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 Cognitive Interviews to Optimize the Drug Facts Label (Task 1)

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 application details procedures and materials for Task 1 only; we will update the application for Tasks 2 and 3 with amendments as the procedures and materials for subsequent Tasks are available and are informed by study results in Task 1.

The cognitive interviewing process to assess concepts and perceptions about the draft DFL (Task 1) comprises the first of three stages of a comprehensive label comprehension testing program:

> **Task 1: Cognitive Interviews to Optimize the Drug Facts Label (N=36).** The purpose of Task 1 is to obtain rapid feedback about the model DFL from potential end users of OTC Naloxone through administration of unstructured cognitive interviews with user segments defined by FDA (see section 3). We will conduct Task 1 activities through partnerships with SouthLight Healthcare in Raleigh, North Carolina and through Shugoll Research in the metro-DC area. Because the purpose of Task 1 is to obtain feedback on the DFL for future testing, the sample for Task 1 is not intended to be nationally representative.

Task 2: Pilot Label Comprehension Study (N=36). The purpose of Task 2 is to design and implement structured interviews to assess comprehension of pilot survey questions and to inform sample sizing for the Task 3 Pivotal Study. Task 2 will involve the same user groups as the previous Task (see section 3), but different participants. We propose to conduct Task 2 activities through partnerships with community-based organizations in Chicago, Illinois and through Shugoll Research in the metro-DC area. Because the purpose of Task 2 is to test and refine survey items in preparation for the quantitative survey (Task 3), the sample is not intended to be nationally representative.

Task 3: Quantitative Pivotal Comprehension Study (N=710). The purpose of Task 3 is to determine if a significant proportion of participants comprehend the key communication objectives and meet the established thresholds for success. Task 3 will involve the same user groups as the previous Tasks (see section 3), but different participants. We will recruit participants from a larger and more geographically diverse set of community-based organizations for Task 3 (up to 7 locations across the U.S.), including the Concentrics Research testing facility in Indianapolis, Indiana for the "all comers" group.

2.**Intended use of information:**

The study objective for Task 1 is to obtain feedback about the model DFL from potential end users of OTC Naloxone through the administration of unstructured cognitive interviews with defined user segments. The information collected in Task 1 will be used to inform the subsequent study stages (Tasks 2 and 3).

3.**Description of respondents:**

The study population for Task 1 will consist of four user groups defined by FDA:

1. **Group 1 (n=9):** Prescription opioid users, including those in drug treatment programs, as well as family/friends of users who are not users themselves (i.e. associates).
2. **Group 2 (n=9):** Heroin users, including those in drug treatment programs, as well as their associates.
3. **Group 3 (n=9):** Adolescents (ages 15-17) who are prescription opioid users and/or heroin users, including those in drug treatment programs and/or their adolescent associates.
4. **Group 4 (n=9):** All comers, primarily consisting of low literacy general consumers and including some pregnant women.

We have developed separate screener questionnaires for Groups 1 – 3 (Attachment A) Group 4 (Attachment B) to assess for potential eligibility.

Eligibility Criteria

Individuals will be included in the study if the following criteria are met. Collection of information on drug use is for screening purposes only and will be assessed by self-report; no medical records or samples will be used in this study.

Group 1 – Prescription Opioid Users & Associates (n=9)

1. Male or female, of any race
2. 18 years of age or older
3. Self-reported use of prescription opioids in the past 30 days (if user)
4. Self-reported associate of prescription opioid user (if associate)

Group 2 – Heroin Users & Associates (n=9)

1. Male or female, of any race
2. 18 years of age or older
3. Self-reported use of heroin in the past 30 days (if user)
4. Self-reported associate of heroin user (if associate)

Group 3 – Adolescent Prescription Opioid Users & Adolescent Associates (n=9)

1. Male or female, of any race
2. 15 to 17 years of age
3. Self-reported use of prescription opioids in the past 30 days (if users)
4. Self-reported use of heroin in the past 30 days (if user)
5. Self-reported associate of 15-17 year old prescription opioid user or heroin user (if associate)

Group 4 – All comers (n=9)

1. Male or female, of any race
2. 18 years of age or older
3. Score 60 or below on REALM
4. Some participants must be pregnant

In addition to this screening information, we will collect ancillary data on use during the past 90 days and frequency of prescription opioid and/or heroin during the past 30 days to distinguish heavy from recreational users. These data will be used for analyses purposes only.

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

1. The participant or anyone in their household is currently employed by any of the following:
    - A marketing or marketing research company
    - An advertising agency or public relations firm
    - A pharmacy or pharmaceutical company
    - A manufacturer of medicines
    - A managed care or health insurance company
    - A healthcare practice
2. The participant has ever been trained or employed as a healthcare professional.
3. The participant normally wears corrective lenses, contacts or glasses to read and does not have them with him/her at the time of the interview.
4. The participant is appears to be significantly impaired (e.g. under the influence of drugs or alcohol) at the time of the interview as observed by the study staff and incapable of providing proper consent or interpretation of verbal or written instructions or materials. All study staff will be trained by qualified researchers on how to identify significant impairment.
5. The participant has participated in any clinical trial, product label study or marketing research study involving a healthcare product or topic in the previous twelve (12) months.
6. The participant cannot read, speak and/or understand English.

FDA has requested that at least 30% of the participants in Groups 1-3 be of lower literacy and that all or nearly all Group 4 participants have low literacy. We will use a validated, one-item question to assess for potential low-literacy at the initial screening for adults (Wallace et al., 2006). We will not use this screening item with adolescents, as it has not been validated for this population. The Rapid Estimate of Adult Literacy in Medicine (REALM) and Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen), also validated literacy screening tools, will be used to assess literacy on-site after consent but prior to conducting the study interview (Davis et al.,1993; Davis et al., 2006). Individuals who are screened for eligibility with the REALM but are ultimately excluded due to their scores will still receive the study incentive.

<u>Recruitment Partners (Task 1)</u>

To recruit participants for Tasks 1 we will work with SouthLight Healthcare (http://www.southlight.org/), a community-based organization located in Raleigh, North Carolina (Groups 1-3) and Shugoll Research, a recruiting firm located in the metro-DC area (Group 4).

Recruitment partners and materials for Tasks 2 and 3 are in development; details will be provided as future amendments to this application.

a. SouthLight Healthcare

SouthLight Healthcare has provided comprehensive substance abuse programs for adolescents, adults, and families in the Raleigh area for over 45 years. SouthLight is an ideal partner for recruitment of user groups 1-3 due to their client volume and the breadth of services they provide.

Participants will be recruited from multiple programs within SouthLight:

- The adult outpatient clinic that provides daily medication-assisted therapy for the management of opioid dependence.
- Two residential facilities for adults, one of which treats pregnant and postpartum women with substance use disorders and another that offers supervised independent living for chronically addicted adults who have experienced homelessness or have co-occurring mental health disorders.
- The youth and family services program that provides prevention, education, and treatment services to youth who have or are at risk for addiction.

To ensure we are able to achieve the desired sample in the time allotted, we are implementing a multipronged recruitment strategy that assumes that the majority of interviews will be scheduled prior to data collection:

1. We will provide SouthLight staff with a Provider Information Sheet about the study so they are aware of the organization's involvement and how they can be of assistance (Attachment C). In addition, they can use the Provider Information Sheet to inform their discussions with clients who may be eligible for the study.
2. We will post study flyers at each SouthLight location (Attachment D). The flyer provides information about the study and contact information should they wish to be screened for eligibility.
3. We will give SouthLight staff palm cards with details about the study to distribute to clients who express interest in participating in addition to placing them in client waiting areas (Attachment E).

The materials make it clear that we are interested in recruiting associates in addition to users. They direct individuals to call the study's toll-free number or contact us by email if they are interested in learning more. A designated RTI staff member will field all phone calls and emails. The RTI staff member will assess eligibility using the Group 1-3 screener (Attachment A).

Regarding associates, we anticipate that some will be exposed to flyers and palm cards placed throughout the clinic as they may be clients themselves or when they transport clients to and

from clinic appointments. Others may learn of the study through word of mouth. We expect that most associated will be family members of the adolescent users.

If we are unable to fully recruit for the data collection prior to the interview dates, we will recruit additional participants onsite. Research study staff will be onsite during peak flow hours to recruit additional participants by handing out flyers and palm cards. We will also ask providers onsite to assist in recruitment efforts by referring patients who have appointments to the research study staff.

All study staff will participate in a cultural competence training to ensure implementation of best practices that adhere to the highest ethical standards when working with drug-using populations (National Commission for the Protection of Human Subjects of Biomedical Behavioral Research, 1978). Researchers with expertise in illicit opioid use and working with this population will conduct the training.

SouthLight will receive a small honorarium ($30 per recruited participant) in appreciation of their time.

Shugoll Research

We will partner with Shugoll Research in the metro-DC area to recruit the group 4 (all-comers group). RTI has a longstanding relationship with Shugoll Research and they have experience recruiting low literacy and hard-to-reach populations. Shugoll's location on the DC metro stop is accessible to diverse populations, and their facility provides a 1-way mirror for FDA observation.

Recruiters from Shugoll Research will identify potential participants through their community partners and will contact them by telephone to assess eligibility using the Group 4 screener (Attachment B). Interviews will be conducted in-person at the Shugoll facility.

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

Data collection for Task 1 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 1 is comprised of one-time, unstructured cognitive interviews to evaluate and optimize the draft DFL. These one-on-one interviews will be conducted in person with participants in each of the four user groups. RTI and Concentrics Research will work in a 2-person team at each location. RTI staff will coordinate data collection logistics and assess individuals for drug or alcohol-related impairment prior to checking them in. Concentrics Research staff will administer informed consent 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 interview study only; no drug will be administered or dispensed.

Once at the study location (a private office or conference room at SouthLight), the participant will be provided with an Agreement to Participate (ATP) that outlines the purpose and voluntary nature of the study (Attachment F). Both adult (age 18 and over) and adolescent (age 15-17)

participants will be required to provide written consent to be in the study. This study will not require parental consent in addition to participant consent for the adolescent group (ages 15-17), which is consistent with published guidelines for market research stipulating that parental consent is required for participants under the age of 13 (MRA, 2007). Further, the study poses no more than minimal risk to participants regardless of age; the purpose of the study is to provide feedback on a DFL and assess comprehension of information. The study questionnaire will not collect sensitive information. In addition, recruitment of adolescent populations could not be practically carried out should parental consent also be required. Adolescents who are patients in the treatment centers where data collection will occur might not be accompanied by a parent (e.g., they may be dropped off for treatment appointments or accompanied by another relative, sibling or friend). It should also be noted that adolescents who are in attendance for treatment have consented to be there. Participants who sign the ATP will next undergo a literacy assessment using the Rapid Estimate of Adult Literacy in Medicine (REALM) Test for participants who are ages 18 and older or the Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen) Test for participants who are ages 15-17. FDA has requested that approximately 30% of group 1-3 participants be of lower literacy and that all or nearly all of group 4 participants are of lower literacy defined as a REALM score of <60.

Following the literacy assessment, the participant will be given the naloxone DFL (Attachment G). The moderator will leave the room to give the participant the opportunity to review the DFL at his/her own pace. Once the participant indicates he/she is finished reading the labeling, the moderator will return to the room and begin the cognitive label assessment interview. Participants will be asked exploratory, open-ended questions to assess their understanding and interpretation of the text and pictograms included on the DFL (see Moderator guide, Attachment H). The DFL will be provided on paper similar in size and shape to the planned commercial package. The DFL may be revised iteratively throughout the interviews, and additional concepts to address points of confusion may be shown to participants as appropriate.

The interviews will be audio recorded. For group 4RTI staff will also take notes during the interviews to record nonverbal cues and behaviors (e.g. apparent participant confusion or difficulty in evaluating the labeling) to accompany the final audio-recording. RTI staff will take notes outside of the interview room from behind a one-way mirror to avoid the possibility of distracting the participant or making him/her uncomfortable. For groups 1-3, RTI staff will take notes only if it is feasible to do without being in the same room as the participant (e.g., from behind a partition). Total interview time will be 45 minutes, which includes time to administer the REALM.

Once the interview is completed, RTI staff will provide the participant with a monetary incentive. Participants in groups 1-3 and group 4 will receive the equivalent of $60 and $75, respectively. Section 7 provides justification for the incentive amounts.

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

Upon completion of Task 1 activities, FDA and the RTI-Concentrics Research team will determine whether a second round of testing on a revised DFL is needed. If additional testing is deemed appropriate, we will recruit the same numbers (N=36), but different participants from the same 4 user groups and locations and using the same study procedures.

6.**Confidentiality of Participants:**

All study participants will be informed both as part of the written consent and again during the interviews that no reports or other information will identify participants by name, that all information will be anonymized and reported in aggregate, and that their information will be kept private to the extent possible given the study methods. For all interviews, all notes taken will be kept in a locked file cabinet or on a password-protected computer. Any forms related to the project that have names or other information that could identify individual respondents will be kept separate from the interview data provided to FDA. The information will be kept in a secured fashion that will permit access only by authorized project staff. All personally identifiable information will be removed from transcripts, audio files, reports, and all other materials before RTI-Concentrics provides them to FDA. All files will be stored on password-protected computers at RTI, Concentrics and FDA. These confidentiality methods will be approved by Concentrics' Institutional Review Board and FDA's Research Involving Human Subjects Committee, (RIHSC) prior to collecting any information.

7. **Amount and justification for any proposed incentive**

Monetary incentives are intended to recognize the time burden placed on participants, encourage their cooperation, and convey appreciation for their contributions to the research. Incentives help ensure that sufficient numbers of participants can be recruited to participate in the data collection. Research has shown that monetary incentives improve response rates (Ryu et al., 2006; Singer et al., 1999), thus it is likely that without the incentive 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.

Participants in Groups 1–3 will receive the equivalent of $60 for participating in Task 1 interviews; this amount is somewhat lower relative to other FDA studies, but it is an amount that has been used successfully for other RTI-lead interviews of a similar length with drug users. Our 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). Participants in Group 4 will receive $75. The amount for this group is higher because the appearance of coercion is not as sensitive of an issue when conducting general population studies. Further, participants in Group 4 will be required to travel to the Shugoll location in the metro-DC area and thus participants may incur more time in commuting and some travel costs. The $75 amount is the minimum of what Shugoll Research suggests to be able to successfully recruit participants for this study.

8. **Questions of a Sensitive Nature**

None of the interview questions for Task 1 are of a sensitive nature. We will ask potentially sensitive questions about opioid use only during the screening process when assessing study eligibility (see screening materials, Attachments A and B). As previously described, the focus of these interviews is to discuss comprehension of key messages in the naloxone DFL (e.g., call 911 immediately). As part of the informed consent 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. To ensure cultural competence, all interviewers will

participate in a cultural sensitivity training led by an expert in the area of illicit opioid use and working with this vulnerable population.

9. **Description of Statistical Methods**

We will use transcribed audio files, interview notes and participant screener data and demographics when summarizing findings for this study. The screener data and demographics will be summarized in aggregate format with no personally identifiable information in table and text format to describe study participants. Data collected through the interviews will all be qualitative data, thus we will conduct a thematic analysis of all data.

Analyses will be organized around the major topics included in the interview guides. Project team members trained in 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 quantitative work. These will be summarized into a final report with quotations from the interviews provided as examples for the key themes.

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)**
Task 1	Screener	350	5	29.2
	Interview	36	45	27
Task 1: *Optional 2nd round of data collection*	Screener	350	5	29.2
	Interview	36	45	27
	Total (Task 1)	**772**	**5-45 minutes**	**112.4**
Task 2	Screener	350	5	29.2
	Interview	36	45	27
Task 3	Screener	910	5	75.8
	Interview	710	30	355
	Total (Tasks 1-3)	**2778**	**5-45 minutes**	**599.4**

Note: *We are estimating 350 participants screened to obtain 36 completed interviews for Task 1. This estimates includes all user groups 1-4. We anticipate needing to screen the largest number of participants (300) to obtain 9 completed interviews for the group 4"all-comers" due to the requirement of including all or nearly all low-literacy participants and some pregnant women. We anticipate screening a smaller number of participants (50) to complete 27 interviews for user groups 1-3 given the targeted recruitment approach and relaxed criteria for low literacy. The burden hour computations also account for the possibility of a second round of testing for Task 1 activities, per FDA's recommendation. Based on results for Task 1, we may adjust these calculations for future tasks (Task 2 and 3) in our study amendments.*

REQUESTED APPROVAL DATE: August/September 2016

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FDA CENTER: CDER

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