**FDA DOCUMENTATION FOR THE GENERIC CLEARANCE,**
**"TESTING COMMUNICATIONS ON DRUGS PRODUCTS"**
**OMB Control No. 0910-0695**

PROJECT CONFER: Comprehension of Over-the-Counter Naloxone for Emergency Response

(#16081)

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**TITLE OF INFORMATION COLLECTION:** Naloxone Pilot Label Comprehension Questionnaire to Optimize the Drug Facts Label (Task 2 – Adolescent All-Comers)

## DESCRIPTION OF THIS SPECIFIC COLLECTION

### 1. Statement of need:

Prevention and treatment of opioid overdose is an urgent public health priority. One way that FDA is addressing this public health problem is by facilitating the development of nonprescription (OTC) naloxone, which is currently only available by prescription. FDA is implementing this through development of a model Drug Facts label (DFL) for an OTC naloxone. This DFL is to include all the information (other than information highly specific to a particular product) that a consumer would need to know to purchase naloxone appropriately, and to use naloxone in an emergency opioid overdose situation. This model DFL will then undergo label comprehension testing by an outside research organization. A pretested DFL with an acceptable level of consumer comprehension would then be available, and commercial sponsors could add their product-specific information to the DFL and conduct final consumer behavior testing. RTI International and Concentrics Research (referred to hereafter as the RTI-Concentrics team) will be partnering on this research study, each bringing to the project their unique expertise in working with vulnerable populations (RTI) and label testing (Concentrics). We will conduct this study in accordance with practices outlined in the FDA Guidance for Industry on Label Comprehension Studies for Nonprescription Drug Products (FDA, August, 2010).

This study is a comprehensive label comprehension testing program. There are three study tasks, the first of which was to conduct individual, in-person cognitive interviews to optimize the DFL. This application details procedures and materials for interviewing adolescent all-comer subjects for Task 2 only (referred to as Group 3). We have obtained separate approval for interviewing adult subjects for Task 2 (adults comprise Groups 1, 2, and 4). We will also seek separate approval for Task 3 as the procedures and materials will be informed by Task 2 study results.

The purpose of Task 2 – Adolescent All-Comers is to conduct one-time individual, in-person interviews to assess comprehension of pilot survey questions that will be asked during and to inform sample sizing for the pivotal study in Task 3 (referred to as 'methodology' hereafter). Nine adolescent all-comers will participate in an individual, in-person interview (see Section 3 for a thorough description of respondents). The RTI-Concentrics team will conduct Task 2 – Adolescent All-Comers activities with a professional recruitment firm in Louisville, KY or

Columbus, OH[1]. Because the purpose of Task 2 – Adolescent All-Comers is to obtain feedback on the survey for the pivotal study, the sample is not intended to be nationally representative.

**2. Intended use of information:**

The study team will use the information they collect in Task 2 – Adolescent All-Comers to inform the methodology for the Task 3 pivotal study.

**3. Description of respondents:**

The study population for Task 2 – Adolescent All-Comers will consist of adolescent (ages 15-17) including those with limited health literacy (approximately 30%).

Eligibility Criteria

Adolescent All-Comers will be included in the study if the following criteria are met (see **Attachment C**).

1. Male or female, of any race.
2. 15-17 years of age (the study team will not enroll anyone who will be turning 18 before November 1, 2017 and all data will be deidentified by November 1, 2017).

FDA has determined that at least 30% of the adolescent all-comers be of limited health literacy. Literacy level will be approximated at the time of screening based on adolescents' answer to a question about their past year average academic grades. The moderator from Concentrics Research will administer the validated Rapid Estimate of Adult Literacy in Medicine (REALM)-Teen to adolescents (Davis et al., 2006) to assess health literacy on-site after assent but prior to conducting the individual, in-person interview (see Structured Interview Guide in **Attachment E** for the health literacy assessment). Individuals excluded from the study due to their REALM scores will still be provided with reimbursement to help defray expenses related to participation. The interviewer will tell them they were selected for a shorter version of the study so they will not know that they were excluded based on their REALM score (participants will not know they are taking the REALM; it will be presented as part of the interview).

Individuals will be excluded from the study if any of the following criteria are met.

[1] The final location will be determined based on availability once the dates of the data collection are known (dependent on the date of RIHSC and OMB clearance).

1. The individual will turn 18 before November 1, 2017.

2. The individual cannot read, speak and/or understand English.

3. The individual normally wears corrective lenses, contacts or glasses to read and does not have them with him/her at the time of the individual, in-person interview.

4. If the parent/guardian of record is not the identified adolescent's parent/guardian (e.g., the adolescent is a ward of the state). We will ask the adult providing permission for screening to verify that they are the adolescent's parent/guardian. If the adult is not the parent/guardian, we will terminate the screening process.

Recruitment

The study team will partner with a recruitment firm with experience recruiting limited health literacy and hard-to-reach populations in Louisville, KY (Personal Opinion, Inc.) or Columbus, OH (L&E Research). The facility will provide a 1-way mirror for FDA observation.

Staff from the recruitment firm will identify parents of children in our age range through their community partners and/or proprietary database and will contact them by telephone. Recruitment firm staff will first present the study to the parent/guardian, confirm that they are the parent/guardian, and request permission to audio record their child's interview (**Attachment C**). If they are not the adolescent's parent/guardian or will not permit audio recording, the screening process will be terminated. Once the parent/guardian grants verbal permission to screen their adolescent, recruitment firm staff will ask to speak with him/her.

After receiving permission from the parent/guardian for screening, the recruiter will administer the screener to the adolescent to determine eligibility. If eligible, the recruiter will invite the adolescent to participate in the study and, if interested, will schedule an individual, in-person interview. After scheduling the interview, the recruiter will speak with the parent/guardian once more to inform them of the scheduled appointment time and to ask for the parent/guardian's email address so that they can send the permission form to him/her to review. The recruiter will inform the parent/guardian that their adolescent must have the permission form signed by a parent/guardian in order to participate in the study; they can return the signed form by email or have their adolescent child bring it with them to the study location. The recruiter will also send the parent/guardian the adolescent assent form so their child has time to review it before the interview, discuss it with their parent/guardian, and prepare questions in advance of the interview. The recruiter will also collect a phone number from the adolescent and parent/guardian so they can be reminded of their upcoming individual, in-person interview 1-2 days beforehand.

It is possible that there will be more than one adolescent aged 15-17 living in the home. If this is the case, recruitment firm staff will ask the parent/guardian if all children in this age range are at home. If the answer is yes, they will ask for permission to speak to the oldest child. If this adolescent is eligible, they will proceed with recruitment and scheduling procedures. If the oldest child is ineligible, they will terminate the call. If the oldest child is not at home when recruitment firm staff contact the parent/guardian, they will ask to speak to the next oldest child in the specified age range and so forth until they can screen at least one of the adolescents in the

specified age range (if the parent/guardian gives them permission to do so and the child wants to). If no children in the specified age range are at home when the recruitment firm contacts the parent/guardian, they will ask the parent/guardian when they should call back to screen the oldest child.

**4. Date(s) to be Conducted:**

Data collection for Task 2 – Adolescent All-Comers will take place during a 4-6-week time frame after OMB and FDA RIHSC approval is received.

**5. How the Information is being collected:**

Task 2 is comprised of individual, in-person interviews to assess comprehension of the pivotal study survey questions that will be administered on a larger scale in Task 3. Concentrics staff will conduct the one-on-one interviews in person with participants. RTI and Concentrics Research will work in 2-person teams at each location. Some interviews may also be observed by additional study staff with permission from the parent/guardian and adolescent. Participants will be informed of the presence of any observers. Concentrics Research staff will administer informed assent and the REALM test, conduct the interviews, and analyze and report on findings. All interviewers are experienced and qualified in cognitive interviewing methods. This is an individual, in-person interview study only; no drug will be administered or dispensed.

Group 3 interviews will take place at a professional recruitment firm. When participants arrive, the logistics coordinator will ask them for the signed parental permission form if it was not previously returned (**Attachment N-2**). If the adolescent does not bring the signed permission form to the interview, the logistics coordinator will tell them that they will be unable to conduct the interview until they receive the signed permission form. Once the logistics coordinator receives the parental permission form, she will give the adolescent the assent form that outlines the purpose and voluntary nature of the study (**Attachment O-2**). This secondary opportunity to review the assent form will be particularly important for individuals who did not read it prior to their appointment (the assent form will be emailed to the parent/guardian along with the parental permission form).

When the moderator first meets with the individual, she will let them know if members of the study team are observing the interview. The adolescent can still participate in the study if they do not want to be observed. Observation will not occur if either the parent/guardian or adolescent objects; in such cases, study staff will ask the observers to leave the observation room and disconnect the live stream for the duration of the interview. The moderator will also remind the individual that the interview will be audio recorded. However, if the individual objects to being audio recorded, they will be dismissed and will not be given the reimbursement to help defray expenses related to participation. This condition of participation was explained during screening, and the individual had an opportunity at that point in time to decline being audio recorded in which case, they would have been ineligible to participate.

Adolescents must provide written assent to participate in the study. Both the parent/guardian *and* adolescent must also provide separate written permission for the interview to be observed. The interviewer will review the assent form with adolescents, emphasizing that participation is voluntary and ensuring that they understand the potential risks of participation, and provide them with an opportunity to ask questions. Also, the moderator will emphasize to the individual that they should not disclose personally identifiable information (PII), such as their last name or birthdate, during the interview to help protect their privacy.

If the Concentrics moderator has concerns about an individual's understanding of the assent form due to potential literacy issues (as evidenced by the number and nature of the questions the individual asks, and the extent to which the questions demonstrate a lack of understanding of the content of the assent form), she will end the interview. If the assent process is terminated due to literacy issues, the moderator will tell the individual that she needs to make sure that people understand the information in the assent form, and given the nature and number of questions they have, she cannot proceed with the interview. In this circumstance, the adolescent will still receive reimbursement to help defray expenses related to study participation.

Participants who sign the assent form will next undergo a health literacy assessment administered by Concentrics staff. The interviewer will use REALM-Teen for this purpose (**Attachment E**). FDA has requested that approximately 30% of participants be of limited health literacy defined as a REALM score based on grade level for teens (unlike the adult REALM, the cut-off score for limited health literacy differs by grade level so it is not possible to provide a single score that will be used to determine health literacy level). If someone does not meet the health literacy requirement, Concentrics staff will end the interview without telling the participant that they were disqualified and the participant will receive reimbursement to help defray expenses related to participation.

Following the health literacy assessment, the Concentrics interviewer will give the participant the naloxone Drug Facts Label (DFL) (**Attachment P**). The interviewer will leave the room to give the participant the opportunity to review the DFL at his/her own pace. The DFL will be a similar size and shape to a possible commercial package. Once the participant indicates he/she is finished reading the DFL, the moderator will return to the room and begin the individual, in-person interview (see **Attachment E**). The moderator will present a series of 3$^{rd}$ person overdose scenarios each of which will be followed by a closed-ended question that requires the participant to make a judgement about what to do next (e.g., give the 1$^{st}$ dose, call 911). After providing a response, the moderator will ask the participant to explain his/her answer which will enable the research team to assess comprehension of the survey questions as well as DFL instructions. There will also be time at the end of the interview to probe on issues that arise during the discussion.

Although participants will not benefit directly from taking part in the study, it is believed that the societal benefits of the study outweigh the potential minimal risks to participants. The public health importance of this project is high, especially considering the current opioid overdose epidemic in the United States. Without this study, FDA will be unable to determine whether potential end users of the OTC product understand the instructions for use, which may limit the product's life-saving potential. Additionally, if the questions that will be asked in Task 3 are not

tested in Task 2, the validity and reliability of the data from the pivotal study may be jeopardized.

The primary risks of participation are breach of confidentiality or distress. The measures to protect confidentiality are described fully in Section 6. Briefly, they include separate collection and storage of PII and screener and interview responses, and their eventual destruction at the end of the study; and storage and destruction of audio recordings at the end of the study. In addition, it is possible that during screening, the parent/guardian may attempt to listen to the discussion. As an extra measure, we will ask the adolescent if they have adequate privacy prior to asking them the screening questions, and if not, request that they move to a private area, preferably a room with a door, or ask their parent/guardian to hang up the telephone.

Although the study team does not anticipate that this will be an issue based on their experiences with Task 1 and the nature of the interview questions, it is theoretically possible that a participant may become distressed during screening or the interview. If this happens, we will give the individual the telephone number for a mental health crisis line near to the study location.

Once the interview is completed, RTI staff will provide the participant with a monetary reimbursement to help defray expenses related to study participation. Adolescents will receive $40 (cash or a check depending on the policy of the recruitment firm). Note that study staff will provide participants with reimbursement to help defray expenses related to study participation even if they withdraw from the study or are dismissed if the health literacy requirements are not met. Section 7 provides justification for the reimbursement amount.

In addition to audio recording the interviews, RTI staff will take notes to record nonverbal cues and behaviors (e.g. apparent participant confusion or difficulty in evaluating the labeling) from behind the one-way mirror. Total interview time will be 45 minutes, which includes time to administer the REALM and informed assent.

After the data collection is complete at all locations, the audio-recordings will be transcribed and the study team will create a summary report of the observations and insights from the interviews.

**6. Confidentiality of Participants:**

During screening, it will be necessary to collect the first names, email addresses, and phone numbers from individuals who are willing to participate and have scheduled a one-time individual, in-person interview appointment . This PII, which will be recorded separately from the screener (see “Closing Script and Contact Information” **Attachment C-2**), will be used to remind individuals of upcoming appointments. The screener and the form that records PII will be stored separately in a locked file cabinet at the recruitment firm and destroyed at the end of the study.

RTI will assign each participant a unique study identification (ID) number to protect privacy, and the ID number will be recorded on each page of the screener so this information can be linked to participants' interview responses (the interview guide also includes a field for the study ID number, but does not record PII). However, the study ID number will not be recorded on the contact information form; therefore, it is not possible to link screener or interview responses to PII which is only recorded on the contact information form.

Linking participant's interview data to some of the screening data is essential for analysis and interpretation of findings. For example, FDA needs to know if there are differences in label comprehension by key demographic characteristics (e.g., age, education level, race/ethnicity, or gender) to determine whether and how to revise the label and/or survey questions to improve comprehension and the validity of the findings from the Task 3 pivotal survey.

Other data from the screener will be used by RTI to inform recruitment and study procedures for Task 3. For example, the screener includes two proxy questions for health literacy: "What grade are you enrolled in" and "During the past 12 months, how would you describe the grades you mostly received in school?". These questions need to be asked in the screener because it is not possible to administer the REALM-Teen (health literacy) test over the telephone. Given the study requirements for limited health literacy representation, these proxy questions will be used to try to predict which participants will turn out to have limited health literacy. If these questions are not predictive of health literacy level, the study team will need to identify an alternative method for Task 3 to avoid possible time and overrun costs to the study.

The professional recruitment firm will provide RTI with demographic data for participants without last names or contact information. Participants will be identified only by study number in the data file that RTI gives to Concentrics. This means that Concentrics cannot link the data to participants' contact information. The recruitment firm will not share PII with RTI, Concentrics, or FDA. The study team will remove extraneous variables from the data file before delivering it to FDA (e.g., screener questions that are not pertinent to describing the sample or are unrelated to eligibility criteria). All data will be deidentified by November 1, 2017.

The study team will audio record the interviews for the purpose of verifying the interview notes, and the recordings will be stored in a locked file cabinet at RTI, Concentrics Research, and FDA. The audio recordings will be destroyed at the end of the study. All data will be reported to FDA in aggregate.

**7. Amount and justification for any proposed incentive (reimbursement to help defray expenses related to participation)**

A reimbursement is intended to recognize the time burden placed on participants and to help defray expenses related to study participation. A reimbursement helps ensure that sufficient numbers of participants can be recruited to participate in the data collection. Research has shown that offering a reimbursement improves response rates (Ryu et al., 2006; Singer et al., 1999), thus it is likely that without the reimbursement as an inducement, more people would need to be screened to achieve the desired cooperation rate, thus increasing the burden hours and overall time needed to complete data collection activities.

The reimbursement will be equivalent to $40. The goal was to select an amount that would be attractive to participants, but was not so large as to appear coercive, which is a consideration when conducting research with vulnerable populations (Festinger et al., 2005).

## 8. Questions of a Sensitive Nature

None of the label comprehension pilot interview questions for Task 2 – Adolescent All-Comers are of a sensitive nature. As previously described, the focus of these individual, in-person interviews is to assess comprehension of the survey questions that will be administered in the Task 3 pivotal study. As part of the assent procedures, interviewers will explain to participants that they do not need to answer any questions that make them feel uncomfortable and can stop participation at any time.

## 9. Description of Statistical Methods

Concentrics Research will use transcribed audio files, interview notes and participant screener data and demographics when summarizing findings for this study. They will summarize screener and demographic data in aggregate format with no personally identifiable information in table and text formats to describe study participants. All of the data collected by the study team is qualitative; thus, they plan to conduct a thematic analysis of all data.

Concentrics Research will organize analyses around the major topics included in the interview guides. Staff trained in quantitative and qualitative analysis methods will work together to prepare an analysis plan and review the data. All analyses will be data-driven. The analysis team will meet periodically to discuss findings and overall themes, as well as recommendations for the Task 3 survey. They will summarize the data into a final report with quotations from the interviews provided as examples to emphasize key findings.

**BURDEN HOUR COMPUTATION** *(Number of responses (X) estimated response or participation time in minutes (/60) = annual burden hours):*

| Type/Category of Participant | No. of Participants | Participation Time (minutes) | Burden (hours)* |
|---|---|---|---|
| Screener | 90 | 5 | 8 |
| Interview | 9 | 45 | 7 |
| **Total** | **99** | **5-50 minutes** | **15** |

*Rounded to the nearest hour.

**Note**: *The study team estimates that they will need to screen 90 adolescents to obtain 9 completed individual, Group 3 interviews due to the need to obtain parental permission prior to screening. The annual burden is estimated to be 15 hours.*

**REQUESTED APPROVAL DATE: August 2017.**

**NAME OF PRA ANALYST: Ila S. Mizrachi; ila.mizrachi@fda.hhs.gov; 301-796-7726.**

**PROGRAM CONTACT: Barbara R. Cohen; 301-796-2480.**

**FDA CENTER: Center for Drug Evaluation and Research.**

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