

# Comprehension for OTC Naloxone (CONFER) Pivotal Label Comprehension Study – Task 3 Study Report

## Executive Summary

Prevention and treatment of opioid overdose is an urgent public health priority, and the FDA recognizes the need to improve access to naloxone for the emergency treatment of known or suspected overdoses until emergency medical help arrives. To address this public health crisis, the FDA is facilitating the development of labeling for an over-the-counter (OTC) version of naloxone, which is currently only available by prescription. The FDA developed a draft model drug facts label (DFL) and an accompanying simple pictogram that could be placed next to the DFL to correspond with the DFL directions, and awarded a contract for the conduct of the label comprehension study.

The pivotal Comprehension for OTC Naloxone (CONFER) label comprehension study (LCS) was a single-visit, open-label, multicenter study designed to evaluate comprehension of the key communication objectives on a novel over-the-counter OTC DFL for naloxone. The study enrolled 710 male and female participants who completed the interview, including 1) adult opioid users (heroin and prescription opioids) and associates (friends and family of opioid users) 18 years of age or older (Group 1-2); 2) adolescent all comers 15-17 years of age (Group 3); and 3) adult all comers 18 years of age or older (Group 4). Of these, 237 participants (33.4%) were of low literacy. Of the eight primary comprehension endpoints, six met the prespecified threshold for correct/acceptable responses. The endpoint, “call 911 immediately” did not meet the prespecified lower bound (LB) threshold of 90%, with 641/710 correct/acceptable responses (90.3% [CI 87.9, 92.4]). In addition, a three component composite endpoint also did not meet the prespecified LB threshold of 85%, largely driven by incorrect responses for “call 911 immediately”. While it is concerning that some participants did not correctly respond for this clinically critical endpoint, the endpoint was close to meeting the threshold, and results were very conservatively coded. In addition, results from a sensitivity analysis combined with the analysis of incorrect responses suggest that comprehension of this endpoint may be higher than was captured, particularly in the population most likely to use naloxone.

We conclude that the results of this study are acceptable to support use of the tested naloxone DFL in the OTC setting. A sponsor submitting an NDA for an OTC version of naloxone must still modify and test the instructions for use that are specific to their product as part of the DFL, and demonstrate adequate comprehension through LCS and human factors testing as appropriate. In addition, we recommend that sponsors further assess whether comprehension of instructions to call 911 immediately in the DFL may be improved. If further testing of alternative language to the DFL demonstrates improved comprehension of the “call 911 immediately” endpoint, the alternative language may be utilized in the sponsor’s DFL. However, if alternatives do not

demonstrate improved comprehension of instructions to call 911 immediately, the language tested in this study is considered adequate and may be utilized.

## **1. Introduction and Background**

### **1.1. Overview**

With the number of overdose deaths from prescription and illicit opioids doubling from 21,089 in 2010 to 42,249 in 2016, FDA is committed to looking at new ways to increase the availability of naloxone as part of the strategy to combat the opioid epidemic. This potentially life-saving treatment is a critical tool for individuals, families, first responders and communities to help reduce opioid overdose deaths. FDA recognizes that emergency treatment of known or suspected opioid overdose is an urgent public health priority. In order to advance these efforts, there is still a need to improve access to naloxone.

Community and state programs have increased availability through standing prescription programs with accompanying training; however, nonprescription status could further increase availability. For nonprescription status, consumers need to understand how to use a drug safely and effectively without the help of a learned intermediary. Sponsors usually conduct consumer behavior testing, such as label comprehension studies, to demonstrate that consumers understand how to use a drug with just the Drug Facts label information. Naloxone sponsors stated that the need to do consumer behavior studies was a barrier to seeking approval to move naloxone over the counter.

To address this barrier, FDA proposed a novel approach: the FDA would design a model naloxone Drug Facts label (DFL), design a label comprehension study (LCS), and issue a contract for an experienced consumer behavior research firm to do label comprehension testing.

This is the first time the FDA has developed a model DFL and designed a label comprehension study (LCS). An FDA team undertook the challenging task to reduce prescription (Rx) Full Prescribing Information and patient instructions down to the essentials for a DFL. To do this, the team solicited input from the addiction treatment community and multiple FDA experts about what is truly essential for consumers to do in an opioid overdose emergency. Additional challenges in the development of a naloxone DFL compared to other OTC drugs are the life-threatening nature of the condition; the emergency, high-stress situation in which the instructions for use are likely to be needed; the person administering the drug may not be the purchaser; and the person administering the drug may be reading the instructions for use for the first time when the product is being administered. Therefore, a decision was made to simplify the DFL further to just information needed for purchase decision and absolute minimum directions for emergency use. Pictograms were also developed to aid in comprehension.

Upon completion of the draft DFL, FDA arranged for the conduct of a label comprehension consumer behavior study via competitive contracting. After completion of the study, a complete

study report and data sets were submitted to FDA. The study was reviewed by an independent team of FDA reviewers not directly involved in the conduct of the study. The review team included reviewers from clinical, social science, and statistical disciplines.

The study was designed to be conducted in three phases (“tasks”) in order to foster an iterative process for label improvements throughout testing, culminating in the pivotal study, Task 3. Results from this study will be published to help ease the process for Sponsors to submit an application to move naloxone from Rx to over-the-counter (OTC). The following is an integrated review of the Task 3 study results by the independent review team.

## **1.2. Data Sources**

On October 3, 2018, RTI/Concentrics sent an encrypted message with all files for the CONFER Task 3 project. The submission for Task 3 included a PDF report with appendices, transcripts, ADaM and SDTM data files, and data tabulations.

Per Division of Biostatistics VII (DBVII) request, Research Triangle Institute (RTI)/Concentrics sent an updated Task 3 report with Statistical Analysis Plan (SAP) deviations on October 9, 2018. Following an information request from DBVII sent on October 23, 2018, RTI/Concentrics submitted on October 29, 2018 an updated annotated Case Report Form, a reviewer guide, and SAS programs. Following information requests from DBVII sent on November 20, 2018 and November 29, 2018, RTI/Concentrics submitted a final dataset with verbatims on December 5, 2018. This final dataset included additional subjects enrolled in the study but not included in the final analysis as well as additional variables collected at screening stage such as reason for disposition.

## **2. Study Design and Analysis Plan**

### **2.1. Study Design**

#### **Study Overview**

The study was a single-visit, open-label, multicenter label comprehension study (LCS) designed to evaluate comprehension of the key communication objectives on a novel over-the-counter (OTC) Drug Facts label (DFL) for naloxone. The study was entitled, “Comprehension of Over-the-Counter Naloxone for Emergency Response (CONFER): Pivotal Label Comprehension Study (Task 3),” and was designed as a pivotal label comprehension study in a population of: 1) adult opioid users (heroin and prescription opioids) and associates (friends and family of opioid users) 18 years of age or older (Group 1-2); 2) adolescent all comers 15-17 years of age (Group 3); and 3) adult all comers 18 years of age or older (Group 4).

The purpose of the study was to conduct individual, in-person interviews as part of a quantitative pivotal comprehension study to evaluate whether the communication objectives established for

the DFL were understood by a significant number of participants. The study was conducted by two Contract Research Organizations (CROs), RTI International and Concentrics Research LLC, from May 21, 2018 (date first participant completed) to August 2, 2018 (date last participant completed), and was performed at six market research facilities, eight community-based organizations (CBOs), and other data collection locations.

To reflect the two approved forms of naloxone available in consumer-friendly format (nasal spray and auto-injector), two label versions were prepared with pictograms for each form. The label content related to the particular dosage form was included as a placeholder and was not tested as part of the study. The remaining content was identical for both DFL versions for naloxone. Participants were assigned to a DFL version based on a simple rotation and were then provided with the assigned DFL on an 8.5" x 11" sheet of paper to read independently and at their own pace.

Initially, a cognitive walkthrough method was used to allow the participant to talk out the sequential steps outlined on the DFL. The cognitive walkthrough was included because of the unique labeling which included a sequence of five pictograms and critical actions. The cognitive walkthrough enables the participant to describe the process more naturally and per the labeling that describes the steps in a more naturalistic sequence. This evaluation was followed by a more structured label comprehension interview that included direct and third-party scenario questions about communication objectives in the labeling.

Data were analyzed based on the Statistical Analysis Plan (SAP) and pre-established coding rules. Responses for the cognitive walkthrough and comprehension interview (initial response and follow-up response) were considered in the analysis to determine a correct or incorrect response.

### **Key Inclusion/Exclusion Criteria**

For participation in the study, all subjects were required to sign informed consent (adults 18 years and older) or assent form (Adolescents age 15-17 years). Signed parental permission was required for adolescent participants.

#### ***Criteria for Inclusion:***

Individuals were included in the study if the following criteria were met:

#### **Group 1-2: Adult opioid users and associates, 18 or older<sup>1</sup>**

- Male or female, of any race

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<sup>1</sup> In prior tasks, Group 1 (prescription opioid users/associates) and Group 2 (heroin users/associates) were recruited separately. Because a large number of participants were found to be dual users, a decision was made to combine them into one overall group for Task 3 (Groups 1-2).

- Age 18 years or older
- User: An individual who reported prescription opioid and/or heroin use in the past 90 days or was in treatment for prescription opioid and/or heroin use
- Associate: An individual who did not report prescription opioid or heroin use in the past 90 days *and* was not in treatment for prescription opioid use *and* knew someone who used prescription opioids or heroin or was in treatment for prescription opioid or heroin use.

Group 3: Adolescent all comers, 15-17

- Male or female, of any race
- Age 15-17 (the study team did not enroll anyone who would be turning 18 before August 31, 2018)

Group 4: Adult all comers, 18 or older

- Male or female, of any race
- Age 18 or older

***Criteria for Exclusion:***

Key criteria for exclusion of individuals from the study included the following:

- Individuals who have been ordered by a judge to participate in treatment (*Group 1-2 only*)
- The individual or anyone in their household was currently employed by any of the following (*Groups 1-2 and 4 only*):
  - a) a marketing or marketing research company
  - b) an advertising agency or public relations firm
  - c) a pharmacy or pharmaceutical company
  - d) a manufacturer of medicines
  - e) a managed care or health insurance company
  - f) a healthcare practice or hospital emergency room
  - g) FDA, HHS, RTI, or Concentrics
- The individual had ever been trained or employed as a health care professional (*Groups 1-2 and 4 only*)
- The individual had participated in any research study in the past 12 months or an earlier phase of this study in the past 2 years (*Groups 1-2 and 4 only*)
- The individual could not read, speak, and/or understand English
- The individual normally wore corrective lenses, contacts, or glasses to read and did not have them with him or her at time of the interview
- The individual had other eye problems that would prevent reading

- The individual appeared too impaired (e.g., under the influence of drugs or alcohol) at the time of the interview as observed by study staff. All study staff received training on how to identify signs of impairment.

## **Recruitment**

For adult opioid users and associates (Groups 1-2), the study team partnered with community-based organizations (CBOs) in each of the four data collection locations (Chicago, Illinois; Charleston, West Virginia; San Francisco, California; and Raleigh/Durham/Vance County, North Carolina) to recruit participants. Participants were recruited through CBOs, advertisements posted online (Craigslist, Facebook, online forums), and participant referral.

Recruitment for adolescent all comers (Group 3) and adult all comers (Group 4) was conducted on a rolling basis for each of six cities where data collection took place: Tampa, Florida; Dallas, Texas; Los Angeles, California; Indianapolis, Indiana; Raleigh, North Carolina; and New York, New York by market research sites with experience recruiting low-literacy and hard-to-reach populations.

## **Study Objectives**

### ***Primary Objectives:***

The primary objectives of the study were composed of the communication objectives on the DFL with the highest potential for clinical consequence if they were not well understood. Thus, the eight primary objectives were to evaluate how the label communicated the following messages:

- Step 1 (Check)
- Step 2 (Give the first dose)
- Step 3 (Call 911 immediately)
- Step 4 (Watch and give: Repeat doses)
- Step 5 (Stay with the person until help arrives)
- Steps 1-3 (Check, give the first dose, call 911) – composite objective
- Use for treatment of opioid overdose
- Signs of overdose: If you think someone used an opioid and the person will not wake up or is not breathing well, these are signs of an overdose.

Target thresholds were established a priori for the primary endpoints as follows.

Table 1. Target Thresholds

Primary Endpoints	Target Lower Bound Threshold
Check for a suspected overdose.	85%
Give the first dose of this medicine.	85%
Call 911 immediately.	90%
Repeat doses every few minutes until fully awake or until emergency personnel arrive.	85%
Stay with the person until ambulance arrives.	85%
Product use: Use for treatment of opioid overdose	80%
Signs of overdose—If you think someone used an opioid, and the person will not wake up or is not breathing well, these are signs of an overdose.	80%
Check for a suspected overdose AND give the first dose of this medicine AND call 911 immediately (composite endpoint)	85%

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The communication objective of highest importance was to call 911. Therefore, the success threshold for this objective (*Call 911 immediately*) was set at a lower bound (LB) of 90%. The remaining four steps were also important to providing urgent care to the victim; these thresholds were set at an LB of 85% for each individual step, and the composite score of Steps 1-3. Two messages on the DFL (product use for opioid overdose and description of the signs of an overdose) were important for the rescuer to understand, and the thresholds were set at 80%.

**Secondary Objectives:**

The five secondary objectives were to evaluate how the label communicated the following messages:

- Some people may experience symptoms when they wake up, such as shaking, sweating, nausea, or feeling angry.
- Determine whether it is safe to keep giving doses.
- Give another dose if the person becomes very sleepy again.
- Order of the “call 911” step.
- Perform steps 1-5 (Check, give a dose, call 911, watch and give, stay)

No target thresholds were set for the secondary endpoints.

Additional qualitative and exploratory questions were asked about the meaning of an opioid, navigation, naloxone familiarity, and timing between doses.

## **Study Design**

Once participants arrived at a designated site and signed the Informed Consent (signed parental permission form for Group 3), the Rapid Estimate of Adult Literacy in Medicine (REALM) test was administered to adult participants, and the REALM-Teen test was administered to adolescent participants (Group 3) to classify the participant as normal (score  $\geq 61$ ) or low literacy (score  $\leq 60$ ). As part of the study design, literacy was enriched to include 30% low-literacy participants (adults and adolescents) to ensure that there would be an adequate number represented in the study to assess comprehension in the low-literacy population. After the REALM test, the interviewer assigned the participant to a DFL version (rotating administration method: injector or nasal). The participant was then given a DFL on an 8"x11" paper and asked to read it at his or her own pace. After the participant completed his or her review of the DFL, the interviewer returned to the room, and the interview began.

The interview questions (cognitive walkthrough and overdose scenarios) were the same across all groups. The interview questionnaire was composed of two parts:

- **Cognitive Walkthrough**: The first part of the interview consisted of a cognitive walkthrough of the label. The participant was asked to imagine that he or she was in a situation where he or she had to use this product on a friend and to talk aloud to explain what he or she would do based on the label ("Imagine you had to use this product on a friend. Talk out loud and tell me what you would do, based on the label."). The trained interviewer documented the steps mentioned by the participant along with the order they were mentioned on the cognitive walkthrough checklist.

**Label Comprehension**: The label comprehension portion of the questionnaire followed the cognitive walkthrough and was composed mainly of open-ended third-party scenario questions; however, direct questions were also included. The interviewer presented a series of third-person scenarios, each of which was followed by a closed-ended question that required the participant to make a judgment about what to do next (e.g., give the first dose, call 911). After providing a response, the interviewer asked the participant to explain his or her answer ("Why do you say that?") to obtain the rationale for their response, which was intended to enable the research team to assess comprehension of the survey questions and DFL instructions. The initial and follow-up questions were used to make an overall assessment of whether the response was correct or incorrect. Once a participant moved on to the next question, he or she was not permitted to change answers



to any previous questions. The questions were presented in a mixed order and not in the order that the communication objectives appeared on the label.

## **Labels**

There was one label version created for each route of administration (auto-injector and nasal spray) for this testing. The labels were rotated between an auto-injector and a nasal spray product in the pictograms; all other wording on these two DFLs was identical. Labels L1-injector and L2-Nasal were used for testing and are shown in Figures 1 and 2 below. In order to copy and paste the DFLs into this report, adjustments were made to size and shape. Therefore, it should be noted that areas that appear blurry in the figures below are not blurry on the actual DFLs utilized in this study.

Figure 1: L1- Injector DFL

<b>Drug Facts</b>	
<b>Active ingredient (in each XX)</b> Naloxone hydrochloride X mg.....	<b>Purpose</b> Emergency treatment of opioid overdose
<b>Uses</b>	
<ul style="list-style-type: none"> <li>To "revive" someone during an overdose from many prescription pain medications or street drugs such as heroin</li> <li>This medicine can save a life</li> </ul>	
<b>Directions</b>	
<p><b>1 CHECK</b></p>	<p><b>Step 1: CHECK:</b></p> <ul style="list-style-type: none"> <li><b>CHECK</b> for a <b>suspected overdose</b>: the person will not wake up or is very sleepy or not breathing well</li> <li>yell "Wake up!"</li> <li>shake the person gently</li> <li>if the person is not awake, go to Step 2</li> </ul>
<p><b>2 GIVE</b></p>	<p><b>Step 2: GIVE 1<sup>st</sup> dose</b></p> <ul style="list-style-type: none"> <li><b>GIVE</b> the 1<sup>st</sup> dose of this medicine</li> <li>place the injector on the <b>LEG</b> above the knee and press down</li> </ul>
<p><b>3 CALL</b></p>	<p><b>Step 3: CALL</b></p> <ul style="list-style-type: none"> <li><b>CALL 911</b> immediately after giving the 1<sup>st</sup> dose</li> </ul>
<p><b>4 WATCH/GIVE</b> 2-3 minutes</p>	<p><b>Step 4: WATCH &amp; GIVE</b></p> <ul style="list-style-type: none"> <li><b>WAIT</b> 2-3 minutes after the 1<sup>st</sup> dose to give the medicine time to work</li> <li>if the person <b>wakes up</b>: Go to Step 5</li> <li>if the person does <b>not wake up</b>: <ul style="list-style-type: none"> <li><b>CONTINUE TO GIVE</b> doses every 2-3 minutes until the person wakes up</li> <li>it is safe to keep giving doses</li> </ul> </li> </ul>
<p><b>5 STAY</b></p>	<p><b>Step 5: STAY</b></p> <ul style="list-style-type: none"> <li><b>STAY</b> until ambulance arrives: even if the person wakes up</li> <li><b>GIVE</b> another dose if the person becomes very sleepy again</li> <li>You may need to give all the doses in the pack</li> </ul>
<b>Warnings</b>	
When using this product some people may experience symptoms when they wake up, such as shaking, sweating, nausea, or feeling angry. This is to be expected.	
<b>Other information</b> - store at room temperature +[advise insert tamper evident statement here]	
<b>Inactive Ingredients</b>	
<b>Questions?</b> (phone number, website)	

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Figure 2: L2-Nasal DFL

<b>Drug Facts</b>	
<b>Active ingredient (in each XX)</b> Naloxone hydrochloride X mg	<b>Purpose</b> Emergency treatment of opioid overdose
<b>Uses</b>	
<ul style="list-style-type: none"> <li>To "revive" someone during an overdose from many prescription pain medications or street drugs such as heroin</li> <li>this medicine can save a life</li> </ul>	
<b>Directions</b>	
<div style="border: 1px solid black; padding: 5px;"> <p><b>1 CHECK</b></p> </div> <div style="border: 1px solid black; padding: 5px;"> <p><b>2 GIVE</b></p> </div> <div style="border: 1px solid black; padding: 5px;"> <p><b>3 CALL</b></p> </div> <div style="border: 1px solid black; padding: 5px;"> <p><b>4 WATCH/GIVE</b></p> <p>2-3 minutes</p> </div> <div style="border: 1px solid black; padding: 5px;"> <p><b>5 STAY</b></p> </div>	<p><b>Step 1: CHECK</b> if you suspect an overdose:</p> <ul style="list-style-type: none"> <li><b>CHECK</b> for a suspected overdose: the person will not wake up or is very sleepy or not breathing well</li> <li>yell "Wake up!"</li> <li>shake the person gently</li> <li>if the person is not awake, go to Step 2</li> </ul> <hr/> <p><b>Step 2: GIVE</b> 1<sup>st</sup> dose</p> <ul style="list-style-type: none"> <li><b>GIVE</b> the 1<sup>st</sup> dose of this medicine</li> <li>insert in <b>NOSE</b> and press</li> </ul> <hr/> <p><b>Step 3: CALL</b></p> <ul style="list-style-type: none"> <li><b>CALL 911</b> immediately after giving the 1<sup>st</sup> dose</li> </ul> <hr/> <p><b>Step 4: WATCH &amp; GIVE</b></p> <ul style="list-style-type: none"> <li><b>WAIT</b> 2-3 minutes after the 1<sup>st</sup> dose to give the medicine time to work</li> <li>if the person <u>wakes up</u>: Go to Step 5</li> <li>if the person does <u>not wake up</u>: <ul style="list-style-type: none"> <li><b>CONTINUE TO GIVE</b> doses every 2-3 minutes until the person wakes up</li> <li>it is safe to keep giving doses</li> </ul> </li> </ul> <hr/> <p><b>Step 5: STAY</b></p> <ul style="list-style-type: none"> <li><b>STAY</b> until ambulance arrives: even if the person wakes up</li> <li><b>GIVE</b> another dose if the person becomes very sleepy again</li> <li>You may need to give all the doses in the pack</li> </ul>
<b>Warnings</b>	
When using this product some people may experience symptoms when they wake up, such as shaking, sweating, nausea, or feeling angry. This is to be expected.	
<b>Other information</b> • store at room temperature • [advise insert tamper evident statement here]	
<b>Inactive Ingredients</b>	
<b>Questions?</b> (phone number, website)	

## 2.2. Statistical Methods

The following sections provide a brief overview of the statistical methods used for the pivotal LCS. A full statistical analysis plan (SAP) was pre-specified and finalized prior to conduct of the Task 3 pivotal study.

### 2.2.1. Sample Size

The sample size in Task 3 was fixed at 710 subjects (430 for Groups 1&2, 140 for Group 3, and 140 for Group 4).

### 2.2.2. Scoring of Endpoints

Participant responses were to be evaluated as “correct,” “acceptable,” or “incorrect”. Some endpoints were scored solely based on responses to the cognitive walkthrough or based on a response to a label comprehension question alone; some endpoints were scored based on a combination of a label comprehension response and responses from the cognitive walkthrough.

The SAP defined how an overall score of “correct” or “acceptable” was derived for each endpoint (Q1-Q11). No mitigation process was planned beyond adjudications of an “acceptable” response discussed in the SAP. Adjudication of unanticipated responses was described in Tables C1-C4 of Appendix 1. For each primary and secondary endpoint, an overall comprehension score was calculated as a composite of the scoring of the answers in part a, part b and the cognitive walkthrough if appropriate. Refer to Table 2 and Table 3 below for the pre-specified definition of an overall correct, acceptable or incorrect score. Note that in Table 2 and Table 3, for those cells that have more than one score such as “Correct/Acceptable/Incorrect”, the overall scores were determined by post-hoc mitigation.

Table 2. Overall Scoring of Comprehension Questions based on Q a and Q b (Q1-Q7)

Follow-up Response (Q b) (“Why do you say that?”)	Initial Response (Q a)		
	Q a: Correct	Q a: Acceptable	Q a: Incorrect
Q b: Correct	Correct	Correct	Correct/Acceptable/Incorrect
Q b: Acceptable	Acceptable	Acceptable	Acceptable/Incorrect
Q b: Incorrect	Incorrect/Acceptable	Incorrect/Acceptable	Incorrect

Source: Table 8 from the SAP

Table 3. Overall Scoring of Comprehension Questions based on Q a and Q b and Cognitive Walkthrough (Q3 and Q5)

	<b>Overall Response from Q a and b: Correct</b>	<b>Overall Response from Q a and b: Acceptable</b>	<b>Overall Response from Q a and b: Incorrect</b>
<b>Walkthrough: Correct</b>	Correct	Acceptable	Acceptable
<b>Walkthrough: Acceptable</b>	Correct	Acceptable	Acceptable/Incorrect
<b>Walkthrough: Incorrect</b>	Acceptable/Incorrect	Acceptable/Incorrect	Incorrect

Source: Table 9 from the SAP

### 2.2.3. Statistical Analyses

#### *Demographics*

Demographic variables, such as gender, age, race, education, and income were reported using descriptive statistics.

#### *Primary Analysis*

The primary analysis consisted of estimating the comprehension rate for each primary and secondary endpoint in the analysis population, which is comprised of those eligible who signed a consent form and who answered at least one question. In the primary analysis, each rate was defined as the number of subjects with an overall correct or acceptable response divided by the number of subjects in the analysis population. Two-sided 95% confidence intervals (CIs) were computed using an exact method (Clopper-Pearson). If the lower bound (LB) for the comprehension rate was equal to or greater than a pre-specified success threshold, it was considered that the objective was comprehended. Refer to Table 1 in Section 2.1 for the pre-specified success thresholds for each of the primary endpoints. No success thresholds were set for the secondary endpoints.

#### *Secondary and Exploratory Analyses*

For the secondary analysis, success for primary and secondary endpoints was defined more strictly as an overall correct score, i.e. strictly correct response. Note that the report's definition of a strictly correct response as 'a correct response at the initial and follow-up probe' deviates from the SAP's definition; however, the results in the report followed the SAP's definition and classified overall correct responses as 'strictly correct'.

For qualitative and exploratory objectives, counts and percentages were reported for each response category.

### *Deep-Dive Analysis for “Call 911 immediately”*

A detailed analysis of participants who provided incorrect responses to the “call 911 immediately” objective was conducted overall, for each user segment (Groups 1-2, 3, and 4), and for opioid users (all users in Group 1-2). The analysis also compared incorrect responders with correct responders in demographics, geographic locations, and whether incorrect responders were more likely to give incorrect responses to other questions.

### *Subgroup Analyses*

For the subgroup analyses, the primary and secondary analyses were repeated

- by user segment,
- by literacy level,
- by recruitment site,
- by familiarity with naloxone, and
- by opioid subgroup

## **3. Study Results**

### *Demographic Characteristics*

A total of 720 participants were initially enrolled in the study, and 710 completed the interview. As shown in Table 4 below, this included 473 of normal literacy; low literacy participants were adequately represented (33.4%, n=237). Of the 710 participants, there were similar proportions of males (~51%) and females (~49%). The mean age of the participants was 41.6 in the adult opioid user and associate population (Group 1-2), 47.2 in the all-comers population (Group 4), and 16.0 in the adolescent user group (Group 3), with 20% of the total study population being younger than 18 years old. Participants were predominantly white (~65%) and African American (~31%); ~10% were Hispanic. The adult educational levels were primarily composed of those who had at least finished high school (84%).

Table 4. Baseline and Demographic Characteristics of Consented Participants

Variable	Overall n (%)	Normal Literacy n (%)	Low Literacy n (%)
<b>REALM Category</b>			
Low literacy	237 (33.4%)	0 (0.0%)	237 (100.0%)
Normal literacy	473 (66.6%)	473 (100.0%)	0 (0.0%)
<b>User Segment</b>			
Opioid user/associate (Group 1-2)	430 (60.6%)	294 (62.2%)	136 (57.4%)
Adolescent all comers (Group 3)	140 (19.7%)	88 (18.6%)	52 (21.9%)
Adult all comers (Group 4)	140 (19.7%)	91 (19.2%)	49 (20.7%)
<b>Highest Education Level*</b>			
Less than high school	93 (16.3%)	42 (10.9%)	51 (27.6%)
High school graduate	227 (39.8%)	143 (37.1%)	84 (45.4%)
Some college (no degree)	140 (24.6%)	110 (28.6%)	30 (16.2%)
Postsecondary nondegree award	17 (3.0%)	15 (3.9%)	2 (1.1%)
2-year college degree	14 (2.5%)	6 (1.6%)	8 (4.3%)
4-year college degree	28 (4.9%)	23 (6.0%)	5 (2.7%)
Some post-graduate	34 (6.0%)	30 (7.8%)	4 (2.2%)
Post-graduate degree	17 (3.0%)	16 (4.2%)	1 (0.5%)
<b>Hispanic or Latino</b>			
Yes	70 (9.9%)	43 (9.1%)	27 (11.4%)
No	638 (89.9%)	428 (90.5%)	210 (88.6%)
Prefer not to answer	2 (0.3%)	2 (0.4%)	0 (0.0%)
<b>Race (multiple responses allowed)</b>			
White	464 (65.4%)	365 (77.2%)	99 (41.8%)
Black or African American	221 (31.1%)	89 (18.8%)	132 (55.7%)
American Indian/Alaska Native	20 (2.8%)	17 (3.6%)	3 (1.3%)
Asian	5 (0.7%)	5 (1.1%)	0 (0.0%)
Native Hawaiian/other Pacific Islander	5 (0.7%)	4 (0.8%)	1 (0.4%)
Prefer not to answer	20 (2.8%)	14 (3.0%)	6 (2.5%)

<b>2017 Household Income*</b>			
Less than \$20,000	344 (60.4%)	216 (56.1%)	128 (69.2%)
\$20,000-\$34,999	93 (16.3%)	65 (16.9%)	28 (15.1%)
\$35,000-\$49,999	30 (5.3%)	24 (6.2%)	6 (3.2%)
\$50,000-\$74,999	31 (5.4%)	25 (6.5%)	6 (3.2%)
\$75,000-\$99,999	23 (4.0%)	19 (4.9%)	4 (2.2%)
\$100,000-\$149,999	11 (1.9%)	10 (2.6%)	1 (0.5%)
\$150,000 or more	12 (2.1%)	11 (2.9%)	1 (0.5%)
Prefer not to answer	21 (3.7%)	12 (3.1%)	9 (4.9%)
Don't know	5 (0.9%)	3 (0.8%)	2 (1.1%)
<b>Gender</b>			
Male	359 (50.6%)	218 (46.1%)	141 (59.5%)
Female	351 (49.4%)	255 (53.9%)	96 (40.5%)
<b>Age (years)</b>			
Mean (SD)	37.6 (15.6)	36.6 (14.8)	39.7 (17.0)
Minimum	15.0	15.0	15.0
Median	36.5	35.4	41.8
Maximum	79.0	79.0	76.0
<b>Age (Categorical, in years)</b>			
Younger than 18	140 (19.7%)	88 (18.6%)	52 (21.9%)
18 to 24	35 (4.9%)	25 (5.3%)	10 (4.2%)
25 to 34	133 (18.7%)	103 (21.8%)	30 (12.7%)
35 to 44	150 (21.1%)	116 (24.5%)	34 (14.3%)
45 to 54	137 (19.3%)	80 (16.9%)	57 (24.1%)
55 to 64	84 (11.8%)	46 (9.7%)	38 (16.0%)
65 or older	31 (4.4%)	15 (3.2%)	16 (6.8%)
<b>Normally wearing corrective lenses, contacts, or glasses to read</b>	309 (43.5%)	202 (42.7%)	107 (45.1%)
<b>Total</b>	710	473	237

Source: Table 8-1 of pivotal Label Comprehension Study. The statistical reviewer verified all results, except for age and gender where there was a discrepancy by one subject and 'Normally wearing corrective lenses, contacts, or glasses to read' where there was a discrepancy by 5 subjects..

\* Question was not asked to adolescents.

Columns may not sum to 100% due to rounding.



## Primary Analysis

### Primary Endpoints

As detailed in Table 5 and Table 6 below, in the total analysis population (N=710), of the eight primary endpoints listed above, six met or exceeded the LB threshold, and seven exceeded the point estimate (PE) scores of 90%.

*Table 5. Comprehension of Primary Endpoints Tested Solely via Cognitive Walkthrough*

<b>Endpoint</b>	<b>Target LB Threshold</b>	<b>Overall n/N (%) (LB, UB)*</b>	<b>Normal Literacy n/N (%) (LB, UB)*</b>	<b>Low literacy n/N (%) (LB, UB)*</b>
Composite of cognitive walkthrough (Steps 1-3)	85%	Correct+Acceptable 576/710 (81.1%) (78.0, 83.9)	Correct+Acceptable 416/473 (87.9%) (84.7, 90.7)	Correct+Acceptable 160/237 (67.5%) (61.2, 73.4)
		Strictly Correct 566/710 (79.7%) (76.6, 82.6)	Strictly Correct 414/473 (87.5%) (84.2, 90.4)	Strictly Correct 152/237 (64.1%) (57.7, 70.2)
Step 1: Check for overdose	85%	Correct+Acceptable 680/710 (95.8%) (94.0, 97.1)	Correct+Acceptable 463/473 (97.9%) (96.1, 99.0)	Correct+Acceptable 217/237 (91.6%) (87.3, 94.8)
		Strictly Correct 680/710 (95.8%) (94.0, 97.1)	Strictly Correct 463/473 (97.9%) (96.1, 99.0)	Strictly Correct 217/237 (91.6%) (87.3, 94.8)
Step 2: Give a dose	85%	Correct+Acceptable 697/710 (98.2%) (96.9, 99.0)	Correct+Acceptable 472/473 (99.8%) (98.8, 99.9)	Correct+Acceptable 225/237 (94.9%) (91.3, 97.4)
		Strictly Correct 680/710 (95.8%) (94.0, 97.1)	Strictly Correct 463/473 (97.9%) (96.2, 98.9)	Strictly Correct 217/237 (91.6%) (87.3, 94.8)
Step 3: Call 911 immediately	90%	Correct+Acceptable 641/710 (90.3%) (87.9, 92.4)	Correct+Acceptable 448/473 (94.7%) (92.3, 96.6)	Correct+Acceptable 193/237 (81.4%) (75.9, 86.2)
		Strictly Correct 604/710 (85.1%) (82.2, 87.6)	Strictly Correct 425/473 (89.9%) (86.8, 92.4)	Strictly Correct 179/237 (75.5%) (69.5, 80.9)

Source: Table 9-1 of pivotal Label Comprehension Study; results reproduced by the statistical reviewer.

\*Lower and upper two-sided 95% exact (Clopper-Pearson) confidence intervals.

Table 6. Comprehension of Primary Endpoints Tested via Comprehension Questionnaire and Cognitive Walkthrough (if needed)

Endpoint	Target LB Threshold	Overall n/N (%) (LB, UB)*	Normal Literacy n/N (%) (LB, UB)*	Low literacy n/N (%) (LB, UB)*
Stay with the person until help arrives	85%	Correct+Acceptable 647/710 (91.1%) (88.8, 93.1)  Strictly Correct 524/710 (73.8%) (70.4, 77.0)	Correct+Acceptable 450/473 (95.1%) (92.8, 96.9)  Strictly Correct 374/473 (79.1%) (75.1, 82.7)	Correct+Acceptable 197/237 (83.1%) (77.7, 87.7)  Strictly Correct 150/237 (63.3%) (56.8, 69.4)
Repeat dose every 2-3 minutes until person is fully awake or until emergency personnel arrive*	85%	Correct+Acceptable 666/710 (93.8%) (91.8, 95.5)  Strictly Correct 500/710 (70.4%) (66.9, 73.8)	Correct+Acceptable 460/473 (97.3%) (95.4, 98.5)  Strictly Correct 369/473 (78.0%) (74.0, 81.7)	Correct+Acceptable 206/237 (86.9%) (81.9, 90.9)  Strictly Correct 131/237 (55.3%) (48.7, 61.7)
Use for treatment of opioid overdose	80%	Correct+Acceptable 685/710 (96.5%) (94.9, 97.7)  Strictly Correct 427/710 (60.1%) (56.4, 63.8)	Correct+Acceptable 464/473 (98.1%) (96.4, 99.1)  Strictly Correct 334/473 (70.6%) (66.3, 74.7)	Correct+Acceptable 221/237 (93.2%) (89.3, 96.1)  Strictly Correct 93/237 (39.2%) (33.0, 45.8)
If you think someone used an opioid and the person will not wake up or is not breathing well, these are signs of overdose	80%	Correct+Acceptable 671/710 (94.5%) (92.6, 96.1)  Strictly Correct 641/710 (90.3%) (87.9, 92.4)	Correct+Acceptable 464/473 (98.1%) (96.4, 99.1)  Strictly Correct 451/473 (95.3%) (93.0, 97.1)	Correct+Acceptable 207/237 (87.3%) (82.4, 91.3)  Strictly Correct 190/237 (80.2%) (74.5, 85.1)

Source: Table 9-2 of Pivotal Label Comprehension Study; results reproduced by statistical reviewer.

\*Lower and upper two-sided 95% exact (Clopper-Pearson) confidence intervals.

\*Note that the contractor incorrectly scored ‘Call911’ as acceptable for this endpoint

### Step 3: call 911 immediately

The primary endpoint that did not meet the target 90% LB threshold was Step 3: **call 911 immediately** (90.3% PE; 88% LB). Nearly two-thirds (63.8%, 44 of 69) of incorrect responses involved calling 911, but not immediately after giving the dose. Common reasons for incorrect responses were as follows:

- Stating they would call 911 but only if the person did not wake up, if the person did wake up, or after waiting to see if the dose worked (n=44)
- Did not mention calling 911 at all (n=25)

Importantly, 44 participants mentioned calling 911 as a result of an outcome, the person not waking up, or after the person did wake up. In the Study Report, it is noted that this suggests some degree of vigilance on the part of the rescuer to evaluate the status of the individual first (waking up/not waking up), then calling 911.

Lower scores for this endpoint were primarily driven by low-literacy participants (193/237; 81.4% correct + acceptable), those who were not previously familiar with naloxone (284/324; 87.7% correct + acceptable), and heroin and/or Rx-opioid associates (18/22; 81.8% correct + acceptable). Specifically, 81.4% (193/237) of low literacy participants had correct + acceptable responses for **Step 3: Call 911 immediately** compared to 94.7% (448/473) of normal literacy participants. In addition, 92.5% (356/385) of those participants who were familiar with naloxone had correct + acceptable responses for **Step 3: Call 911 immediately** compared to 87.7% (284/324) of those participants who were not familiar with naloxone. This suggests that individuals who would be more likely to seek out and use this product may have some familiarity with the drug and be more likely to complete this important step as instructed.

Subgroup analyses for this endpoint by opioid subgroup revealed that Rx-opioid users, heroin users, and illicit fentanyl users had higher percentage of correct + acceptable responses (92.4%, 254/275; 90.0%, 289/321; and 93.8%, 135/144; respectively) compared to Rx-opioid associates (82.4%, 14/17) and heroin associates (75.0%, 12/16). However, these results must be interpreted with caution due to the small total base sizes for the associate group (n=22).

The Deep-Dive Analysis for “Call 911 immediately” revealed following key learnings:

- Incorrect responders were more likely to be of low literacy, less than high school education, black/African American, and from the Chicago research location. The contractors noted that differences within race and within site may be caused by a higher proportion of low literacy in these participant groups.
- After removing the endpoints directly related to calling 911, incorrect call 911 responders scored about 13% lower on average across the remaining primary and secondary endpoints than correct responders.

#### Composite Endpoint (cognitive walkthrough: Steps 1-3)

The primary endpoint that did not meet the 85% target threshold and had a point estimate score below 90% (81.1% PE, 78% LB) was the composite endpoint (composite of cognitive walkthrough: Steps 1-3). The majority of incorrect responses included not calling 911 or calling 911 after waiting; however, some incorrect participants stated they would wait for the

ambulance, even if not specifying to call 911. Reasons for the 134 incorrect responses were summarized as follows:

- Mentioned calling 911 but only after waiting a few minutes (not immediately) – 26.1 %; 35 of 134
- Mentioned giving the dose and waiting with the person but did not mention calling 911 – 24.6%; 33 of 134
- Mentioned giving a dose and watching/giving additional doses but did not mention calling 911 – 15.7%; 21 of 134
- Did not mention checking the person at all –13.4%; 18 of 134
- Did not mention administering a dose (only stated would check, would check and call 911, or would check and call 911 and wait for an ambulance) – 9.7%; 13 of 134
- Mentioned only check and give a dose (nothing else) – 5.2%; 7 of 134
- Mentioned giving a dose before checking the person – 5.2%; 7 of 134

An additional subset of incorrect participants (n=44) was classified into one of the categories listed previously and did not mention calling 911 but qualified it by saying they would call 911 only “if the person did not wake up” or only “if/once the person did wake up.”

### Secondary Endpoints

There were five secondary endpoints. In the total analysis population (N=710), point estimates (PEs) for four of the secondary endpoints were 80% or higher. Scores for the secondary endpoints ranged from 74.6% to 95.6%, as follows:

- Safe to keep giving doses (95.6% PE)
- Give another dose if the person becomes very sleepy again (92.3% PE)
- Order of the “call 911” step (85.2% PE)
- Some people may experience symptoms when they wake up, such as shaking, sweating, nausea, or feeling angry (82.4% PE)
- Steps 1-5 (check, give a dose, call 911, watch and give, stay) – composite objective (74.6% PE). Common reasons for the 180 incorrect responses for the composite objective were as follows:
  - Mentioned only four of the five steps – 53.9%; 97 of 180
  - Mentioned only three steps – 25.0%; 45 of 180

The results indicated that these messages were well understood by the participants with point estimates exceeding 80% for all secondary endpoints with the exception of the composite score for getting all five steps correct, which was slightly lower (74.6% PE). More than half of the incorrect participants stated four of the five steps correctly (53.9%; 97 of 180), and more than three quarters of the incorrect participants stated at least three of the five steps (78.9%; 142 of 180). Importantly, of the participants who mentioned at least three steps, nearly all of them

(84.5%; 120 of 142) mentioned the two important interventions of checking the victim for an overdose and giving a first dose.

### Exploratory and Qualitative Endpoints

Two exploratory endpoints related to navigation of the DFL and prior familiarity with naloxone identified the following:

- Navigation: More than 80% of participants (83.2%, n=591) found the DFL easy to navigate with no confusion; very few mentioned issues locating information (0.7%, n=5) or confusion with words (2.0%, n=14) or pictures (0.7%, n=5). The main confusion mentioned was with instructions on how to use or administer the actual product (2.5%, n=18). As pointed out by the contractors in the Study Report, this was expected because there was no intention to provide explicit instructions on how to use the nasal spray or the auto-injector; this will be managed by manufacturers for their specific product.
- Familiarity with naloxone
  - Previously aware of naloxone: Approximately half (53.4%, n=379) of participants self-reported awareness of naloxone before the study.
  - Previously used naloxone: Just below one-third (30.0%, n=213) of participants indicated that they or a friend had previously used naloxone.
  - Of the participants who were familiar with naloxone, nearly all of them (90.9%, 350 of 385) were opioid users or associates.

Two qualitative endpoints were also explored to assess whether participants reported the specific time required to wait before re-dosing, as well as how well the term “opioid” was understood.

- Wait 2-3 minutes between doses: Nearly all (95.1%) participants provided at least one response in the cognitive walkthrough or one of the pre-determined comprehension questions (Question 3, Question 6, or Question 7) that specified waiting 2-3 minutes between giving doses; 3.2% (n=23) of participants did not mention any time, whereas 1.3% (n=9) referenced 1.5-4 minutes or a few/couple minutes.
- What is an opioid: Participants provided varying responses when asked to define what “opioid” meant; however, the majority did correctly understand the drug categories for which naloxone is effective. The contractors concluded that, although the definition of the term “opioid” is not universally understood, most individuals in the population understood the general concept and definition. The most common responses were as follows (not mutually exclusive):
  - Heroin – 21.8%, n=155
  - Pain medicine (but did not specify prescription) – 21.8%, n=155
  - Drug/type of drug (non-specific) – 12.4%, n=88
  - Prescription pain medications – 11.0%, n=78
  - Drug with opiates/made from opiates – 10.4%, n=74

- Medicine/drug derived from poppy/poppypseed/opium – 7.3%, n=52
- Narcotic/narcotic drug/pain medicine/narcotic – 6.8%, n=48
- Opium – 5.4%, n=38
- Prescription pain medications or street drugs such as heroin – 5.2%, n=37

### *Subgroup Analyses*

Primary and secondary analyses were repeated by user segment, literacy level, recruitment site, familiarity with naloxone, and opioid subgroups. Key learnings were as follows:

- User Segment: Comprehension scores were similar across the user segments, although adolescent all comers (Group 3) scored higher (~4-9 percentage points) on three endpoints (composite of Steps 1-3, order of “call 911” step, stay with the person until help arrives) than the opioid users and associates (Group 1-2). Group 1-2 participants scored higher than adult all-comers (Group 4) for the product use endpoint.
- Literacy: Comprehension scores were lower (~5-20 percentage points) for participants with low literacy.
- Recruitment site: Comprehension scores were more frequently lower (~5-10 percentage points) for participants in Chicago (Groups 1-2), Los Angeles, and Tampa (Groups 3 and 4), as compared with other research sites. This appears to have been caused by the higher proportion of low literacy in those sites.
- Familiarity with Naloxone: Participants familiar with naloxone scored higher on five endpoints (give first dose, call 911 immediately, safe to keep giving doses, product use, signs of overdose) as compared with those who were not familiar with naloxone. This prior knowledge of the drug may have helped to reduce potential concern around the drug itself and the concept of administering in an emergency situation to an overdose victim.
- Opioid Subgroups: Comprehension scores were similar across the opioid user groups (prescription opioid users, heroin users, illicit fentanyl users), although there were high levels of overlap across these groups. However, it is noted that results from the opioid subgroups must be considered with caution because of the small base sizes (total base size for associates: n=22).

### *Post-hoc and Sensitivity Analyses by FDA*

After receipt of the final Task 3 report, FDA reviewed the contractor’s scoring algorithms as well as responses in the final dataset or transcripts to assess the quality of the contractor’s scoring (See **Appendix 1**). The FDA reviewers conducted the following post-hoc and sensitivity analyses:

- A stratified random sample (stratified by site) of 10% of subjects was generated to check if the review team agreed with the coding of responses. The team compared the responses to three selected questions (“Check” step from cognitive walkthrough, Question 1, and

Question 6) from the interview transcriptions to the coded responses for each subject in the sample. No issues were detected in the coding methods for the selected questions.

- An additional analysis was performed for the “Call 911 immediately” endpoint for this review. It should first be noted that upon FDA’s recommendation a very conservative method of analyzing responses for coding was utilized for the cognitive walkthrough. All incorrect “call 911 immediately” responses from the cognitive walkthrough were analyzed along the same conservative coding guidelines provided by FDA, and it was determined that 3 responses could be re-coded to correct. Additionally, a sensitivity analysis was conducted for mentions of “call 911” at Question 3 and Question 5 of the LCS interview. That analysis revealed that among the 69 subjects who had an incorrect response for “call 911” in the cognitive walkthrough, 17 of them mentioned calling 911 in their answer to Question 3, 14 of them mentioned calling 911 in their answer to Question 5, and 9 of them mentioned calling 911 in their responses to both Questions 3 and 5. These results indicate that the comprehension levels of “call 911” are higher than what was captured in the results from the cognitive walk though.
- An additional analysis was performed for the composite (steps 1-3) endpoint for this review. The reviewer assessed two types of incorrect coding for the composite a) correct for the composite but acceptable/incorrect for any of steps 1-3, and b) acceptable for the composite but incorrect for any of steps 1-3. The reviewer found that:
  - 10 participants were scored as correct for the composite but acceptable/incorrect for any of the step 1-3;
    - 1 of them was scored as incorrect in Step 1: check for overdose
    - 8 of them were scored as acceptable in Step 2: give a dose
    - 1 of them was scored as acceptable in Step 3: call 911 immediately
  - No error was found for the participants scored as acceptable for the composite.Although the errors from the contractor are concerning, the reviewer concluded that 10 incorrect responses (1.4%) will not change the conclusions for the composite (steps 1-3) endpoint.
- A sensitivity analysis was conducted for the endpoint 'Repeat dose every 2-3 minutes until person is fully awake or until emergency personnel arrive' tested in Question 3. For this endpoint, the contractor incorrectly scored a mention of ‘Call 911’ as acceptable, which was not pre-specified in the SAP. Based on a review of the transcripts, among those who did not mention Call 911 in the cognitive walkthrough but did in Question 3a, only 3 subjects were inappropriately scored as acceptable for 'Repeat dose every 2-3 minutes until person is fully awake or until emergency personnel arrive'. The reviewer concluded that this inappropriate scoring will not change the conclusion related to Question 3.

## 4. Summary and Conclusions

### 4.1. Summary of Issues

#### Biostatistics

There were no major statistical issues found in the LCS study. The primary and secondary analyses methods (i.e. comparing the lower bound of the two-sided exact 95% CI to a pre-specified threshold) were valid, and the statistical analyses followed the pre-specified statistical analysis plan in general. The statistical reviewer was able to reproduce most results for disposition, demographics, and primary and secondary analyses using the submitted data. Below, we summarize several issues that we identified in our review.

- Some endpoints ('Call 911 immediately', 'Composite (Step 1-3)', and 'Repeat dose every 2-3 minutes until person is fully awake or until emergency personnel arrive') that involved complex scoring algorithms were not appropriately scored. For the validity of the scoring algorithms by the contractors, we defer to the Social Scientist. However, several post hoc sensitivity analyses by the FDA reviewers show that these inappropriate scorings did not impact the study conclusion.
- Target thresholds were not met for two primary endpoints
  - For the primary endpoint 'Call 911 immediately', the observed comprehension rate was 90.3% with 95% CI (88%, 92%). Thus, the LB of the 95% CI was lower than the target threshold of 90%. However, FDA sensitivity analyses show that many of the participants who did not mention "Call 911" in the cognitive walkthrough mentioned it in their response to Question 3 or Question 5. Therefore, it appears that most participants understood that they need to call 911 at some point in time, although some thought calling 911 only as a result of an outcome such as the person did not wake up.
  - For the primary endpoint 'Composite of Steps 1-3', the observed comprehension rate was 81.1%, with 95% CI (78%, 84%). Thus, the LB of the 95% CI was lower than the target threshold of 85%. However, the majority of incorrect responses for this endpoint related to not calling 911 immediately.

#### Social Science

Overall, I agree with the conclusion that the Naloxone DFL performed well in the LCS study. The point estimates for all primary endpoints exceeded 80% correct comprehension, and the primary endpoints were met or nearly met based on the a priori success thresholds. The subgroup analysis did not reveal any populations of significant concern related to comprehension of key messages of the DFL; scores for participants of lower education and literacy scored lower, as expected. The endpoints that did not meet the a priori thresholds consisted of a composite endpoint for the first three steps of the cognitive walkthrough and the "call 911 immediately" endpoint. Composite endpoints are difficult to meet and are not commonly utilized in LCS



testing unless there is a specific safety or efficacy reason to do so. For the purposes of this review more emphasis was placed on the individual components making up the composite.

The statistical reviewers generated stratified random sample (stratified by site) of 10% of subjects to check if the review team agreed with the coding of responses. The responses to three selected questions (“Check” step from cognitive walkthrough, Question 1, and Question 6) from the interview transcripts were compared to the coded responses for each subject in the sample. No clinically important issues were detected in the coding methods for the selected questions. There were a few coding discrepancies for the endpoints ‘Call 911 immediately’, ‘Composite (Step 1-3)’, and ‘Repeat dose every 2-3 minutes until person is fully awake or until emergency personnel arrive’ that were concerning. However, the post hoc sensitivity analyses showed that these discrepancies did not impact the study conclusion.

Outside of the composite endpoint, the one endpoint that did not meet the threshold was the “call 911 immediately” endpoint which scored a 90.3% PE with a LB of 88% (threshold was a LB of 90%). Nearly two-thirds (63.8%, 44 of 69) of incorrect responses involved calling 911, but not immediately after giving the dose. Lower scores were primarily driven by low-literacy participants (81.4% correct + acceptable; 193 of 237), those who were not previously familiar with naloxone (87.7% correct + acceptable; 284 of 324), and associates (81.8% correct + acceptable; 18 of 22). It is generally expected that low literacy subjects will score about 10% lower than normal literacy respondents. While we strive to make labels universally understood, greater emphasis is placed on comprehension within the population most likely to use the drug product being tested. In this case those subjects familiar with naloxone either from prior knowledge or use, and more likely to be within the population using naloxone over the counter, scored higher (92.5%) on this endpoint. It also needs to be taken into consideration that calling 911 as part of the directions for use of an over the counter medication is unprecedented.

Additional analysis was performed for the “Call 911 immediately” endpoint for this review. It should first be acknowledged that upon FDA’s recommendation a very conservative method of analyzing responses for coding was utilized for the cognitive walkthrough. All incorrect “call 911 immediately” responses from the cognitive walkthrough were analyzed along the same conservative coding guidelines provided by FDA, and it was determined that 3 responses could be re-coded to correct. Additionally, a sensitivity analysis was conducted for mentions of “call 911” at Question 3 and Question 5 of the LCS interview. That analysis revealed that among the 69 subjects who had an incorrect response for “call 911 immediately” in the cognitive walkthrough, 17 of them mentioned calling 911 in their answer to Question 3, 14 of them mentioned calling 911 in their answer to Question 5, and 9 of them mentioned calling 911 in their responses to both Question 3 and Question 5. The results indicate that comprehension levels of “call 911” are higher than what was captured in the results from the cognitive walk though.

Note that during the review analysis of the cognitive walkthrough transcripts several discrepancies between the transcript data and corresponding codes were found, including the

three incorrect “call 911” responses that could be re-coded to correct. One weakness observed in the final report for this study was the reliance on coding drawn from the interviewer recorded verbatims rather than analyzing the transcripts. These discrepancies were not found in the random 10% sample analysis conducted for this review; possibly owing to the simpler nature of the selected questions/responses as compared to the entirety of the cognitive walkthrough response.

Although some participants stated variances in the order of key steps or provided a conditional response to the 911 endpoint in the cognitive walkthrough portion of the interview, overall the data suggest that individuals will be able to utilize the label to administer the drug in an overdose situation.

However, improvements could be made to the “call 911” language and directions on the label to boost comprehension. Additional language, highlighting, bolding, or text coloring could be added to ensure that consumers fully understand that 911 must be called in each instance of naloxone use. The tested label can serve as a baseline from which additional improvements could be made for the “call 911” directions when sponsors undertake comprehension testing of their device-specific directions for use.

## **Clinical**

Overall, I agree with the contractors’ conclusion that the OTC DFL for naloxone performed well in facilitating understanding of the important steps one needs to take in evaluating a victim and administering naloxone. The demographics of the population studied were acceptable and included a diverse population, with low literacy subjects adequately represented. Regarding the primary objectives, the point estimates for all primary endpoints exceeded 80% correct comprehension, and the primary endpoints were met or nearly met based on the a priori success thresholds.

However, in the total analysis population (N=710), of the eight primary endpoints listed above, two did not meet the lower bound (LB) threshold, and one did not meet the point estimate (PE) scores of 90%. The primary endpoint that did not meet the target 90% LB threshold was Step 3: ***call 911 immediately*** (90.3% PE; 88% LB), although it is acknowledged that the LB was close to the 90% threshold. Nearly two-thirds (63.8%, 44 of 69) of incorrect responses involved calling 911, but not immediately after giving the dose. Common reasons for incorrect responses included stating that they would call 911 but only if the person did not wake up, if the person did wake up, or after waiting to see if the dose worked (n=44). A total of 25 subjects did not mention calling 911 at all. Although the fact that 44 of these subjects mentioned calling 911 as a result of an outcome suggests some degree of vigilance on the part of the rescuer to evaluate the status of the individual first, this is still less than ideal. Rescuers need to call 911 regardless of the situation.

It is possible that unknown cultural factors contributed to these results. For example, some participants may hesitate to call 911 for fear of getting in trouble or because they are not familiar with local good Samaritan laws. These types of concerns would not be the result of lack of understanding of the DFL. As noted in the Social Science section above, conservative coding guidelines were utilized in this study, and it appears that some participants who were coded as “incorrect” could be re-coded as “correct.” Nevertheless, the importance of achieving the best possible understanding of the important message to call 911 cannot be overemphasized.

The Deep Dive revealed that lower scores for calling 911 were primarily driven by low-literacy participants (81.4% correct + acceptable; 193 of 237), those who were not previously familiar with naloxone (87.7% correct + acceptable; 284 of 324), and associates (81.8% correct + acceptable; 18 of 22). In general, for label comprehension, one can expect about a 10% drop for low literacy. The results of the Deep Dive also suggest that individuals who would be more likely to seek out and use this product may have some familiarity with the drug and would be more likely to complete this step as instructed. Therefore, if naloxone products are approved for OTC use, aggressive outreach campaigns may be of benefit to improve public familiarity. Regarding associates, it is difficult to draw any firm conclusions about this group due to small total sample size. However, it is still important for others (friends and family members) to have the best possible comprehension and to understand to call 911 as soon as possible.

The primary endpoint that did not meet the 85% target threshold and had a point estimate score below 90% (81.1% PE, 78% LB) was the composite endpoint (composite of cognitive walkthrough: Steps 1-3). Most of the incorrect responses included not calling 911 or calling 911 after waiting; however, some incorrect participants stated they would wait for the ambulance, even if not specifying to call 911. In general, it is difficult to assess composite endpoints as there is always the possibility that the subject understands all the steps but fails to verbalize them all. For example, for the participants who stated they would wait for the ambulance, it would seem reasonable to assume that someone had called 911, even if they did not specifically say so. Nevertheless, it is concerning that for composite endpoint, the step of calling 911 is again the issue that participants seemed to have the most trouble with.

Regarding the secondary analyses, the results indicated that these messages were well understood by the participants with point estimates exceeding 80% for all secondary endpoints with the exception of the composite score for getting all five steps correct, which was slightly lower (74.6% PE). However, as mentioned above, composite endpoints are difficult to assess, and it is reassuring that, of the participants who mentioned at least three steps, most of them (84.5%; 120 of 142) mentioned the two important interventions of checking the victim for an overdose and giving a first dose.

The results of the two exploratory qualitative endpoints, “Wait 2-3 minutes between doses,” and “What is an opioid,” were acceptable. Regarding “Wait 2-3 minutes between doses,” nearly all (95.1%) participants provided at least one response in the cognitive walkthrough or one of the

pre-determined comprehension questions (Question 3, Question 8, or Question 7) that specified waiting 2-3 minutes between giving doses. A total of 23 participants did not mention any time, and 9 participants referenced 1.5-4 minutes or a few/couple minutes. In my experience, time is difficult to monitor in an emergency, and, for laypersons, a few minutes may seem much longer. The important point is that nearly all participants understood to give another dose after some brief period of time. For the few participants who might give a second dose early or slightly later, it is unlikely to cause harm and is certainly better than not giving a needed second dose at all.

Regarding “What is an opioid,” it is clear that the definition of the term “opioid” is not universally understood; however, the majority of participants did correctly understand the drug categories for which naloxone is effective. The important point is that most participants understand enough to recognize a potential drug overdose in order to administer naloxone, even if they do not fully understand what an opioid is.

## 4.2. Conclusions and Recommendations

In conclusion, the DFLs tested in this LCS are acceptable as is, with appropriate changes to the DFL template to address individual sponsor’s delivery systems and Instructions for Use (IFU). However, we recommend that sponsors further assess whether comprehension of instructions to call 911 immediately in the DFL may be improved. If further testing of alternative language to the DFL demonstrates improved comprehension, the alternative language may be utilized in the sponsor’s DFL. However, if alternatives do not demonstrate improved comprehension of instructions to call 911 immediately, the DFLs tested in this study are considered adequate and may be utilized. In addition, adequate comprehension of IFUs for individual products will need to be demonstrated through label comprehension and human factors testing as appropriate.

The OTC DFL for naloxone performed well in facilitating understanding of the important steps one needs to take in evaluating a victim and administering the drug. The subgroup analyses did not reveal any populations of significant concern related to comprehension of key messages on the DFL; scores for participants of lower education and literacy scored lower, as expected.

However, Step 3: ***call 911 immediately***, did not meet the target 90% LB threshold, although it is acknowledged that it *nearly* met the 90% threshold (88% LB) and, as discussed in the Social Science section above, the results from the sensitivity analysis combined with the analysis of incorrect responses from the conservative coding method indicate that comprehension levels of “call 911” are higher than what was captured in the results from the cognitive walk through. Because naloxone is a potentially life-saving treatment, it may be reasonable to consider a LB of 88% to be acceptable. If naloxone is given and most users call 911, many lives can be saved, and this is a much better alternative than not giving naloxone at all. Nevertheless, it is important that efforts continue to ensure the best possible comprehension of this message.

If opioid overdose is recognized and a dose of naloxone is given, it is possible that, even if the victim responds, he/she will relapse (due to the short-acting effect of naloxone compared to the longer-lasting effect of most opioids), in which case, although repeat doses may be given, further treatment by medical personnel remains crucial. Conversely, if the victim does not respond to naloxone, either the overdose is so severe that naloxone doses are insufficient, the overdose is due to drugs not responsive to naloxone (e.g. barbiturates, alcohol), or the victim is not suffering from an overdose but instead has another serious medical condition. In all of these scenarios, no harm is done by attempting to revive the victim with naloxone as long as 911 is called and medical help is on the way. Therefore, although comprehension of instructions to ***call 911 immediately*** may be influenced by cultural factors as noted above and the results described in this study may be the best that can be hoped for, it is possible that additional information provided in the DFL may help inform users of the importance of this step. We recommend that, in the future, sponsors that are developing naloxone products for OTC use consider how comprehension of this message may be further improved as they develop their DFLs.

## Appendix 1. Summary of post-hoc mitigation

**Table C1. Scoring of responses for communication messages tested solely via the cognitive walkthrough**

Endpoint	Correct Response for CW	Acceptable Response for CW	Additional Unanticipated Responses Received <sup>1</sup>
<p><b>Primary:</b> Check for a suspected overdose</p> <p><u>AND</u> Give the 1<sup>st</sup> dose of this medicine <u>AND</u> Call 911 immediately</p>	<p>List in the cognitive walkthrough <b>the first three steps</b> as “Check”, then “Give a dose”, then “Call 911</p> <p>(see coding for correct statements for each step below)</p>	<p>Lists in the cognitive walkthrough <b>the first three steps</b> as “Check”, then “Call 911”, then “Give a dose”</p>	<ul style="list-style-type: none"> <li>• Consider if 1<sup>st</sup> 3 steps listed in any order within 1<sup>st</sup> 3 could be considered <i>Acceptable</i></li> <li>• Examples: <ul style="list-style-type: none"> <li>○ Listed order as “Give 1<sup>st</sup> dose”, “Check”, “Call 911” <ul style="list-style-type: none"> <li>▪ Code as <i>Incorrect</i> <ul style="list-style-type: none"> <li>• Rationale - ‘Check’ is after ‘Give’</li> </ul> </li> </ul> </li> <li>○ OR “Give 1<sup>st</sup> dose”, “Call 911”, “Check” <ul style="list-style-type: none"> <li>▪ Code as <i>Incorrect</i> <ul style="list-style-type: none"> <li>• Rationale - ‘Check’ is after ‘Give’</li> </ul> </li> </ul> </li> <li>○ OR “Call 911”, “Check”, “Give 1<sup>st</sup> Dose” <ul style="list-style-type: none"> <li>▪ Code as <i>Correct</i> <ul style="list-style-type: none"> <li>• Rationale – ‘Call 911’ can be first; ‘Check’ is before ‘Give’</li> </ul> </li> </ul> </li> </ul> </li> </ul>
<p><b>Primary:</b> Check for a suspected overdose</p>	<p>Mention “Check” in cognitive walkthrough.</p> <p>Other correct responses are</p> <ul style="list-style-type: none"> <li>• Check: YELL WAKE UP</li> <li>• SHAKE THE PERSON GENTLY</li> <li>• TRY TO WAKE THE PERSON UP</li> <li>• IF THE PERSON IS NOT AWAKE, GO TO STEP 2</li> </ul>		N/A

<sup>1</sup> While efforts were made to identify the majority of these responses *a priori*, additional unanticipated responses were received and coding was discussed with FDA to confirm “correct” versus “incorrect” responses for those unanticipated items. FDA remained blinded to the potential impact on study results as a part of these post-study coding decisions.

Endpoint	Correct Response for CW	Acceptable Response for CW	Additional Unanticipated Responses Received <sup>1</sup>
<p><b>Primary:</b> Give the first dose of this medicine</p>	<p>Mention “Give a dose” in cognitive walkthrough</p> <p>Other correct responses are</p> <ul style="list-style-type: none"> <li>• GIVE 1ST DOSE</li> <li>• GIVE THE MEDICINE</li> </ul>		<ul style="list-style-type: none"> <li>• Code responses like the following to be <i>Acceptable</i>: <ul style="list-style-type: none"> <li>○ “Insert in nose”</li> <li>○ “Put it in the nose, press button/spray”</li> <li>○ “Give it to them”</li> <li>○ “Go to application of naloxone”</li> <li>○ “Give”</li> <li>○ Rationale: all relate to giving the medicine and manufacturers will provide more specific instructions</li> </ul> </li> <li>• Consider the following response to be <i>Incorrect</i>: <ul style="list-style-type: none"> <li>○ “Give the pill”</li> </ul> </li> <li>• Example response that qualifies giving dose only if person is awake: <p>“If he is awake, give the medicine; if not awake, call 911”; at Step 3 states “If he is not awake, call 911”, but at Step 4 mentions “Continue to give doses every 2-3 minutes until the person wakes up”</p> <ul style="list-style-type: none"> <li>○ Code as <i>Incorrect</i> at Step 2 (Give 1<sup>st</sup> dose)</li> <li>○ Rationale: Suggests would not give dose if person was not awake until Step 4</li> </ul> </li> </ul>
<p><b>Primary:</b> call 911 immediately</p>	<p>Mention “Call 911” in cognitive walkthrough as one of first three steps.</p>	<p>Mention “call 911” in cognitive walkthrough as one of first five steps.</p>	<ul style="list-style-type: none"> <li>• Mentioned Call 911, but qualified with ‘see if the person wakes up, then call 911’ or ‘call 911 if the person doesn’t wake up’ <ul style="list-style-type: none"> <li>○ Code as <i>Incorrect</i> for this step and Composite of Steps 1-3</li> <li>○ Rationale: Consider that as waiting to see if woke, also does not confirm would call if woke up; however, does include mention of calling 911 in the overall process</li> </ul> </li> <li>• Did not mention calling 911 but stated they would wait for ambulance to arrive <ul style="list-style-type: none"> <li>○ Code as <i>Incorrect</i> for Call 911, Steps 1-5, Steps 1-3</li> <li>○ Rationale: Did not specifically mention that step so conservatively did not want to make the assumption that they would have called or would have remembered to call</li> </ul> </li> </ul>

Endpoint	Correct Response for CW	Acceptable Response for CW	Additional Unanticipated Responses Received <sup>1</sup>
<p><b>Secondary:</b> mention all five steps in cognitive walkthrough</p>	<p>Mention in the cognitive walkthrough the following five steps: “Check”, “Give a dose”, “Call 911”, “Repeat doses every few minutes”, “stay with the person until ambulance arrives”.</p> <p>“Call 911” must be mentioned as part of the first 3 steps and “Check” must be mentioned as the first step</p>	<p>Participant mentions all 5 steps AND “call 911” in any of the first 5 steps</p>	<ul style="list-style-type: none"> <li>• General: <ul style="list-style-type: none"> <li>○ Only mentioned step # (e.g. I would start with Step 1, then give a dose...)</li> <li>▪ If did not mention any description of the step, code as <i>Incorrect</i></li> <li>▪ Rationale: Not enough mentioned to confirm understanding</li> <li>○ Initially described order as steps 1/2/4/3, but corrected self that it should have been 1/2/3/4</li> <li>▪ Code as 1/2/3/4 <ul style="list-style-type: none"> <li>• Rationale: If they self-correct quickly, it is okay.</li> </ul> </li> </ul> </li> <li>• Step 4: <ul style="list-style-type: none"> <li>○ Mentioned ‘Wait 2-3 minutes’ but not ‘give another dose’</li> <li>▪ Assumption: Count it as mentioned Step 4 only IF also mentions it is safe to keep giving doses at Step 4 or giving more doses (e.g. if the person gets sleepy again) at Step 5</li> <li>▪ Rationale: Continuing verbatim suggests they understand to give another dose if needed after waiting</li> <li>○ Mentioned ‘Continue to give doses’ but no waiting 2-3 min</li> <li>▪ Code as mentioned Step 4 - <i>Acceptable</i></li> <li>▪ Rationale: Was <i>acceptable</i> in Comprehension. This has more clinical implications for some dosage forms more than others. Therefore, we are ok with a reassessment in the HF study that will need to be done for each specific product. It can be acceptable.</li> </ul> </li> <li>• Step 5: <ul style="list-style-type: none"> <li>○ Only mentioned ‘Give another dose if person gets sleepy again’</li> <li>▪ Code as mentioned for Step 5</li> <li>▪ Rationale: Assumes staying with person in order to give more doses</li> </ul> </li> </ul>
<p><b>Secondary:</b> order “call 911” is mentioned</p>	<p>3<sup>rd</sup></p>	<p>2<sup>nd</sup></p>	<ul style="list-style-type: none"> <li>• Order mentioned 1<sup>st</sup> <ul style="list-style-type: none"> <li>○ Code as <i>Acceptable</i></li> <li>○ Rationale: Standard response is often to call 911 first</li> </ul> </li> </ul>



**Table C2. Scoring of responses for communication messages tested via the comprehension questionnaire and cognitive walkthrough (if needed)**

Endpoint	Questions used for assessing Endpoint	Correct Responses for Comprehension Questions	Acceptable Responses for Comprehension Questions	Additional Unanticipated Responses Received <sup>2</sup>
<p><b>Primary:</b> Product Use:</p> <p>Use for Treatment of Opioid Overdose</p>	Q1a/b	<p>States one of the following:</p> <ul style="list-style-type: none"> <li>EMERGENCY TREATMENT OF OPIOID OVERDOSE</li> <li>EMERGENCY TREATMENT OF OVERDOSE TO “REVIVE” SOMEONE DURING AN OVERDOSE FROM MANY PRESCRIPTION PAIN MEDICATIONS OR STREET DRUGS SUCH AS HEROIN</li> <li>OPIOID OVERDOSE</li> </ul>	<p>States one of the following:</p> <ul style="list-style-type: none"> <li>DRUG OVERDOSE</li> <li>OVERDOSE</li> <li>HEROIN OVERDOSE</li> <li>OVERDOSE OF PRESCRIPTION PAIN MEDICATIONS</li> </ul>	<p>Use responses to all 3 questions to evaluate Q.1</p> <ul style="list-style-type: none"> <li>2<sup>nd</sup> column references only Q1a/b, but will use Q1a/b/c</li> </ul> <p>States:</p> <ul style="list-style-type: none"> <li>Overdose on heroin or Rx pain meds (both mentioned), but did not specify reviving/treatment <ul style="list-style-type: none"> <li>Code as <i>Correct</i></li> <li>Rationale: Similar to “Opioid Overdose”, which is classified as <i>Correct</i></li> </ul> </li> <li>‘Opiate’ overdose <ul style="list-style-type: none"> <li>Code as <i>Acceptable</i></li> <li>Rationale: Discuss ‘opiate’ vs ‘opium’ vs ‘from drugs made from poppies’</li> </ul> </li> <li>‘Reviving if overdosing’ but doesn’t specify on what <ul style="list-style-type: none"> <li>Code as <i>Acceptable</i></li> <li>Rationale: Similar to ‘Overdose’ but not enough detail to be <i>Correct</i></li> </ul> </li> <li>Mention of ‘pain meds’ or ‘pain pills’ or ‘strong pain meds’, but not specifically ‘Rx pain meds’ <ul style="list-style-type: none"> <li>Code as <i>Acceptable</i></li> <li>Rationale: Understand enough of pain meds, but didn’t state prescription</li> </ul> </li> </ul>
<p><b>Primary:</b> Signs of overdose – If you think someone used an opioid and the person won’t wake up or is not breathing well, these are signs of</p>	Q2a/b	<p>State one of the following:</p> <ul style="list-style-type: none"> <li>WILL NOT WAKE UP, IS VERY SLEEPY OR NOT BREATHING WELL</li> <li>WILL NOT WAKE UP</li> <li>VERY SLEEPY</li> <li>CAN’T AROUSE THE</li> </ul>	<p>State one of the following:</p> <ul style="list-style-type: none"> <li>NOT BREATHING WELL (E.G. BREATHING SLOWLY, SHALLOW, ETC.)</li> </ul>	<p>State:</p> <ul style="list-style-type: none"> <li>“Unconscious” or “comatose” <ul style="list-style-type: none"> <li>Code as <i>Correct</i></li> <li>Rationale: Similar to “will not wake up” / “can’t arouse person”</li> </ul> </li> <li>“Not moving” <ul style="list-style-type: none"> <li>Code as <i>Correct</i></li> <li>Rationale: Similar to can’t arouse person</li> </ul> </li> <li>“Sleeping” <ul style="list-style-type: none"> <li>Code as <i>Incorrect</i> if that is all that’s mentioned (or only in conjunction with laying down)</li> </ul> </li> </ul>

<sup>2</sup> While efforts were made to identify the majority of these responses *a priori*, additional unanticipated responses were received and coding was discussed with FDA to confirm “correct” versus “incorrect” responses for those unanticipated items. FDA remained blinded to the potential impact on study results as a part of these post-study coding decisions.

Endpoint	Questions used for assessing Endpoint	Correct Responses for Comprehension Questions	Acceptable Responses for Comprehension Questions	Additional Unanticipated Responses Received <sup>2</sup>
an overdose.		PERSON (OR OTHER SIMILAR RESPONSES)		<ul style="list-style-type: none"> <li>○ Rationale: Not similar enough to 'very sleepy'</li> <li>○ Review if person mentioned in the cognitive walkthrough that they would try to wake someone up. If there is some recognition that a "sleeping" person can be aroused and that you give the medicine if they can't be, that could be an analysis to include in the report</li> </ul>
<p><b>Primary:</b></p> <p>Repeat doses every few minutes until fully awake or until emergency personnel arrive.</p>	Q3a/b <u>and</u> cognitive walk-through	<p>State one of the following:</p> <ul style="list-style-type: none"> <li>• GIVE ANOTHER DOSE EVERY 2-3 MINUTES UNTIL THE PERSON WAKES UP</li> <li>• CONTINUE TO GIVE DOSES UNTIL THE PERSON WAKES UP</li> <li>• CONTINUE TO GIVE DOSES UNTIL EMERGENCY PERSONNEL ARRIVE</li> </ul>	<p>State one of the following</p> <ul style="list-style-type: none"> <li>• GIVE ANOTHER DOSE</li> <li>• CONTINUE TO GIVE DOSES</li> </ul>	<p>If only mention wait 2-3 minutes or stay with the person/wait until ambulance arrives:</p> <ul style="list-style-type: none"> <li>• Code as <i>Incorrect</i></li> <li>• Rationale: Did not provide any action to give additional doses</li> </ul>
<p><b>Primary:</b></p> <p>Stay with the person until ambulance arrives</p>	Q5a/b <u>and</u> cognitive walk-through	<p>State the following:</p> <ul style="list-style-type: none"> <li>• STAY WITH THE PERSON UNTIL THE AMBULANCE ARRIVES</li> </ul>	<p>State the following:</p> <ul style="list-style-type: none"> <li>• STAY WITH THE PERSON</li> </ul>	<p>Consider if state the following:</p> <ul style="list-style-type: none"> <li>• "Monitor the patient/friend" or "Keep an eye on her and continue to watch" <ul style="list-style-type: none"> <li>○ Code as <i>Acceptable</i></li> <li>○ Rationale: Similar to stay (assumes would have to stay to monitor/watch)</li> </ul> </li> <li>• "Continue giving doses every 2-3 minutes" <ul style="list-style-type: none"> <li>○ Code as <i>Acceptable</i></li> <li>○ Rationale: Similar to stay (assume would have to stay to continue giving doses)</li> </ul> </li> <li>• "Stay until help arrives" <ul style="list-style-type: none"> <li>○ Code as <i>Correct</i></li> <li>○ Rationale: Scenario states 911 was called, so can assume 'help' = ambulance</li> </ul> </li> </ul>

Endpoint	Questions used for assessing Endpoint	Correct Responses for Comprehension Questions	Acceptable Responses for Comprehension Questions	Additional Unanticipated Responses Received <sup>2</sup>
				<ul style="list-style-type: none"> <li>• “Keep giving doses every 2-3 minutes and then hopefully 911 has arrived” <ul style="list-style-type: none"> <li>○ Code as <i>Correct</i></li> <li>○ Rationale: assumes staying to continue to give doses and references 911 arriving</li> </ul> </li> <li>• Consider how to handle if specify ‘if person does not wake up’ <ul style="list-style-type: none"> <li>○ Code as <i>Incorrect</i></li> <li>○ Rationale: Seems to indicate would not stay if person woke up, which is incorrect</li> </ul> </li> </ul>
Secondary: withdrawal symptoms of opioid overdose	Q4a/b	<p>State one of the following:</p> <ul style="list-style-type: none"> <li>• SOME PEOPLE MAY EXPERIENCE SYMPTOMS WHEN THEY WAKE UP, SUCH AS SHAKING, SWEATING, NAUSEA, OR FEELING ANGRY</li> <li>• SOME PEOPLE MAY EXPERIENCE SYMPTOMS WHEN THEY WAKE UP</li> <li>• THE DRUG IS MAKING THEM FEEL THIS WAY AND IT SAYS SO ON THE LABEL</li> </ul> <p>(OR SOMETHING SIMILAR)</p>	<p>State the following:</p> <ul style="list-style-type: none"> <li>• I took away their high so of course they’re going to be mad.</li> </ul>	N/A
Secondary: It is safe to keep giving doses of this medicine	Q6a/b	“Yes”		<ul style="list-style-type: none"> <li>• Rationale (<i>Why do you say that?</i>) may reference “continue to give doses every 2-3 minutes”, or “give all doses in the pack” or “might have to use all doses in the pack” and still be considered <i>Correct</i></li> </ul>

Endpoint	Questions used for assessing Endpoint	Correct Responses for Comprehension Questions	Acceptable Responses for Comprehension Questions	Additional Unanticipated Responses Received <sup>2</sup>
Secondary: If person becomes sleepy again, give another dose	Q7a/b	State one of the following <ul style="list-style-type: none"> <li>GIVE ANOTHER DOSE IF THE PERSON BECOMES VERY SLEEPY AGAIN</li> <li>GIVE ANOTHER DOSE</li> </ul>		<ul style="list-style-type: none"> <li>Consider how to handle if person references only Step 4:               <ul style="list-style-type: none"> <li>Give every 2-3 minutes</li> <li>Wait 2-3 minutes and give another dose                   <ul style="list-style-type: none"> <li>Code as <i>Acceptable</i></li> <li>Rationale: demonstrates understanding of giving another dose and may need to continue giving doses every 2-3 minutes until they wake back up again, even though specific Step 5 information not mentioned</li> </ul> </li> </ul> </li> </ul>

Table C3. Overall Scoring of Comprehension Questions based on Q a and Q b (Q.1-Q.7)

Follow-up Response (Q b) ("Why do you say that?")	Initial Response (Q a)		
	Q a: Correct	Q a: Acceptable	Q a: Incorrect
Q b: Correct	Correct	Correct	<b>Correct/Acceptable/Incorrect</b>
Q b: Acceptable	Acceptable	Acceptable	<b>Acceptable/Incorrect</b>
Q b: Incorrect	<b>Incorrect/Acceptable</b>	<b>Incorrect/Acceptable</b>	Incorrect

- For the cells highlighted in yellow, Concentrics has used standard coding assumptions (bolded) as a starting point.
- Where participants mentioned "I guess", or "I would do xyz because I've done that before", as long as they mentioned something related to the label and try to explain it, they were coded as *Correct* or *Acceptable* (depending on their response). Alternatively, for someone who responds more along the lines of "I don't know, I'm just guessing", then that would be coded as *Incorrect*.

**Table C4. Overall Scoring of Comprehension Questions based on Q a and Q b and Cognitive Walkthrough (Q.3 and Q.5)**

	Overall Response from Q a/b: Correct	Overall Response from Q a/b: Acceptable	Overall Response from Q a/b: Incorrect
Walkthrough: Correct	Correct	Acceptable	Acceptable
Walkthrough: Acceptable	Correct	Acceptable	Acceptable/Incorrect
Walkthrough: Incorrect	Acceptable/Incorrect	Acceptable/Incorrect	Incorrect

For the cells highlighted in yellow, assumptions were made as follows (Q.3 example):

- If walkthrough response mentioned at least a part of the relevant step but not enough to be considered *Correct* or *Acceptable* (e.g. 'Wait 2-3 minutes'), but the comprehension response was *Correct* or *Acceptable*, then overall code = *Acceptable*
- If walkthrough did not mention any part of the relevant step at all, then the overall code = *Incorrect*

For the cell highlighted in blue (Q.5 example):

- If the walkthrough response mentioned staying with the person, and participant had also mentioned Call 911, but no *Acceptable* response was provided in comprehension, then overall code = *Acceptable*
- If the walkthrough response mentioned staying with the person, but there was no mention of calling 911 and no *Acceptable* response was provided in comprehension, then overall code = *Incorrect*