in scope for lock and was locked with discordant data, which cannot be changed or queried now. In this situation, the participant died while the AE was ongoing. Site entered date of death as end date instead of leaving it ongoing at time of death.	AE was not in scope for lock. Data now updated to indicate resolved.	AE was in scope for lock and was locked discordant data, which cannot be changed or queried now. Per site the worsening pain was not resolved/recovered until the subject had the surgery which is the worsening spinal stenosis AE.	AE was not in scope for lock. Data now updated to indicate resolved.

ITEM #4:
Regarding ongoing solicited events:

a. We have found 2428 records in P301 in which reactogenicity events reported in CE and lasting longer than the 7-day evaluation period (CERFTDTC + 6) were not reported in the AE dataset, e.g. subject 300- 2231 had myalgia from Day 3-16 as reported in CE, but myalgia was not reported in AE for this subject's ongoing event following dose 1. Please update the AE dataset if these events should have been reported as ongoing. Please also provide revised summary safety data tables accordingly.

Response to a:
The Sponsor acknowledges this comment. Please note that:
• The e-Diary data (subsequently mapped to CE domain) were entered by study participants via electronic devices. Once the eDiary data was submitted, no change could be made.
• For study P301, the study sites have been instructed to enter the solicited ARs persisting beyond 7 days into the AE eCRF page (per Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review Guidance for Industry Technical Specifications Document).
• The records identified by CBER resulted from no corresponding AE eCRF entries for SAR persisting beyond 7 days. For each planned database lock, the study team tried very hard to clean the eCRF data as much as possible. However, given that the eDiary and eCRF are two independent systems, it may be possible that the entries into the 2 systems when needed do not match perfectly.

CBER Discussion Points:

- **As CBER only provided one example of the 2428 events identified, please clarify what is meant by "The records identified by CBER resulted from no corresponding AE eCRF entries for SAR persisting beyond 7 days."**
- **We have provided the list of records for you to use, but it also may not be all inclusive because of the lack of days/dates in CE used to identify them.**
- **Please update the CE and AE datasets as requested and resubmit.**

Sponsor Response:

TC Discussion:

Moderna agreed to do a detailed review of the 2428 events and provide a comprehensive assessment of these discrepancies. In the initial spot check, there were a number of terms that may be considered a match between the Diary and AE, but may not be included in the pre-specified Preferred Terms (PT) that corresponds to symptoms for SAR (i.e. 'lookup table'). In these instances, Moderna will review data and the pre-specified list of Preferred Terms. After review of these events, and the pre-specified PT for symptoms for SAR, we will conduct an impact assessment on the relevant analyses.

Post-Meeting Follow-up:
The Sponsor has so far reviewed about 75% of the list since last week.

In the meantime, an updated review of the Preferred Terms has been conducted in response to CBER's comments that the version of Preferred Terms corresponding to symptoms of SAR used for the BLA SDTM/ADaM datasets may be too restrictive. The updated lookup table (pre-specified Preferred Terms (PT) that corresponds to symptoms for SAR) is submitted with this response for your review.

Below is a summary of our assessment:
A total of 349 records were not included in CE domain due to lookup table being too restrictive.

Impact on analysis:

DOSE 1:

- Erythema: 3 Subjects on Placebo group and 5 subjects on mRNA-1273 not included in current analysis
- Underarm Gland Swelling or Tenderness - 1 Subject on Placebo and 2 subjects on mRNA-1273 not included in current analysis

DOSE 2:

- Erythema: 1 Subjects on Placebo group and 5 subjects on mRNA-1273 not included in current analysis
- Underarm Gland Swelling or Tenderness - 1 Subject on Placebo and no subject on mRNA-1273 not included in current analysis
- Myalgia: 1 Subject for Placebo, and no mRNA-1273 not included in current analysis
- Pain: 1 Subject for Placebo and no mRNA-1273 not included from analysis

	Actual Treatment for Period 01	Time Point Reference	Reported Term for the Clinical Event	Frequency Count
1	Placebo	DOSE 1	Erythema	3
2	Placebo	DOSE 1	Underarm Gland Swelling or Tenderness	1
3	Placebo	DOSE 2	Erythema	1
4	Placebo	DOSE 2	Myalgia	1
5	Placebo	DOSE 2	Pain	1
6	Placebo	DOSE 2	Underarm Gland Swelling or Tenderness	1
7	mRNA-1273	DOSE 1	Erythema	5
8	mRNA-1273	DOSE 1	Underarm Gland Swelling or Tenderness	2
9	mRNA-1273	DOSE 2	Erythema	5

Sponsor's Proposal: As the number of events not included in current analysis is small given the size of this study, the impact on analysis would be minimum. The Sponsor propose:

1. to re-submit the following domains with application of the updated lookup table:
   - CE
   - FACE
   - FAAE
   - AE
2. to re-submit the analysis of duration of SAR using CBER's definition of last day-first day+1. As the impact on other SAR analyses is minimum, the Sponsor propose not to re-run other analyses of SAR.

Does CBER agree?

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.

TC Discussion:

CBER agreed to Moderna's proposal.

Post-Meeting Follow-up

Moderna agrees to update CE domain as above, a detailed document on CE domain mapping including examples to help address comment 4b, 4c and 10 is included in this response. We would much appreciate CBER's feedback and comments before we implement.

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.

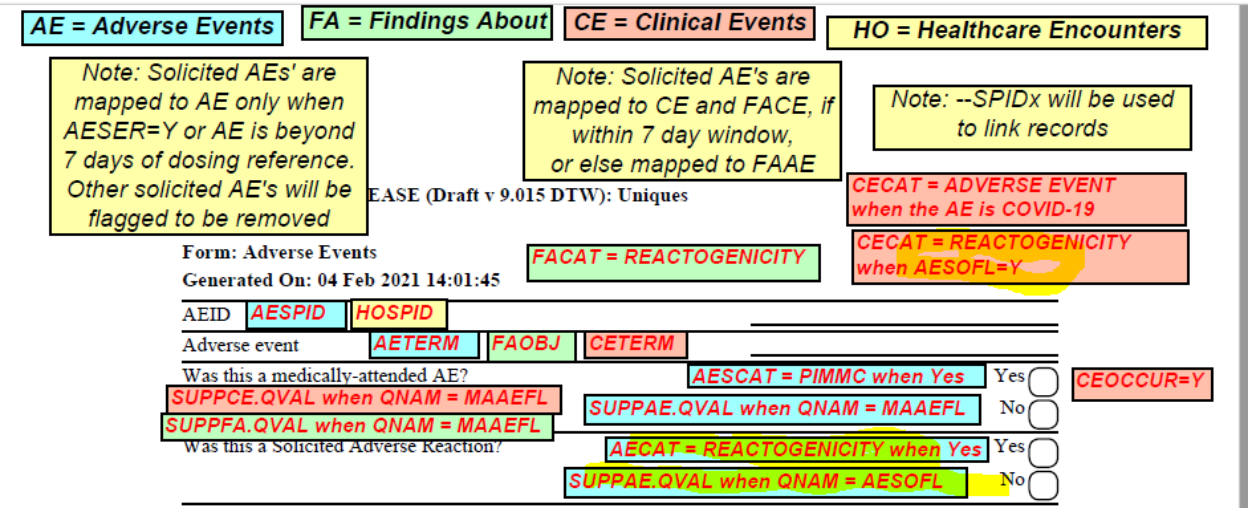
Example 2. A subject reported Symptom Pain on Day 1 and 2 after Dose 1 using eDiary; missed reporting Symptom Pain at Day 3 and Day 4 during the window opening for eDiary reporting (not done). The Investigator captured this event in AE eCRF form.

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.

TC Discussion:

For example #2 above, CBER suggested that if the event is both subject and investigator reported, that it should only have "INVESTIGATOR" in the CE domain. FAAE for more detailed information, but ideally should be FACE domain for solicited events. Investigator derived events go into subCE and another line can be added on why the investigator changes the assessment. This does not need to be corrected in the current dataset, but should be implemented in future submissions.

To correct the current dataset, the category "REACTOGENICITY" should be removed, if it is not ongoing and not an SAE. We will add an additional flag in the subAE that the category is changed.

ACTION: Moderna will provide a few examples to CBER for concurrence then will correct and resubmit.

Post-Meeting Follow-up:

Please find in the table below some suggestions based on example cases. Does CBER agree with the suggested AESCAT?

Study ID	AECAT	AESCAT	Comments	Data Selection
mRNA-1273- 301	REACTOGENICITY	MISSING REPORTED WITHIN 7 DAYS	Subject miss-reported before e-Diary data entering window closed	Set AESCAT to "MISSING REPORTED WITHIN 7 DAYS" where

	(AESOLFL= "Y")			AECAT="REACTOGENICITY " and REMOVEFL="Y"
		WRONG CATEGORY	AESOLFL is Y, but Event is not belonging Solicited Adverse Event	Set AESCAT to "WRONG CATEGOARY" where AECAT="REACTOGENICITY " and AELNKGRP is empty
		SAE/ONGOING-LOCAL SAE/ONGOING-SYSTEMIC	SAE or Ongoing Reactogenicity Event for Local Symptoms (Last beyond day 7) SAE or Ongoing Reactogenicity for Systemic Symptoms (Last beyond day 7)	Set AESCAT to "ONGOING-LOCAL" or "ONGOING-SYSTEMIC " where AECAT="REACTOGENICITY " and AELNKGRP is not empty

In the situation where there are both subject-reported event and investigator assessments contributing to CE topline records (example 2), regarding EVAL, at TC, CBER suggested to use "INVESTIGATOR". In order to keep traceability, the Sponsor would like to propose to "STUDY SUBJECT/INVESTIGATOR", does CBER agree?

d. We have identified events that are reported in the 'Events' datasets and 'Findings About' datasets but are not connected to provide a combined assessment for the event., e.g., subject 300-2215 had lymphadenopathy reported in CE (on Days 2-null), FACE (on Days 2 and 7), AE (on Days 7-9) and FAAE (2 rows provided for event but no days are indicated). In ADARSUM the number of days for underarm gland swelling or tenderness is 2 days, which appears to be incorrect. Please correct all events in which this situation may have occurred.

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. We will discuss internally.

TC Discussion:

CBER asked a follow-up question: "Were all cases of lymphadenopathy AE accounted for in SAR regardless if categorized as reactogenicity in AE dataset?" Moderna confirmed that is correct, they were all included in the analysis of the AE.

ACTION: Correct and resubmit.

Post-Meeting Follow-up

The Sponsor has provided the proper mapping/look-up table to our CRO and they are updating the datasets. Once the datasets are corrected for all issues discussed in this document, they will be resubmitted (2-3 week timeframe).

Overall Sponsor Response
The Sponsor has proactively taken actions to redesign the eCRF forms for future studies at the time of discussions with CBER on these related topics. A newly designed separate reactogenicity eCRF page has been added for new studies (other than P201 and P301) to streamline data collection and mapping to desired SDTM domains.

CBER Discussion Point:
CBER appreciates this proactive action. Could you please share the eCRF with us.

TC Discussion:

ACTION: Moderna to submit new eCRF for CBER comments.

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.

TC Discussion:

CBER questioned if even though the category was wrong, was the overcome and included in ADAE, and Moderna confirmed yes that was the case. An ADAE would need to satisfy 2 variables: AECAT=REACTOGENICITY and ARTERM=prespecified term. If both conditions were met, it was excluded from the analysis, and this was done for all reactogenicity categorized events.

To facilitate CBER's review, a subcategory AESCAT will be applied. Moderna will look at several examples an provide suggestions for CBER's review. For the future, Moderna will look for more stringent review criteria to catch if the category is incorrectly assigned on the eCRF to avoid this issue.

Post-Meeting Follow-up:

We have provided some examples in response to Item 4c. Please confirm if CBER agrees.

ITEM #6:
We have identified instances where CE was not updated with the investigator collected information. For example, subject 301-2023 had severe underarm gland tenderness on Day Page 6 – STN: 125752/2 29 (Dose 2 day 1) in AE, and in CE the event was reported as occurring Days 30-33 with moderate severity. In ADARSUM underarm gland tenderness number of days is reported as 4 instead of 5, and the worst analysis toxicity grade is moderate. Please correct all datasets where this may have occurred and update the safety analyses results where appropriate.

Sponsor Response
In Study P301, SAR event captured on AE eCRF was identified through clinical review of AE referred terms in correspondence of AR symptoms as collected on eDiary. For subject 301-2023, AEDECOD="Lymph node pain" and such preferred term was not identified in correspondence of the pre-defined SAR symptoms.

CBER Discussion Points:
• You may be excluding events in AE that are actually SARs by being too restrictive in your search. The solicited term "underarm gland swelling or tenderness" should = axillary lymphadenopathy (and potentially other closely associated terms or dictionary derived 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 4b).
• Please update the AE and CE datasets, and any other dataset if applicable.

Sponsor Response
No presubmitted response.

TC Discussion:

Moderna committed to take a deeper look at these events and correct if possible. For those that cannot be corrected, we will provide an impact assessment on the analyses.

Post-Meeting Follow-up
Moderna looked at these events and agree that some of the terms should be mapped to one of the prespecified symptom terms. This has been corrected and we will resubmit the AE and CE datasets. The updated mapping may impact our analysis results and we will resubmit the impacted analyses. This needs to be performed by our CRO PPD, and we expect this to take approximately 2-3 weeks. We will update the Agency with a firm submission date ASAP.

ITEM #7:

We have identified 3290 records where 'Reactogenicity' events reported in the AE dataset have either the start date or the end date not equal to the dates reported in CE. This impacts our ability to determine the actual dates/days of occurrence, and also becomes problematic in discerning which events are ongoing. For example, erythema was reported for subject 300-2107 in which the days of the event are 31-37 in CE and 31-36 in AE (Dose 2). Please ensure consistency of the dates/days reported for each reactogenicity event in CE and AE and correct where necessary.

Sponsor Response
As explained to response to Item 4 and 5, such "Reactogenicity" events in AE domain represent data collected on AE eCRF form; while CE domain includes topline events collected in eDiary. Given that the eDiary and eCRF are two independent systems, it may be possible that the entries into the 2 systems when needed do not match perfectly.

CBER Discussion Points:
** Please revise the data to ensure consistency of days/dates and resubmit the AE and CE datasets.**

Sponsor Response:

No presubmitted response.

TC Discussion:

Moderna explained the challenges with patient reported data (eDiary) and the same data being reported by the Investigator. eDiary data is unquery-able and unchangeable, and sometimes the Investigator after speaking with the participant, has a slightly different interpretation of the event, such as the start and end dates. It is not always possible for it to match. In situations where the data is very close, it is not queried, but in instances where it changes the interpretation of the safety event, or the two reports are very different, this is queried and resolved.

CBER further asked for details on how the communication between the eDiary/participant and the Investigator is handled, such as if the participant is not filling out the eDiary, if the Investigator or site reaches out to them.

ACTION: Moderna will provide a detailed description of the eDiary compliance process.

Post-Meeting Follow-up:

An eDiary review and compliance process was put into place on the 14th August 2021 for study, site, and subject level reactogenicity eDiaries. Please see below summary outline of the process for CRO and Site Staff:

- eDiary Dashboard for CRAs/RSMs, showing study, site, and subject level compliance, that refreshed daily
- eDiary Dashboard reviewed nightly by XUS study team for missing entries
- CRA/RSMs sent daily emails to sites according to the following schedule:
    - **MISSING EDIARY ENTRIES**
        - Either the entry is missing in totality – so outside of the allowable entry window.
            - Site needs to follow up with subject to confirm reason for missing entry (forgot, issues with app or phone, lack of wifi, etc.).
            - Site should provide mitigation steps should issue be with app/device or wifi. Site should retrain subject on proper eDiary

completion steps if subject forgot. Any discussions should be documented within the subject source.

- Or, if the pending entry window is still open, the site must reach out to the subject prior to the cut off of 11:59am their time zone, to ensure entry completed in the eDiary/app

- Schedule below for daily reminders regarding eDiary entry issues noted:
  - **MON & THUR** – Team to focus on specific subjects pending daily entry at the time the dashboard is run (3:00am EDT)
    - Email will be sent using template with cut/paste of subject list from excel pivot table
  - **TUE/WED/FRI** – Team to focus on multiple days in a row missing (to include most current day of time series)
    - Email will be sent using template for subjects who are missing multiple days in a row from day of dashboard update.

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

Does not need discussion.

TC Discussion:

There was no additional discussion of Item 8.

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

TC Discussion:

CBER explained their concern is that in AE, the investigator reported the event on Days 6-16. In the FAAE, this information should have been present and matching the AE, but it wasn't. The AE didn't convey to the FAAE, and it was untraceable. Also, if the event began on Day 6, within the eDiary assessment period, this should be in the ADAE, or be a SAR that is ongoing.

Moderna explained that the CE start/end date is based on eDiary data, but neither the AE data or the eDiary in this instance were complete. CBER responded that per guidance, in the CE and AE, the start and end dates should be the same, and this should have been an ongoing AE. The event should be reviewed with the totality of data. The eDiary start/end dates should be in the CE, but the investigator ongoing assessment should be incorporated to get the end date. ADAR and ADAE should be included in the analysis.

CBER asked if this would affect the duration of SAR analysis. Moderna confirmed it would not, that the FAAE was used for duration analysis in the ADAR dataset.

Post-meeting follow-up:

Please refer to the document "CE Mapping" included in this submission for examples for CBER to review and provide comments on.

Reference information on CDISC VXUG1-1 is included in this response:

- Therapeutic Area Data Standards User Guide for Vaccines- Version 1.1 (Provisional)
- Mapping examples are included in the Excel sheets