



**Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research (CBER)  
Office of Biostatistics and Pharmacovigilance (OBPV)  
Division of Analytics and Benefit Risk Assessment (DABRA)  
Analytics and Real-World Evidence Branch (ARWEB)**

**DIGITAL HEALTH TECHNOLOGY (DHT) CONSULTATION**

**Date:** 5/20/2025

**From:** Aneesha Sahu, PhD  
DHT Reviewer, ARWEB  
DABRA, OBPV, CBER, FDA

**To:** Sylvia Park, PhD  
Regulatory Program Manager  
CBER/OVRR/DRMRR/RRB2

**Through:** CDR Stephen Chang, PharmD, MPH  
Branch Chief, ARWEB  
DABRA, OBPV, CBER, FDA

**Subject:** BLA 125835/0

**Sponsor:** Moderna

**Application Type/Number:** BLA 125835/0

**Action Due Date:** 5/25/2025

**Document(s) Reviewed:**

- Mrna-1283-p301-synopsis
- Mrna-1283-p301-body
- Mrna-1283-p301-add-jpn-synopsis
- Mrna-1283-p301-add-jpn-body
- Mrna-1283-p301-16-1-1
- resp-stn-125835-0-ir-5-digi-hlth-tech-ed diary-19nov2024

**DHT product:** eDiary is used to collect solicited adverse events and safety data.

## **I. OVERALL REVIEW CONCLUSION:**

The overall integrity of the data captured by the electronic diary (eDiary) is acceptable. We arrive at this conclusion based on the following:

- 1) There were protocol deviations in regard to the eDiary missed eDiary entries
- 2) There were no major differences in overall eDiary compliance across the study groups/sites
- 3) Sensitivity analyses indicate that missing eDiary data did not impact safety conclusions.

**Use of DHT Summary:** The solicited administration site and systemic events are collected using a participant diary (eDiary) during the 7 days following administration of each dose of the study intervention. For solicited events that are still ongoing between Day 8 and Day 30, participants will also be instructed to record these in the eDiary, irrespective of intensity. There were no protocol deviations in relation to eDiary use.

Section 12.1, Page 104: “Compliance in completing solicited administration site and systemic event information was 98.7% participants in the Co-Ad group and 94.0% participants in the Control group”

Participants must use an eDiary for 7 days after receiving a study injection to record:

- Local reactions (redness, swelling, hardness) at the injection site
- Systemic reactions (e.g. body temperature)
- Any other adverse events (ARs)

To ensure accurate recording, participants will:

- Receive training on eDiary completion and thermometer/ruler usage at the dosing visit
- Record data in the eDiary starting 15 minutes after injection under site staff supervision
- Measure body temperature daily at the same time using a provided thermometer
- Self-assess for localized reactions (swelling, tenderness) under the arm on the same side as the injection.

## **II. Information Requests submitted by FDA:**

### **1.1 FDA Information Request:**

**1. Your protocol deviations frequently note missing entries in the 7-Day eDiary, specifically when two or more solicited entries are missing from evening entries on days 1 to 7. However, you have not provided data on compliance in completing solicited administration site and systemic event information in the eDiary. Please determine compliance rates for these entries, broken down by each dose and overall, and clearly define the criteria used to measure compliance.**

**For a more detailed analysis, consider including tables with the following information:**

- a) **Proportion of participants who completed eDiary entries for each reporting day for each solicited reaction (Exposed Set).**
- b) **Proportion of participants who completed eDiary entries for each solicited reaction for Day 1 through Day 3, Day 1 through Day 5; and Day 1 through Day 7 consecutively post-vaccination.**

#### **1.1.1 Sponsor Response:**

In clinical study mRNA-1283-P301, eDiary compliance was available through 2 compliance reports offered by the eDiary vendor, (b) (4), within the EDC system. The following, (b) (4) eDiary reports provide the following information related to eDiary compliance:

- **ePRO Up to Day 7 Diary Data:** – This report shows line-by-line responses by participant and by timepoint for all instances of the 7 Day eDiary data collection period for each trial participant. This report pulls data in real time from the collected 7 Day eDiary responses that are available in the electronic data capture (EDC) electronic case report forms (eCRFs) associated with the 7 Day eDiary data. This report also displays dosing date/time information and the date/time the specific eDiary data was submitted to the EDC system.
- **eCOA Compliance Report-7 Day eDiary** – This report shows a cumulative compliance for all subjects and is itemized as:
  - 7 Day eDiary compliance at the site level,
  - Site level compliance by dose, and
  - Trial Participant level Compliance.

#### **1.1.2 FDA Response: We find this response acceptable.**

### **1.2 IR submitted by the FDA**

**Please also include sensitivity analyses of eDiary safety data, for example:**

- a. **Sensitivity analysis of percentages of subjects with solicited local and systemic adverse events by max intensity within 7 days following each vaccination.**
- b. **To explore whether safety data (reported through adverse events rates) is not impacted by missing eDiary data entries, please provide sensitivity analyses that include the denominator from the following groups: subjects who completed all eVRC reports Days 1-3, Days 3-6, and Days 1-7.**

#### **1.2.1 Sponsor Response**

- a. The percentages of participants with solicited local and systemic adverse reaction by maximum reported toxicity grade within 7 days were presented in the mRNA-1283-P301 CSR (please refer to Table 14.3.1.1.1.1: Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Injection by Grade (Overall and by Age Groups) Solicited Safety Set.).

- b. The Sponsor conducted the requested sensitivity analyses of solicited local and systemic adverse reaction within 7 days by maximum reported toxicity grade for participants who completed eDiary during Days 1-3, Day 3-6 and Days 1-7. Refer to the following tables:
- i. Table 14.3.1.1.1.50: Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Injection by Worst Toxicity Grade Participants who completed eDiary entries from Day 1 to Day 7
  - ii. Table 14.3.1.1.1.51: Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Injection by Worst Toxicity Grade Participants who completed eDiary entries from Day 1 to Day 3
  - iii. Table 14.3.1.1.1.52: Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Injection by Worst Toxicity Grade Participants who completed eDiary entries from Day 3 to Day 6

A summary of solicited local and systemic adverse reactions of solicited safety set and sensitivity analyses sets are provided below in Table 1.

The sensitivity analyses results of solicited local and systemic adverse reaction are consistent with the main analysis results based on solicited safety set. Review of the reported solicited adverse reactions, including local and systemic adverse reactions, according to the different eDiary compliance groups (Day 1 to 3, Day 3 to 6, and Day 1 to 7) requested by the agency, did not show any relevant differences in the percentage of reported events, when comparing to the overall reported solicited adverse reactions using the solicited safety set.

Of note, one Grade 4 solicited AR (fever; occurred on Day 2 and resolved on the same day) was reported in the mRNA-1273.222 group in study mRNA-1283-P301 (solicited safety set). However, this Grade 4 solicited AR does not appear in the Day 1-3 table (Table 14.3.1.1.1.51), nor the Day 1-7 table (Table 14.3.1.1.1.50), as the participant did not complete the eDiary on Day 3. The omission of this Grade 4 event does not impact the overall reactogenicity/tolerability conclusion.

### **1.2.2 FDA response: We find this response acceptable.**

### **III. REVIEW SUMMARY:**

Overall, our analysis of the eDiary data for BLA 125835 indicates no significant issues or concerns with eDiary safety data reporting. The overall integrity of the data captured by the electronic diary (eDiary) is acceptable. This conclusion is based on several factors, including:

- High compliance rates: Participants demonstrated high compliance with eDiary entries, with 98.7% of participants in the Co-Ad group and 94.0% of participants in the Control group completing their eDiary entries.
- Low rate of missing data: The sponsor's analysis showed that there was no significant impact on safety data due to missing eDiary entries.
- Sensitivity analyses: The sponsor conducted sensitivity analyses to assess the potential impact of missing eDiary data on safety outcomes and found that the results were consistent with the main analysis.