FDA DOCUMENTATION FOR THE GENERIC CLEARANCE,
"TESTING COMMUNICATIONS ON DRUGS PRODUCTS"
(OMB Control Number 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 – Adult 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 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 Research). 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:

- Task 1: The RTI-Concentrics Research team (hereafter referred to as the 'study team') conducted cognitive interviews with adult prescription opioid and/or heroin users and their non-using friends and family (i.e., associates) (Group 1 and 2) and adult all-comers (Group 4) to optimize the DFL.

- Task 2: The study team conducted individual, in-person interviews with participants representing Groups 1 and 2, 4, and an additional group comprised of adolescent all-comers (Group 3) to assess comprehension of pilot survey questions that will be asked during and to inform sample sizing for the pivotal study in Task 3.

- Task 3 (this protocol): The study team will conduct individual, in-person survey interviews with participants representing Groups 1, 2 and 4 to test comprehension of the DFL.

This application details procedures and materials for Task 3 - adult all-comers (Group 4) and prescription opioid and/or heroin users/associates (Groups 1 and 2) only; we will seek separate approval for Task 3 – adolescents (Group 3).

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 - adults will consist of two user groups defined by FDA:

1. **Group 1 and 2 (n=430):** Adult prescription opioid users and/or heroin users, including those in drug treatment programs, as well as family/friends of users who are not users themselves (i.e. associates), including 30% limited literacy users/associates. (Note that in Tasks 1 and 2, Group 1 and Group 2 were treated as separate groups. They are combined in Task 3 because many users reported dual use.)
2. **Group 4 (n=140):** Adult all comers, including 30% limited literacy general consumers.

Eligibility Criteria

Individuals will be included in the study if the following criteria are met. (There are separate screeners for Group 1 and 2 [**Attachment A** is the online screener and **Attachment B1** is the telephone screener for this group] and Group 4 [**Attachment B2** is the telephone screener for this group] to assess eligibility).

Group 1 and 2 – Prescription Opioid and/or Heroin Users & Associates (n=430)

1. Male or female, of any race
2. 18 years of age or older
3. User: An individual who reports prescription opioid and/or heroin use in the past 90 days or is in treatment for prescription opioid and/or heroin use
4. Associate: An individual who does not report prescription opioid or heroin use in the past 90 days *and* is not in treatment for prescription opioid or heroin use *and* knows someone who uses prescription opioids or is in treatment for prescription opioid use

Group 4 – All comers (n=140)

1. Male or female, of any race
2. 18 years of age or older

FDA has determined that at least 30% of the participants in all three groups be of limited literacy. For Groups 1 and 2, the study team will use responses to income- and education-level questions to assess for potential low-literacy at the initial screening. For Group 4, the study team will use responses to two validated, single item questions (Wallace et al, 2006; Morris et al, 2006) to assess for potential limited literacy at the initial screening, The interviewer will administer the validated Rapid Estimate of Adult Literacy in Medicine (REALM) to adults

(Davis et al., 1993) to assess literacy on-site after consent but prior to conducting the study interview (see "Group 1-2 Structured Interview Guide" in **Attachment C1** and **"**Group 4 Structured Interview Guide" in **C2** for the literacy assessment). Individuals excluded from the study due to their REALM scores will still be provided with a token of appreciation 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. Individuals who do not choose one of the identified cities/areas as their location during the screening process (Group 1 and 2 online screening only).

2. Individuals who have been ordered by a judge to participate in treatment (Group 1 and 2 only).

3. The individual or anyone in their household is currently employed by any of the following (for Groups 1 and 2, 4)

    - 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 or hospital emergency room

4. The individual has ever been trained or employed as a healthcare professional (for Groups 1 and 2, 4).

5. The individual has participated in any research study in the past 12 months (for Groups 1 and 2, 4) or an earlier phase of this study in the past 2 years (for Groups 1 and 2).

6. The individual cannot read, speak and/or understand English (for Groups 1 and 2, 4).

7. The individual normally wears corrective lenses, contacts or glasses to read and does not have them with him/her at the time of the interview (for Groups 1 and 2, 4).

8. The individual appears too 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 consent or interpreting verbal or written instructions or materials. Overt signs of impairment include difficulty staying awake or 'nodding off', or unsteadiness (e.g., stumbling or swaying), or an inability to actively interact with study staff. All study staff received training on how to identify signs of impairment. If a participant exhibits any of these signs and/or study staff have other concerns about the participant's ability to participate in the study, the study team will terminate the interview process. Study staff will urge the participant to call a family member or friend to pick them up or to remain at the study site until they are no longer impaired. However, the study team cannot force the participant to remain on the premises if he/she does not want to (for Group 1 and 2 only).

<u>Recruitment and Screening</u>

Recruitment and screening procedures will vary by group. An overview of the process is shown in ***Exhibit 1***. The remainder of this section describes the recruitment methods followed by the screening procedures, by group.

Exhibit 1. Overview of Recruitment and Screening Methods, by Group

Group	Recruitment Method	Screening Process
Group 1 and 2: Prescription opioid and/or heroin users/associates	Targeted community outreach Online advertising Participant referral	Online* Telephone
Group 4: All comers	Recruitment firm	Telephone

* Note that individuals recruited through online mechanisms will only have the option to be screened online.

Groups 1 and 2

Recruitment. As shown in Exhibit 1, adult users and associates representing Groups 1 and 2 will be recruited through a variety of mechanisms, each of which is described below.

Targeted Community Outreach. This strategy encompasses working with a variety of organizations to advertise they study through posting flyers and distributing palm cards. This includes organizations that provide substance abuse treatment services (e.g., medication-assisted treatment, or MAT), as well as other types of community-based organizations (CBOs) frequented by potential participants, such as harm reduction or literacy-based organizations. To ensure that we reach our target numbers, we have identified at least one CBO in each location that will allow us to conduct onsite recruitment and data collection. Furthermore, the inclusion of CBOs that provide services other than substance abuse treatment or harm reduction will enable us to reach potential associates who may not interact with treatment centers and harm reduction organizations.

If permissible, we will also post flyers in other venues frequented by potential participants (e.g., community centers, grocery and convenience stores, public notice boards like those found at libraries and other venues of this type).

When we work with service providers (i.e., organizations that provide substance abuse treatment services and CBOs) for recruitment purposes, we will use the following mechanisms to ensure they are informed about the study and prepared to assist:

1. To ensure the study team can achieve the desired sample in the time allotted, they are implementing a multipronged recruitment strategy that assumes that most interviews will be scheduled prior to data collection. They will do the following:

2. Give service providers the Provider Information Sheet which explains the study and how they can be of assistance (**Attachment D**). In addition, they can use the Provider Information Sheet to inform their discussions with clients who may be eligible for the study.

3. Post study flyers throughout the facility (**Attachment E**). The flyer provides information about the study and contact information should they wish to be screened for eligibility.

4. Provide service providers 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 F**).

The materials make it clear that the study is interested in recruiting associates, who may be family members or friends of clients, in addition to users (associates may be exposed to study materials when they transport their friend/family member to the location or if they attend a counseling session or other activity at the site). They direct individuals to visit the study's website or to call the study's toll-free number to see if they are eligible.

Exhibit 2 lists the organizations (by type) that RTI and Concentrics will work with to facilitate recruitment. We also show their form of participation as some of these organizations will serve as data collection sites. (A more detailed description of each is included in **Attachment G**.) Additional organizations for advertising may be identified.

Exhibit 2. Recruitment and data collection sites and their forms of participation, by location

Location	Site Name (Type)	Form of Participation
Chicago, IL	Family Guidance Centers, Inc. (MAT)	Onsite data collection[1] and advertising
	Hazelden Betty Ford (substance abuse treatment other than MAT)	Advertising only
	Chicago Recovery Alliance (harm reduction organization)	Advertising only
	Community Outreach Intervention Projects (harm reduction organization)	Advertising only
	Literacy Chicago (adult literacy organization)	Advertising only
North Carolina	Vance Recovery (MAT)	Onsite data collection and advertising
	SouthLight (MAT)	Onsite data collection and advertising
	Durham Literacy Council (adult literacy organization)	Advertising only
West Virginia	Charleston Treatment Center (MAT)	Onsite data collection and advertising
	The Kanawha-Charleston Health Department / Harm Reduction – Syringe Service Program	Advertising only
San Francisco, CA	Westside Community Services (MAT)	Advertising only
	BAART Turk (MAT)	Onsite data collection and advertising

[1] CBOs that participate in the form of onsite data collection are referred to as 'onsite CBOs'.

Online Advertising. The study team will post advertisements online. The online advertisement (**Attachment H**) provides similar details to what is included in the flyers and palm cards. Potential online advertising venues include the following:

- Craigslist: The study team will post the advertisement in the 'services' category.

- Facebook: The study team will post the advertisement on Facebook. They will focus on Facebook groups for people who use prescription opioids and/or heroin or who are in treatment for or in recovery from prescription opioid and/or heroin use (e.g., Heroin Addiction Support, Methadone Maintenance Treatment Support). They will request permission from group administrators to post study information on the groups' pages if it is necessary to do so as some groups may be closed to non-members.

- Online forums: The study team will post the advertisement on online forums that target prescription opioid and/or heroin users or people in treatment for or in recovery from prescription opioid and/or heroin use (e.g., BlueLight, SoberRecovery). If necessary, they will request permission from forum administrators to post study information on the website.

Participant referral. Eligible individuals will be asked to mention the study to others in their social networks who may be interested in participating. This will occur in one of two ways depending on how individuals are screened. If eligibility is determined through online screening, individuals will be invited to refer others to the study when they receive the link to the online scheduler (if a referral tries to schedule an appointment through the online scheduler before they are screened and invited to participate, their appointment will be rejected by RTI staff; only those invited by RTI are able to schedule an appointment. If rejected, the potential participant will receive an email directing them to the study website and phone line to be screened for the study- see "Telephone and Email Scripts" **Attachment I)**. If eligibility is determined by telephone, the RTI recruiter will convey the invitation to refer others to the study as part of the closing script (see "Group 1 and 2 Closing Script" in **Attachment J1**). In both cases, the referral script makes it clear that referring others to the study is not a requirement for participation.

Screening. Screening can be accomplished online or by telephone; however, individuals who learn about the study through the online advertisement must take the screener online (only the study web address is provided). We are using the Qualtrics.com platform for the online screener which has several measures in place to ensure security to the extent provided by law and data quality (see Section 6). Individuals who choose to access the screener online via the study's website will be presented with information about the study; told that they will be asked questions, some of which are about drug use (their own use and among people they know), to see if they are eligible to participate; that their responses will be kept private and that their contact information will be kept separately from their responses to the screener questions; and that they can choose not to answer any question and stop participating at any time (see "Group 1 and 2 Online Screener" in **Attachment A**). The script will also inform individuals that if they are eligible and wish to participate, they will need to provide their first name, email address, and/or phone number so study staff can send them a link to the online interview scheduler and remind

them of their interview appointment. Finally, the introductory script will inform individuals that the survey interviews will be audio recorded, which is a condition of participation.

After reviewing this information, individuals will be asked to indicate their consent to be screened by selecting "next" which will advance them to the first screener question. If they do not wish to proceed, they will be instructed to close their internet browser. Individuals who are eligible for the study based on their answers to the screening questions will be presented with an invitation script. The script will inform them that they are eligible for the study and that if there is space available, they will be contacted by email with a link to the online scheduler in the next 48 hours. They will be asked to provide their email address and telephone number if they would like to proceed with this step.

Designated RTI staff (i.e., RTI recruiters) will monitor online screener responses daily and determine which eligible participants to invite into the study. This determination will be made based on two factors:

1. *Established targets to ensure diversity in the sample in terms of drug type (i.e., prescription opioid, heroin, or dual users), literacy level, and user vs. associate status.* If an individual is eligible, but the quota has been met for their segment, RTI will send them an email alerting them that they are on a waiting list and will be contacted if space becomes available.

2. *Limited risk of screening fraud.* It is possible that someone may complete the online screener more than once if they do not qualify for the study the first time. RTI will use IP addresses and timestamps together as a heuristic for identifying duplicates to help ensure that individuals who complete the screener more than once are not invited to take part in the study.

The RTI recruiters will send eligible individuals an email from the online scheduling system, 10to8.com, that is specific to their city. They will be prompted to sign up for an interview slot in the preset schedule for that city. The scheduler will show only blocks of time that are available; no information about other participants will be visible. **Exhibit 3** shows a screenshot of the online scheduler. Scheduled participants will automatically be sent a confirmation email from 10to8.com. The system allows a user to sign up for one slot only. The system will be set so that it only allows email addresses inputted by RTI recruiters to sign up for an interview slot, thus limiting the risk of non-screened individuals signing up an appointment (if an invited participant forwards the invite to someone else that person will not be able to sign-up if they are not in the database of invited participants) If the participant does not respond to the email within 48 hours, the RTI recruiters may initiate a follow-up contact through email and/or telephone to ensure the scheduling email was not diverted to their spam folder. **Exhibit 4** shows what the scheduler will look like when someone selects an interview slot.

Individuals also have the option to call the study's toll-free telephone number for screening. RTI recruiters will field all inquiries from potential participants and screen those who are interested by telephone using a standardized screening process (**Attachment B1**). The recruiter will introduce the study to potential participants and let them know that they will need to ask them sensitive questions about drug use, both their own use and among people they know, to see if

they are eligible to participate; that their responses will be kept private and that their contact information will be kept separately from their responses to the screener questions (see "Group 1 and 2 Closing Script" in **Attachment J1)**; and that they can choose not to answer any question and stop participating at any time. RTI staff will inform them that if they are eligible and wish to participate, they will need to record their first name, email address and/or phone number so they can remind them of their interview appointment. Prior to asking any questions, the recruiter will request individuals' permission to proceed with the screening process. They will only screen those individuals who grant permission. The RTI recruiter will invite people who are eligible to participate in the study and schedule an interview should they wish to participate.

To help protect privacy, RTI will use the Qualtrics system to complete the screener whenever possible; i.e. staff will enter responses directly into the online screener. This will eliminate having hard copies of files with sensitive information or personally identifiable information (PII). In some cases, however, it may not be possible to access the online screener during screening (e.g., if Qualtrics is experiencing technical issues). In such cases, only RTI-RTP staff (considered 'onsite') will be permitted to conduct screening by telephone to help protect privacy. This is because offsite staff cannot store the hard copy screeners in the project director's locked filing cabinet until they can access the Qualtrics database (which increases the risk of a privacy breach). If the Qualtrics database is inaccessible when offsite staff field a screening call, they will transfer the call to an onsite recruiter. Onsite staff must enter screener data into the online database within 24 hours and will shred the hard copies immediately thereafter.

If RTI recruitment staff are unable to answer the phone, the caller will be asked to leave a message with his/her first name and telephone number so staff can call him/her back for screening purposes. The voicemail box will be password protected and only accessible to RTI staff responsible for screening potential participants.

If study staff are unable to fully recruit for the data collection prior to the interview dates, or if there are last minute cancellations or no-shows, they may recruit additional participants by handing out flyers and palm cards at onsite CBOs during data collection.

Group 4 (all comers)

The study team will work with recruitment firms in the designated locations to recruit Group 4 participants. See **Exhibit 5** for a list of facilities by location.

Exhibit 5. Group 4 Recruitment Firms, 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

Recruitment firm staff will identify potential participants through their community partners and/or proprietary databases and will contact them by telephone to assess eligibility using the Group 4 screener (**Attachment B2**). Recruitment firm staff will inform participants that their responses will be kept private, that their contact information will be kept separately from their responses to the screener questions (see "Group 4 Closing Script" in **Attachment J2)**, and that they can choose not to answer any question and stop participating at any time. They will schedule interview appointments with individuals who are eligible and interested in participating.

4. Date(s) to be Conducted:

Data collection for Task 3 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 3 is comprised of 30-minute, one-time, individual, in-person survey interviews to assess comprehension of the DFL. RTI and Concentrics staff will work in teams to conduct the survey interviews at each location for Groups 1 and 2. Concentrics staff will conduct the Group 4 survey interviews on their own (with the recruitment firm staff assisting with logistics). RTI staff will coordinate data collection logistics and assess individuals from Group 1 and 2 for drug or alcohol-related impairment prior to checking them in. Recruitment firm staff will be responsible for checking in Group 4 participants. For Groups 1 and 2, RTI and Concentrics Research staff will share responsibility for administering informed consent, the REALM and conducting the interviews. For Group 4, Concentrics staff will be responsible for these activities. All interviewers are experienced and qualified in the requisite data collection methods. Concentrics Research will provide specific training on administering the survey interview via tablet to RTI staff (and Concentrics Research staff who were not involved in previous tasks) prior to data collection since they did not conduct interviews for Task 1 or 2. RTI will provide training to all staff on the consent process.

This is an individual, in-person survey interview study only; no drug will be administered or dispensed.

Group 1 and 2 interviews will take place at onsite CBOs (see **Exhibit 2**), RTI offices (Research Triangle Park, NC; Chicago, IL; and San Francisco, CA), and private rented office space (Charleston, WV only). Group 4 interviews will take place at the designated recruitment firms (see **Exhibit 5**).

When participants arrive to the data collection location, study staff will provide the participant with the consent form that outlines the purpose and voluntary nature of the study (**Attachment K1**). This secondary opportunity to review the consent form will be particularly important for individuals who did not read it prior to their appointment [the consent form will be emailed with the invitation email (Group 1 and 2; online screening), confirmation email (Group 1 and 2; telephone screening), or appointment reminder (Group 4)]. Individuals will be required to provide written consent to be in the study (first and last names).

Participants who sign the consent form will next undergo a literacy assessment. The interviewer will use the REALM for this purpose (see "Group 1-2 Structured Interview Guide" in **Attachment C1** and "Group 4 Structured Interview Guide" in **Attachment C2** for the health literacy assessment). FDA has requested that approximately 30% of participants be of limited literacy defined as a REALM score of 60 or below for adults. If someone does not meet the literacy requirement, the interviewer will end the data collection without telling the participant that they were disqualified, and the participant will receive the full token of appreciation.

Following the literacy assessment, the interviewer will give the participant one of two versions of the naloxone DFL (**Attachment L1** or **L2**); there are separate DFLs for route of administration (i.e., nasal or intramuscular injection). These will be rotated such that each label version is assessed with approximately the same number of participants. The interviewer 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 DFL, the interviewer will return to the room and begin the interview (see "Group 1-2 Structured Interview Guide" in **Attachment C1** and "Group 4 Structured Interview Guide" in **Attachment C2**).

The interview will start with a cognitive walkthrough of the label. This includes asking the participant to imagine that s/he was in a situation where they had to use the product on a friend. Next, the interviewer will ask the participant to explain what s/he would do based on the label. After this exercise is complete, the interviewer will present a series of third 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 their 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.

The risk of participation in an interview is minimal. 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, they have developed processes for handling impairment or distress:

- Impairment: If an individual is too impaired to participate, the study team will terminate the interview process and request that he/she call a friend or family member to pick them up or remains at the study site until they are no longer impaired. The study team, however, cannot force them to follow through with these measures.
- Distress: The study team will give the individual the telephone number for a mental health crisis line near to the study location.

The study team will audio record the interviews. Total interview time will be 30 minutes, which includes time to administer the REALM and informed consent.

Once the interview is completed, the study team will provide the participant with a monetary token of appreciation to help defray the costs of study participation. Participants will receive the equivalent of $40. (Participants in Groups 1 and 2 will receive a Visa gift card and participants in Group 4 will receive cash). Note that study staff will provide participants with the token of appreciation to help defray the cost of study participation even if they withdraw from the study or are unable to participate if the literacy requirements are not met. **Section 7** provides justification for the amount of the token of appreciation to help defray the cost of time and travel.

After the data collection is complete at all locations, the audio recordings will be transcribed and the study team will create a report summarizing the results from the in-person, individual survey interview 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:

Group 1 and 2

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

a) 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 survey interview appointment. This PII will be recorded separately from the screener by RTI recruitment staff (see "Group 1 and 2 Closing Script" in **Attachment J1**) and will be used to remind individuals of upcoming appointments. All PII will be destroyed within one month of the study's end date.

b) As part of the consent process for online screening, individuals are advised to close their browser window when they are done taking the screener or if they decide to stop the screening process after they have already started. For telephone screening, the recruiters will suggest during the consent process that individuals go to a room by themselves to answer the questions. Further, when conducting telephone screening in a shared office, the recruiter will use a headset.

c) For telephone screening, recruitment staff will use the Qualtrics system to complete the screener whenever possible; i.e. staff will enter responses directly into the online screener. This will eliminate having hard copies of files with sensitive information or personally

identifiable information (PII). In some cases, however, it may not be possible to access the online screener during screening (e.g., if Qualtrics is experiencing technical issues). If this happens, only RTI staff based in Research Triangle Park (considered 'onsite') can conduct screening because offsite staff cannot store the hard copy screeners in the project director's locked filing cabinet until they can access the Qualtrics database (which increases the risk of a privacy breach). Offsite recruitment staff will transfer the call to an onsite staff person to complete the screening process; they must then enter screener data into the online database within 24 hours and shred the hard copies immediately thereafter.

d) Participants will be identified by a unique Participant ID number in the participant database. 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 4) and within groups (users vs. associates) and by key demographic characteristics (e.g., education level, race/ethnicity, or gender).

e) RTI staff involved with screening will provide the logistics coordinators and interviewers with a schedule that will include participants' first names (for greeting purposes only), participant IDs, and basic demographic information (e.g., race, ethnicity, gender). Interviewers will input the Participant ID and screening data into their tablet prior to each interview. Participants will be identified only by Participant ID number in the data files. PII will not be shared with FDA. All data will be reported in aggregate and de-identified with no PII included.

f) At the start of the survey interview, the interviewer will ask the participant 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 transcript (the transcription firm will be given specific information on what the PII is that should be excluded). 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.

g) All data collection activities, including consent, review of the DFL, and the survey interview, will take place in a private room with a door to help protect privacy.

h) FDA provided a Certificate of Confidentiality for this study for Groups 1 and 2.

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

> ***Screener Data.*** We will use Qualtrics, a software-as-a-service tool, to administer the screening instrument for this study. Qualtrics has several measures in place to ensure security to the extent provided by law and quality data management.

The Federal Information Processing Standards (FIPS) Publication Series of the National Institute of Standards and Technology (NIST) is the official series of publications relating to standards and guidelines adopted and promulgated under the provisions of the Federal Information Security Management Act (FISMA) of 2002. Publication 200, "Minimum Security Requirements for Federal Information and Information Systems," states the basis for sound security practices in any organization. Qualtrics meets all requirements as listed in Section 3 of the Publication 200, such as awareness and training, incident response, media protection, and risk assessment.

Respondents will submit screener data from their computer using HTTPS (TLSv1.2 with AES 128/256-bit encryption depending on browser) to Qualtrics. RTI has invested in a data isolation feature at Qualtrics that adds increased security over the already secure Qualtrics platform. With data isolation, Qualtrics offers RTI an extra layer of data encryption. Qualtrics will send the screener data to us, and these data are accessible only by RTI's Master Key.

The process for recording a screener response are as follows:

1. A respondent takes the screener and the response is submitted to Qualtrics short-term response storage over HTTPS.

2. All data for every screener collected is then encrypted.

3. The Encryption Service uses RTI's customer-specific Master Key in Amazon KMS service to retrieve the survey's AES 256-bit data encryption key from the Amazon Key Management Service.

4. The Encryption Service uses the key, plus a response-specific initialization vector, to encrypt the data and write it to the Qualtrics Response Database.

The process for retrieving screener data are as follows:

1. RTI authenticates to Qualtrics using a password known only to RTI research team members.

2. RTI makes a request to retrieve data from the screener.

3. The Encryption Service uses RTI's customer-specific Master Key in Amazon KMS service to retrieve the survey's AES 256-bit data encryption key from the Amazon Key Management Service.

4. The encrypted data are retrieved from the Qualtrics Response Cache and/or Response Database and then decrypted with the customer's key and the response's unique initialization vector.

5. The data are returned in plaintext comma-separate value (csv) file to RTI over HTTPS.

In the addition to the above, the password used to access the Qualtrics data will be limited to our staff conducting screening. PII from the screener will be disaggregated from the dataset before the dataset is shared with FDA or Concentrics Research. When these de-identified data are transmitted from RTI to FDA or Concentrics, we will use either a secure file transfer protocol (SFTP) or encrypted zip file.

In summary, all screening data are encrypted end-to-end, in transport from the participant's computer to Qualtrics, while at rest at Qualtrics, and in transport from Qualtrics to RTI. While the data are stored at Qualtrics, the data are owned fully by RTI. Qualtrics has no "back door" access to the screening data. Even in the event of a physical intrusion at Qualtrics, and theft of the hard drive with the screener data, the data would be encrypted and unusable by any party, including Qualtrics staff. Data decommissioned on Qualtrics' hard drives are destroyed by U.S. DOD methods and delivered to a third-party data destruction service. Finally, the screener data will be stored in the U.S. and will not be moved to outside the country.

Appointment self-scheduling tool (offsite 10to8). Participants who are eligible for the study will be emailed a link by an RTI staff member that will let them self-enroll for an appointment time. The link will take participants to 10to8.com, a software-as-a-service. Within 10to8.com, there is no text that would allude to the study's purpose. Additionally, participants are not asked any sensitive questions on 10to8.com. Participants are asked for their name, a contact phone number, an email address and their study ID number. Connections to 10to8.com are secured by HTTPS so that traffic between the site and a participant's computer cannot be intercepted. When a participant signs up for an appointment they will only be able to see slots that are open. They will not see information entered by other participants.

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. Audio files will be stored in a restricted location on the Concentrics network, with controls in place as specified in "data security". Concentrics will not send RTI audio files that contain PII. 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 (including the 10to8 account) 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.

In addition to the specified data handling procedures, the study team also offers the following data security features (all of which were in place for Task 2 with the exception of the SFTP site that is described above):

Concentrics Data Security. Concentrics utilizes Active Directory to control access to all network resources located on their network. Each user is assigned a unique network account they use to login to network devices and access network shares that contain project data. Concentrics Research requires their staff to change their network passwords every 90 days. Physical access to Concentrics' server room is limited to the IT Director and the Finance Director (responsible for facilities). The door to the server room is locked and secured by an electronic keypad with the code known only by the IT and Finance Directors. Physical access to the DatStat datacenter is secure and monitored 24/7. Each visitor must sign-in and is escorted everywhere in the facility. All server areas are tightly monitored and secured by badge readers, cameras and keylocks. The Concentrics Research office building is secured by key fob access from the exterior, 24-hour monitoring, and motion detectors. Storage of data on the Concentrics Research file servers is encrypted.

Qualtrics Data Security (screener). Data security procedures for Qualtrics are described in-depth above. Encryption is end-to-end and only RTI, with the master key, can decrypt the data.

TierPoint Data Security (DatStat). Data from DatStat, the survey tool, are initially saved at TierPoint before transferred to Concentrics**.** Access to DatStat is limited to assigned user accounts with each user granted access only to specific projects to which they are assigned. Staff must also enter a password to access to DatStat (and to open the CAPI program on the tablets). Password complexity requirements are included in the minimum 8-character password. The tablets are also password protected. Data will be encrypted and secured during transmission from the field to Concentrics' server through a private SSL-VPN connection. Data are captured and stored real-time by the interviewer utilizing a computer-assisted personal interview (CAPI) program; no data are kept on the tablet.

RTI Data Security. RTI currently maintains two separate peer data centers on our Research Triangle Park campus, affording us the capability to replicate critical data and provide redundancy as required. Each data center can independently sustain Internet, project, and user connectivity. Physical security to the primary data center is provided inside a reinforced concrete room that is restricted only to specific IT staff.

Beginning April 2018, the back-up data location will be TierPoint in Raleigh, NC. Having an offsite backup offers greater security in case a catastrophic event occurred on RTI's campus across multiple buildings. Physical security is provided by a locked cage and TierPoint staff will not have account or logical access to the servers. Additionally, TierPoint uses CCTV to monitor the server room.

Network security is provided by a firewall that only allow authorized users to access the share drive. Connecting behind the firewall is only possible with an RTI username and password. If offsite, network access also requires multi-factor authentication and traffic is secured by VPN between the user's computer and the RTI network. Access to share drives for this project are available only to project staff.

Group 4

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

a) 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 will be recorded separately from the screener by recruitment firm staff (see "Group 4 Closing Script" in **Attachment J2)** and will be used to remind individuals of upcoming appointments. The screener and the form that records PII will be stored separately a locked file cabinet at the recruitment firm and 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.

b) 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.

c) 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 these cases, the interviewer will record the Participant ID so that the audio file with PII will not be sent to RTI. The audio files will be destroyed within two years of the study's end date.

d) All data collection activities, including consent, review of the DFL, and the survey interview, will take place in a private room with a door to help protect privacy.

In addition to these measures, data will be handled in the following ways to protect privacy (all of which were in place for Task 2 with the exception of the SFTP site that is described above):

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. The audio files will be transcribed (excluding any portions containing PII). They 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. Audio files will be stored in a restricted location on the Concentrics network, with controls in place as specified in "data security." Concentrics will not send to RTI any audio files that contain PII. The audio files will be transferred to RTI using an SFTP or encrypted zip file.

In addition to the specified data handling procedures, the study team also offers the following data security features (all of which were in place for Task 2 with the exception of the SFTP site that is described above):

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 Data Security. Concentrics utilizes Active Directory to control access to all network resources located on their network. Each user is assigned a unique network account they use to login to network devices and access network shares that contain project data. Concentrics Research requires their staff to change their network passwords every 90 days. Physical access to Concentrics' server room is limited to the IT Director and the Finance Director (responsible for facilities). The door to the server room is locked and secured by an electronic keypad with the code known only by the IT and Finance Directors. Physical access to the DatStat datacenter is secure and monitored 24/7. Each visitor must sign-in and is escorted everywhere in the facility. All server areas are tightly monitored and secured by badge readers, cameras and keylocks. The Concentrics Research office building is secured by key fob access from the exterior, 24-hour monitoring, and motion detectors. Storage of data on the Concentrics Research file servers is encrypted.

TierPoint Data Security (DatStat). Data from DatStat, the survey tool, are initially saved at TierPoint before transferred to Concentrics**.** Access to DatStat is limited to assigned user accounts with each user granted access only to specific projects to which they are assigned. Staff must also enter a password to access to DatStat (and to open the CAPI program on the tablets). Password complexity requirements are included in the minimum

8-character password. The tablets are also password protected. Data will be encrypted and secured during transmission from the field to Concentrics' server through a private SSL-VPN connection. Data are captured and stored real-time by the interviewer utilizing a computer-assisted personal interview (CAPI) program; no data are kept on the tablet.

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Beginning April 2018, the back-up data location will be TierPoint in Raleigh, NC. Having an offsite backup offers greater security in case a catastrophic event occurred on RTI's campus across multiple buildings. Physical security is provided by a locked cage and TierPoint staff will not have account or logical access to the servers. Additionally, TierPoint uses CCTV to monitor the server room.

Network security is provided by a firewall that only allow authorized users to access the share drive. Connecting behind the firewall is only possible with an RTI username and password. If offsite, network access also requires multi-factor authentication and traffic is secured by VPN between the user's computer and the RTI network. Access to share drives for this project are available only to project staff.

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 to help defray costs of time and travel is intended to recognize the time burden placed on participants, encourage their cooperation, and convey appreciation for their contributions to the research. These tokens of appreciation help ensure that sufficient numbers of participants can be recruited to participate in the data collection. Research has shown that monetary tokens of appreciation improve 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. This would increase the burden hours and overall time needed to complete data collection activities.

The token of appreciation amount will be equivalent to $40; this amount is somewhat lower relative to other FDA studies. 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). A lower token of appreciation could jeopardize the quality of the data. A lower token of appreciation amount could also increase the no-show/cancellation rate and potentially overly bias the sample toward lower income populations, which could affect the validity and reliability of the data.

8. Questions of a Sensitive Nature

As describe previously, screening for Group 1 and 2 entails asking sensitive questions about individuals' drug use and drug use among people they may know, which is necessary to determine eligibility. None of the individual, in-person survey interview questions for Task 3 are of a sensitive nature. The focus of these interviews is to assess comprehension of the DFL. As part of the informed consent procedures for the individual, in-person survey interview, interviewers will explain to participants that they do not need to answer any questions that make them feel uncomfortable and can stop participating at any time. To ensure cultural competence, all interviewers who have not done so already will participate in a cultural sensitivity training led by an expert in illicit opioid use and working with this vulnerable population.

Group 4 participants will not be asked sensitive questions about drug use (their own or among people they may know) to determine eligibility as this is an all-comer population.

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 PII in table and text formats to describe study participants.

FDA staff will prepare an 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/Category of Respondent	No. of Respondents	Participation Time (minutes)	Burden (hours)*
Group 1 and 2			
Screener	1,720	5	143
Survey interview	430	30	215
Total			***358***

Group 4			
Screener	840	5	70
Survey interview	140	30	70
Total			***140***
Total for Groups 1 and 2 and 4			**498**

Note: *The study team estimates an annual burden of 498 hours; 213 hours for screening and 285 hours for the individual, in-person survey interview for all groups. For Group 1 and 2, they will need to screen 1,720 respondents to obtain 430 completed interviews (n=2,150; 358 annual burden hours), and for Group 4, they will need to screen 840 respondents to obtain 140 completed interviews (n=980; 140 annual burden hours). Proportionately, they will need to screen fewer Group 1 and 2 respondents than Group 4 respondents given the targeted, multipronged recruitment approaches that will be utilized for Group 1 and 2.*

REQUESTED APPROVAL DATE: April, 2018

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