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)

TITLE OF INFORMATION COLLECTION: Naloxone Label Comprehension Questionnaire to Optimize the Drug Facts Label (Task 3 – 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. Task 1 did not include adolescents. Tasks 2 and 3 have incorporated adolescents (Group 3) into the label testing program:

- Task 2: The study team conducted individual, in-person interviews with a group comprised of adolescent all-comers (Group 3) to assess comprehension of pilot survey questions and to inform sample sizing for the pivotal study in Task 3.

- Task 3 (the focus of this protocol): The study team will conduct individual, in-person survey interviews with adolescents to test comprehension of the DFL for this pivotal, quantitative study.

This application details procedures and materials for Task 3 - adolescent all-comers (Group 3) only; we will seek separate approvals for adults representing Groups 1-2, and Group 4.

The individual, in-person survey interviews will be conducted with 140 adolescents representing a general population audience; see Section 3 for a thorough description of respondents. The study team will work with professional recruitment firms from several locations to recruit participants for Group 3 interviews: Raleigh, NC; Los Angeles, CA; Dallas, TX; Tampa, FL; Indianapolis, IN; and New York City, NY. The individual, in-person survey interviews will take place at the designated recruitment firms.

2. Intended use of information:

The study team will use the information they collect in Task 3 to determine if key communication objectives in the DFL have been achieved.

3. Description of respondents:

The study population for Task 3 – 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 "Adolescent Telephone Screener" in **Attachment B3**).

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 June 30, 2018 and all data will be deidentified by June 30, 2018)

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 interviewers will administer the validated 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 "Adolescent Structured Interview Guide" in **Attachment C3** for the health literacy assessment). Individuals excluded from the study due to their REALM scores will still be provided with a token of appreciation to help defray time and travel costs 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 individual will turn 18 before June 30, 2018.

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 and Screening

The study team will partner with recruitment firms with experience recruiting limited health literacy and hard-to-reach populations in Raleigh, NC; Los Angeles, CA; Dallas, TX; Tampa, FL; Indianapolis, IN; and New York City, NY. **Exhibit 1** provides the specific recruitment firms in each city.

Exhibit 1. Recruitment firms for Group 3, by Location

Location	Recruitment Firm
Raleigh, NC	L&E Research 5505 Creedmor Rd. Raleigh, NC 27612
Los Angeles, CA	Atkins Research Group 4929 Wilshire Blvd. #102 Los Angeles, CA 90010
Dallas, TX	Bryles Research 3308 Essex Dr. Richardson, TX 75082
Tampa, FL	L&E Research 5110 Sunforest Dr. #300 Tampa, FL 33634
Indianapolis, IN	Concentrics Center for Research 9335 Delegates Row Indianapolis, IN 46240
New York City, NY	Schlesinger Group 711 3rd Ave, 9th floor New York, NY 10110

Staff from the recruitment firms 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 (see "Adolescent Telephone Screener" in **Attachment B3**). 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 to participate in the study. They can return the signed form by email, bring it with them if they come to the interview appointment with their child, or have their child bring it with them to the study location if they are unable to come to the interview appointment. 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 3 – Adolescent All-Comers will take place during a 2-4-week time frame after OMB and FDA RIHSC approval is received.

5. How the Information is being collected:

Task 3 is comprised of 30-minute individual, in-person survey interviews to assess comprehension of the DFL. Concentrics staff will conduct the survey interviews at each location which includes confirming the signed parental permission forms have been received, administering assents, administering the REALM-Teen tests and conducting the interviews. Recruitment firm staff will be responsible for checking participants in for the data collection. All interviewers are experienced and qualified in the requisite data collection methods. This is an individual, in-person survey interview study only; no drug will be administered or dispensed.

When participants arrive at the data collection location, study staff will ask them for the signed parental permission form if it was not previously returned (**Attachment K2**). If the adolescent does not bring the signed permission form to the interview, the interviewer will tell them that they will be unable to conduct the interview until they receive the signed permission form.

Once the interviewer receives the parental permission form, they will take the participant to the interview room where they will review the assent form with the participant, emphasizing the purpose of the study and that participation is voluntary, ensuring that they understand the potential risks of participation, and providing them with an opportunity to ask questions (**Attachment K3**). 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). The interviewer will also 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. Finally, the interviewer will 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 token of appreciation 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.

If the interviewer 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), they will terminate the process. If the assent process is terminated due to literacy issues, the interviewer 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 the token of appreciation to help defray time and travel costs related to participation.

Participants who sign the assent form will next undergo a health literacy assessment administered by the Concentrics' interviewer. The interviewer will use REALM-Teen for this purpose (included in the "Adolescent Structured Interview Guide", **Attachment C3**). 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 the token of appreciation to help defray time and travel costs related to participation.

Following the health literacy assessment, the Concentrics interviewer will give the participant one of two versions of the naloxone DFL (**Attachment L-1 or L-2**); there are separate DFLs for route of administration (i.e., nasal or intramuscular injection). These DFLs will be rotated so that approximately 70 participants will look at one version, and approximately 70 participants will look at the other version. 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 interviewer will return to the room and begin the interview. The interview questions will be administered by a Concentrics interviewer and participant responses will be recorded by the interviewer on a tablet using the Adolescent Structured Interview Guide (see **Attachment C3**).

The interviewer will start with a cognitive walkthrough of the label. This includes asking the participant to imagine that they were in a situation where they had to use the product on a friend. Next, the interviewer will ask the participant to explain what they would do based on the label. After this exercise is complete, the interviewer will present a series of 3rd-person overdose scenarios, each of which will be followed by a question that requires the participant to make a judgment about what to do next (e.g., wait for the ambulance to arrive; continue giving doses) or to demonstrate his/her understanding of what the label says (e.g. sweating and feeling angry are to be expected when using this product). After providing a response, the interviewer will ask the participant to explain his/her answer to confirm the participant is not guessing and to better understand his/her rationale. The combined scenario response and rationale will enable the research team to assess comprehension of the DFL communication objectives, including instructions and warnings.

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.

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 survey interview responses and their eventual destruction (PII will be destroyed within a month of the study's end date and screener and survey interview responses will be destroyed within two years of the study's end date), storage of audio recordings and their eventual destruction (within two years of the study's end date), and not transcribing portions of audio files that contain PII. In addition, it is possible that during screening, the parent/guardian may attempt to listen to the discussion. As an extra measure, recruitment firm staff 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 Tasks 1 and 2 and the nature of the interview questions, it is 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, the participant will receive a token of appreciation to help defray time and travel costs related to participation. Adolescents will receive $40. Section 7 provides justification for the token of appreciation. Note that study staff will provide participants with the token of appreciation to help defray time and travel costs related to participation even if they withdraw from the study or are dismissed if the health literacy requirements are not met.

After the data collection is complete at all locations, the audio-recordings will be transcribed and the study team will create a summary report based on an analysis plan provided by FDA. RTI and Concentrics will be the only ones who will possess the audio files. FDA will not be given the audio files from the interviews; however, FDA will receive the transcripts.

6. Confidentiality of Respondents:

The study team is implementing several measures to protect participants' privacy.

1. To ensure that adolescents have adequate privacy for screening, recruitment firm staff will ask parents to give their children privacy for the discussion, defining privacy as "By privacy, I mean that you are not listening to our discussion in person (i.e., you are not in the same room as or within hearing distance of your child) or over the telephone." Likewise, to ensure that adolescents who assent to be screened are aware of privacy considerations, recruitment firm staff will ask them if they have privacy for the discussion; "Do you have privacy for the discussion? This means your parent/guardian is not listening to our conversation in person (i.e., he/she is not in the same room as you or within hearing distance) or over the phone." If they say no, the recruiter will suggest to the adolescent that they move to a private area (a separate room with a door, if possible) or ask their parent/guardian to hang up the telephone before proceeding with the screening questions.

2. 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 an interview appointment. This PII, which will be recorded separately from the screener by recruitment firm staff (see "Closing Script and Contact Information" **Attachment J3**), 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. The screener and the form with PII will be destroyed within one month of the study's end date. Neither Concentrics, RTI, or FDA will have access to the PII recorded or maintained by the recruitment firms.

3. Participants will be identified by a unique Participant ID number in the participant database; this ID number will be assigned by Concentrics staff at the beginning of each interview. The ID number will not be recorded on any other forms. The ID number will be used to link survey interview data to some of the screening data. This linkage is essential for analysis and interpretation of findings. For example, FDA needs to know if there are differences in label comprehension across (Group 1 and 2 vs. Group 3 vs. Group 4) and within groups (low vs. normal health literacy) and by key demographic characteristics (e.g., education level, race/ethnicity, or gender).

4. The recruitment firms will provide Concentrics staff with an interview schedule that will include participants' first names and basic demographic information only (e.g., race/ethnicity, gender). They will not share PII with RTI, Concentrics, or FDA. All data will be reported to FDA de-identified with no PII included.

5. At the start of the interview, the interviewer will ask participants not to disclose PII, describing what is meant by PII and providing examples. If a participant does share PII, the interviewer will remind the participant not to disclose PII. In such cases, the interviewer will record the participant's ID number so they know which audio files contain PII. These audio files will be flagged for the transcription firm so they know which ones contain PII that should be excluded from the transcripts. Additionally, the flags will indicate which audio files should not be transferred to RTI. If Concentrics inadvertently emails RTI audio files with PII, RTI will destroy them immediately (i.e., the email will be deleted from the sender and recipients' sent and deleted items folders) and replaced with deidentified versions on RTI's share drive. The audio files will be destroyed within two years of the study's end date.

6. All data collection activities, including assent, review of the DFL, and the interview, will take place behind closed doors.

In addition to these measures, data will be handled in the following ways to protect privacy:

Individual, in-person survey interview data. Survey data will be captured directly into an electronic tablet using DatStat. DatStat is a software-as-a-service and all data entered in DatStat are saved to the cloud, rather than on the tablet directly. DatStat uses TierPoint to host their data. Data will be downloaded from DatStat's Tierpoint server by HTTPS directly to Concentrics for analysis.

While data capture by tablet is the preferred method, data may need to be captured on paper if the technology fails. Data captured on paper forms will be placed in sealed envelopes by Concentrics staff and shipped to Concentrics for data entry.

Audio recordings. Audio files will be transcribed (excluding any portions containing PII). The audio recordings are meant to serve as backups for the notes and will allow the RTI Project Director and Associate Project Director to listen to a subset of the survey interviews for quality assurance and control purposes. Concentrics will not send RTI audio files that contain PII. Audio files will be stored in a restricted location on the Concentrics network, with controls in place as specified in "data security". The audio files will be transferred from Concentrics to RTI using an SFTP or encrypted zip file.

Data handling across types. The electronic audio files, electronic and hard copy transcripts, and electronic and hard copy survey interview data will be destroyed within two years of the study's end date, and all electronic and hard copy PII will be destroyed within one month of the study's end date. Access to data will be restricted to team members approved by Project Management. This may include (but is not limited to) the Project Manager/Director, Associate Project Manager/Director, Data Coordinator, Coders, and statistician. Data transmission between RTI and Concentrics will need to occur. Notably, Concentrics will need to provide RTI with the individual, in person survey interview data. To facilitate secure transmission of data, RTI will set up an SFTP account at RTI and use a client such as FileZilla to securely transmit data between the two entities. Concentrics staff will store signed parental permission forms and adolescent assent forms at Concentrics to avoid the potential for forms to get lost in transit.

FDA's RIHSC will be reviewing this study as an expedited review, and RTI's IRB will also review as an expedited review. RTI IRB's address is: RTI's Office of Research Protections, 3040 Cromwell Road, Durham, NC 27709. Juesta Caddell is the contact person, and the FWA is 3311.Claudia Squire, MS of RTI is the principal investigator for this study. Her telephone number is 919-541-6613.

7. Amount and justification for any proposed incentive

A token of appreciation is intended to recognize the time burden placed on participants and to help defray expenses related to study participation. A token of appreciation helps ensure that sufficient numbers of participants can be recruited to participate in the data collection. Research has shown that offering a token of appreciation improves response rates (Ryu et al., 2006; Singer et al., 1999), thus it is likely that without the token of appreciation, 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 token of appreciation 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). Although we considered a lower amount, two recruitment firms experienced with similar data collections advised against this for several reasons based on past experience.

- Equity – All respondents should be treated equally regardless of subgroup; in this case, the subgroups are based on age. The screening and data collection procedures for adolescents and adult all-comers (Group 4) are the same.

- Participant burden – Transportation time may vary significantly by geographic area which would affect adolescents attending on their own via public transportation or personal vehicle as well as parents/guardians who bring their adolescent child to the data collection.

- Data quality – The no-show/cancellation rate may increase with a lower payment amount, and skew toward the inclusion of lower income populations, which would affect the validity and reliability of the data.

8. Questions of a Sensitive Nature

None of the screener or survey interview questions for Task 3 – Adolescent All-Comers are of a sensitive nature. As previously described, the goal of these individual, in-person survey interviews is to assess comprehension of the DFL. 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

The study team will use transcribed audio files and participant screener and individual, in-person survey interview data when summarizing findings for this study. These data will be aggregated

in tables and text with no personally identifiable information in table and text formats to describe study participants.

FDA staff will prepare a statistical analysis plan, with analyses organized according to the primary and secondary objectives defined in the protocol. Concentrics Research staff trained in quantitative and qualitative analysis methods will review and code the data. Confidence intervals using the exact method will be calculated to evaluate success thresholds. All analyses will be data-driven. The RTI analysis team will meet with the Concentrics team periodically to discuss findings and conclusions. The study team 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	No. of Respondents	Participation Time (minutes)	Burden (hours)*
Screener	1,120	5	93
Survey interview	140	30	70
Total			**163**

Note: *The study team estimates that they will need to screen 1,120 adolescents to obtain 140 completed individual, in-person survey interviews due to the need to obtain parental permission prior to screening. The annual burden is estimated to be 163 hours.*

REQUESTED APPROVAL DATE: April 2018

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FDA CENTER: Center for Drug Evaluation and Research

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