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Inflexxion Task Order #5, Aim 2, Accuracy of Opioid Product Ascertainment

Study Design and Protocol

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1. Introduction

Data on the use and misuse of prescription opioids are frequently collected via self-report (Substance Abuse and Mental Health Services Administration, 2019). However, a variety of respondent characteristics and situational factors can affect the validity of self-reported use of prescription opioids (Del Boca & Noll, 2000; Smith, Rosenblum, Parrino, Fong, & Salvatore, 2010). Additionally, data on the use of opioid products have often been grouped under the broader category of opioids or at the level of active pharmaceutical ingredient (e.g., hydrocodone), rather than product-specifically (e.g., Vicodin). Having accurate product-specific information about opioid use would be helpful for determining whether pharmaceutical interventions, such as abuse-deterrent formulations of prescription opioids, or other intervention efforts are effective in reducing the rates of abuse of specific products.

Using photographs to identify prescription drugs has been suggested as a promising strategy to increase the accuracy of prescription drug identification and to capture product-specific information about opioid use. For example, photographs are being used in national surveys, such as the National Survey of Drug Use and Health (Center for Behavioral Health Statistics and Quality, 2019). The Addiction Severity Index-Multimedia Version (ASI-MV), developed by Inflexxion as a tool to assess addiction severity in treatment settings, also uses photographs to assist patients in reporting their use of prescription drugs.

A small study by Smith and colleagues (2010) provided some evidence, supporting the use of photographs as a valid strategy for identifying opioid products and reporting use. However, more research is needed to determine the accuracy of self-report in opioid product ascertainment; the role of product brand names, active pharmaceutical ingredients, slang terms, and photos in identifying products; and the overarching strategies used to identify products.

The purpose of this study is to assess the accuracy of opioid product ascertainment among patients undergoing treatment for substance abuse. Thus, this study will use a within-subjects experimental design to examine whether the accuracy of patient identification of opioid products varies, depending on the information provided about the product (e.g., product name, only, vs. product name and active ingredient vs. photo, only). Additionally, we will investigate individual patient characteristics that affect the accuracy of opioid product ascertainment. Finally, we will examine decision making and strategies used to identify opioid products via brief cognitive interviews with patients.

Specifically, the primary objectives of this study are to:

- Assess the accuracy of opioid product ascertainment among patients in treatment programs for substance abuse
- Determine the influence of photographs on the accuracy of opioid product ascertainment
- Evaluate the impact of nonspecific product endorsements (e.g., by active pharmaceutical ingredient) and potential analytic approaches to account for nonspecific data
- Identify factors that affect the accuracy of opioid product ascertainment and strategies employed in the identification of opioid products

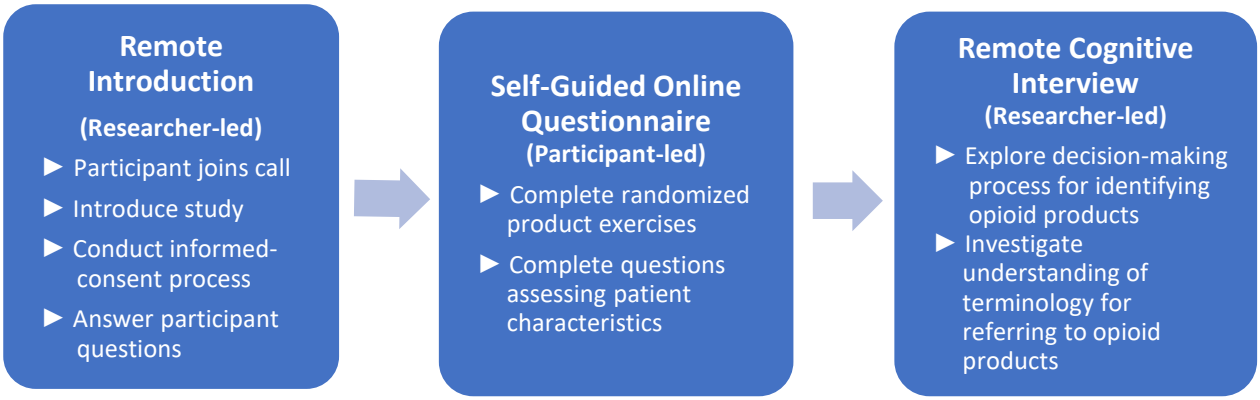
This protocol describes the study design and data collection procedures for conducting this research.

2. Study Design

2.1 Overview

This study will use a mixed methods approach to assess the accuracy of opioid product ascertainment among patients undergoing treatment for substance abuse as well as learn about decisional factors and identification strategies that influence the ascertainment process (***Exhibit 1***).

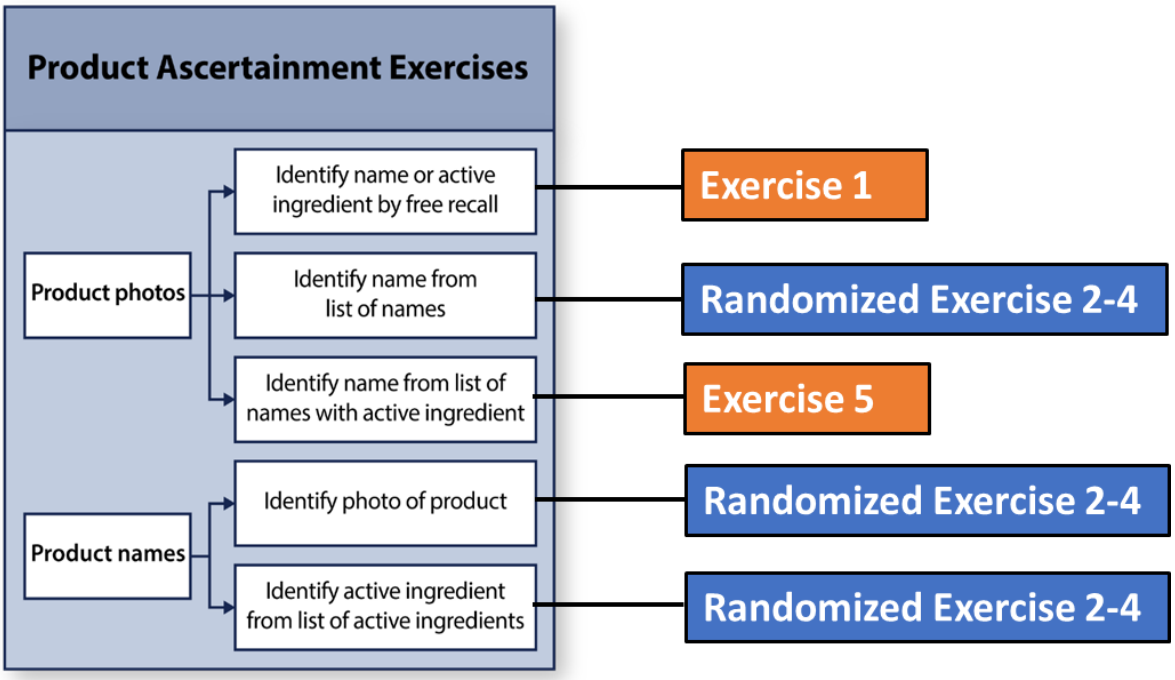
Exhibit 1. Overview of Study Design



First, we will assess the accuracy of opioid product ascertainment among patients undergoing treatment for substance abuse, using five ascertainment exercises that will be administered individually to each participant in a within-subjects experiment (***Exhibit 2***). We will present participants with photographs of opioid products in random order, and depending on the type of question, participants will identify the product through free recall or by multiple choice. For example, by selecting the product name (e.g., Vicodin), the active pharmaceutical ingredient (e.g., hydrocodone), or both the product name and active

pharmaceutical ingredient (e.g., Vicodin [hydrocodone]) from a list of options. For some exercises, participants will, instead, be shown a specific product name and asked to identify it from a set of product photographs or to identify the active ingredient contained in the product. The same five questions will be asked for each opioid product. This self-report data will be collected, using an online questionnaire. The study design will allow us to meet project objectives by testing whether ascertainment (i.e., correct identification of opioid products) differs by the type of ascertainment measure used (free recall, list of product names, list of product names with active ingredient option, thumbnail photo of product, and list of active ingredients). The questionnaire will also include questions about patient characteristics, which we will use to test whether individual differences influence the accuracy of opioid product ascertainment.

Exhibit 2. Opioid Product Ascertainment Exercises in Online Assessment



Following completion of the online questionnaire, we will conduct brief cognitive interviews to explore patient decision making and strategies for identifying opioid products as well as patients' understanding of language used to describe prescription opioids.

2.2 Experimental Stimuli

Participants will be shown a sequence of stimuli (opioid products) presented as photographs or written product names. The product photographs and names will be taken from the ASI-MV and programmed to display within the online questionnaire. We will standardize extraneous details in the product images to eliminate potential confounding factors, like background color and frame dimensions.

If experimental design considerations allow, a total of 32 prescription opioid pain medications included in the ASI-MV will be used as stimuli. See **Appendix A** for a complete list of opioid products from ASI-MV to be included in the experiment. These 32 opioid products represent opioid products that include the most common active pharmaceutical ingredients (hydrocodone, oxycodone, hydromorphone, oxymorphone, morphine, and tapentadol), single-entity and combination formulations, brand name and generic versions, short-acting (e.g. immediate-release) and long-acting (e.g. extended-release) formulations, and nonspecific active pharmaceutical ingredient options (e.g., other hydrocodone IR product). Stimuli will include products with greater market share and likelihood of being used in a way not prescribed by a doctor as well as products with a lower market volume. In this study, to maintain consistency across products, we will include only opioid products designed to be ingested by mouth in either tablet or capsule form and exclude other categories of products, such as films or patches.

With 32 opioid products as stimuli and 5 questions per product, a complete within-subjects design would require a minimum of 160 questions per participant. Since this is a repeated measures experiment, participant fatigue from repeatedly responding to the same questions is an important factor to take into account. To reduce burden and corresponding measurement error that would arise by asking that many questions, we will aim to devise a fractional design that allows participants to complete a smaller number of questions, while nonetheless, gathering data on all 32 opioid products across the experiment. Each participant will respond to a sequence of questions, addressing a smaller subset of the stimuli, but across all participants, data for the full set of 32 opioid products will be gathered (see **Appendix B**). We will also group the free recall questions together on one screen, similar to the way they appear in the ASI-MV (see ***Exhibit 3*** as an example). This will reduce the number of screens participants will see throughout the survey. The free recall exercises will be completed first so that the experience of responding to other product identification questions does not influence these responses.

Exhibit 3. Example of a Free Recall Exercise

Below each photo, please fill in what you know about the opioid medication in that photo.
If you do not know the answer, please select "Don't know" instead of skipping the question.
Note that the images may not be the same as their actual size.

1. Brand name: _____
☐ Not applicable (drug is a generic version)
☐ Don't know

2. Time-release formulation
☐ Extended release/long-acting (ER, XR)
☐ Immediate release/short-acting (IR)
☐ Don't know

3. Active ingredient: _____
☐ Don't know

4. Slang name or street name: _____
☐ Don't know

1. Brand name: _____
☐ Not applicable (drug is a generic version)
☐ Don't know

2. Time-release formulation
☐ Extended release/long-acting (ER, XR)
☐ Immediate release/short-acting (IR)
☐ Don't know

3. Active ingredient: _____
☐ Don't know

4. Slang name or street name: _____
☐ Don't know

Following the free recall questions, participants will complete the remaining four exercises for each opioid product. The order of products and response options will be randomized. However, participants will complete all of one type of exercise before moving to the next exercise, and the order of exercises that include active ingredients in response options may need to be completed last to avoid learning effects. To avoid introducing a threat to external validity, we will present participants with exercises for each product individually, as in ***Exhibit 4***. Combining multiple questions on one screen is an option for reducing the overall number of screens participants see, but under this approach, responses to products that are displayed on the same screen may become correlated through a process of elimination.

Exhibit 4. Example Exercise with a List-of-Product-Names Response Format

Please select the name of the medication shown in the image below.

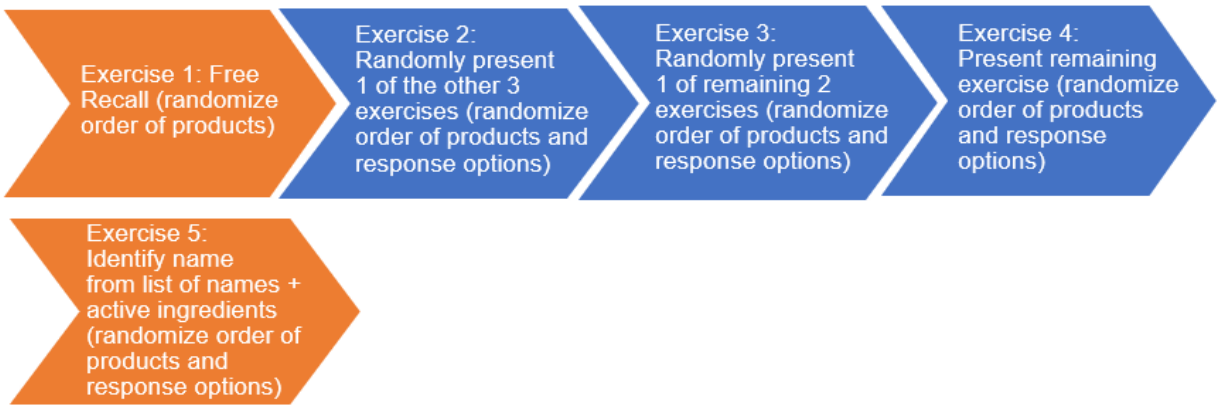
Note that the image may not be the same as its actual size.

- ○ Percocet®
- ○ Roxicodone®
- ○ Xtampza ER
- ○ Generic short-acting Vicodin®-type generic
- ○ Vicodin®
- ○ Generic extended-release hydromorphone
- ○ Lorcet®
- ○ Exalgo
- ○ Opana®
- ○ Kadian®
- ○ None of the above
- ○ Don't know

2.3 Randomization

Since each participant will evaluate multiple photographs and product names, it is important to address the potential issue of incidental effects caused by the serial order in which stimuli and questions are presented. To mitigate this issue, we will randomize the order in which stimuli and exercises are presented. The free-recall exercises will always be completed first to avoid the influence of other questions on these responses, and exercises that show the product name, along with an inactive ingredient, will always be completed last. Exercises with the same type of ascertainment measure (e.g., identify name from list of names) will be grouped together. However, the order in which participants are presented with the other three measurement types will be randomized. Lastly, although all participants will view the same set of product photographs and names, the order in which they are presented within ascertainment exercises will also be randomized (***Exhibit 5***). We will implement this randomization scheme by programming it into the online questionnaire.

Exhibit 5. Randomization Scheme



Note. Exercises refer to the tasks in *Exhibit 2*. Exercises 2, 3, and 4 will be presented in random order and will include "Identify name from list of names," "Identify photo of product," and "Identify active ingredient from list of active ingredients."

2.4 Measures

The primary outcome of this study will be accuracy of opioid product ascertainment, which we will operationalize by flagging whether participants correctly identify the product displayed in each ascertainment exercise. The recognition items used in the five types of exercises differ in response format, but they can all be recategorized and combined into a single dichotomous variable, indicating whether the product in each exercise was identified correctly or incorrectly. The free-recall exercises will consist of open-ended measures, where participants will be asked to type in the name of the opioid product depicted in the stimulus. These responses will be coded as correct or incorrect, during the data preparation phase of analysis (see Section 2.5.2). The remaining measures used in the ascertainment exercises will be modeled on questions from the ASI-MV that ask participants to select medications they recognize from a list of options. The format of the response options will differ, depending on the type of exercise (list of product names, list of product names with active ingredient option, or thumbnail photo of product), but in all cases, participants will be asked to select one option from a close-ended list.

In addition to the ascertainment questions, we will also include a measure designed to assess the level of exposure to each product. For the sake of brevity, these measures will likely have closed-ended response options that indicate increasing levels of familiarity (e.g., heard of it, seen it, used it). Level of exposure may be useful as a product-level covariate to include in main analyses, examining factors that influence opioid product ascertainment.

We will also measure patient characteristics that we expect might impact the accuracy of opioid product identification, such as lifetime recreational drug use; primary or most used/abused drug; mental health issues; health literacy; history of medical treatment for pain; history of prior substance abuse treatment; route of administration (e.g., swallowed,

snorted, injected); availability of other opioids; source of opioids used (e.g., prescription, friend); and demographics.

2.5 Interview Guide

We will develop a guide for conducting brief semi-structured interviews to explore participants' decision-making process, while identifying opioid products. The guide will allow us to probe on the features and characteristics of opioid products that participants use to identify products. We will also inquire about participants' level of confidence in the strategies they use to identify products and the accuracy of their decision making and identification processes. We will also explore participants' understanding and interpretation of terms used to refer to opioid products, such as "prescription opioids" and "medications." Interviews will be conducted remotely, using a web-based video conferencing software, and will take about 10-15 minutes to complete.

2.6 ASI-MV Data Access

In a two-step consent process (see **Section 3.3.2**), the researcher will ask the participant for permission to access their responses to the ASI-MV assessment, which participants would have completed, during intake to their substance abuse treatment program. These data would be used to gather additional patient characteristics, such as their drug severity score, to further investigate factors that may influence the accuracy of opioid product recall. The participant may choose to deny access to their ASI-MV assessment data without penalty. Analysis will be based upon the subset of participants who agree to allow access to their ASI-MV assessment information.

2.7 Analysis Plan

The primary outcome of this study will be correct identification of opioid products displayed.

2.7.1 Descriptive Analysis

As a first step, we will produce descriptive statistics for continuous variables (i.e., means, standard deviations, medians, quartiles, and frequencies) and categorical variables (i.e., frequencies and percentages). For composite measures, we will assess internal consistency among the items for each measure, using Cronbach's alpha as our metric. For scales that fail to meet our threshold of 0.75, we will examine whether dropping items will improve reliability or use a single-item measure.

2.7.2 Coding Open-Ended Opioid Product Ascertainment Measures

We will conduct a content analysis of responses to the open-ended questions to classify responses as either correctly or incorrectly identifying the product shown in each free-recall exercise. We will first develop a codebook that captures whether the answers provided constitute correct ascertainment for each product and the degree to which answers are correct. For example, did participants correctly identify the brand name (if applicable), the active ingredient, the time release formulation, the street or slang name (see ***Exhibit 6***)?

Exhibit 6. Example Codebook Questions to Analyze Open-Ended Responses to Free Recall Questions

	Brand Name Product	**Generic Product**
Did participants correctly identify the brand name?	Yes/No	NA
Did participants correctly identify the active ingredient?	Yes/No	Yes/No
Did participants correctly identify the time release formulation (ER/IR)?	Yes/No	Yes/No
Did participants correctly identify the street or slang name?	Yes/No	Yes/No

Given the study objective related to evaluating the impact of nonspecific product endorsements and the related issues when conducting product-specific analyses, we recommend including an additional code for responses that refer to the product category or active ingredient, so we can differentiate those from responses that refer to the product by name. To establish reliability of the codebook, we will draw a random sample of responses, related to each product (10% of total responses), and two independent coders will classify responses, using the first draft of the codebook as a guide. We will then compare the results and calculate Krippendorff's alpha for each code to assess intercoder reliability (Hayes & Krippendorff, 2007). The coders will work together to resolve any discrepancies and revise the codebook as necessary until all codes obtain a Krippendorff's alpha coefficient of 0.8 or higher. After the codebook is finalized, we will split the remaining open-ended responses between the two coders, who will complete the rest of the coding, independently. The resulting coded variables will be used to construct part of the opioid product ascertainment outcome variable.

2.7.3 Main Analysis

To understand the effect of stimuli and exercises on product ascertainment, repeated measures will be conducted on each participant. Whenever within-subjects factors are used in an experiment, the statistical methods need to adjust for data-correlated errors that are likely to arise, due to multiple measurements made on the same subject. Hierarchal models or mixed models will be used to analyze and account for variability, among participants and within participants, from measure to measure.

The proposed study design can be thought of as a multi-level model with crossed random effects. Each ascertainment exercise is a Level-1 fixed factor nested both within participants and products, which are Level-2 random factors. Participants and products are crossed at

Level 2 because every participant will rate several products. A general example of this design, a *replicated fully crossed design*, is described by Judd, Westfall, & Kenny (2016). The comparative effects of specific products used as stimuli are not the inferential focus of this statistical analysis; instead, the products have been chosen for the sake of ecological validity to represent the various kinds of opioid products that participants might have been exposed to or used in the past and because they are included on the ASI-MV.

Since our primary outcome measure is dichotomous, we will conduct a multilevel mixed-effects logistic regression. In this model, correct ascertainment is the outcome and is measured at Level 1 (i.e., the ascertainment exercise level). The main predictors of interest also occur at Level 1 and relate to the type of measure (free-recall, product list, product list with active ingredient option, active ingredient list, or photograph). The multilevel regression equation for the model[1] predicting correct ascertainment by type of measure is

$$
\begin{aligned}
\text{logit}(\text{CORRECT}_{ijk} = 1) = {} & \gamma_0 + \gamma_1(\text{TASK\_2}_{ij}) + \gamma_2(\text{TASK\_3}_{ij}) + \gamma_3(\text{TASK\_4}_{ij}) + \gamma_4(\text{TASK\_5}_{ij}) + \\
& \gamma_5(\text{BLOCK\_2}_{ij}) + \gamma_6(\text{BLOCK\_3}_{ij}) + \gamma_7(\text{BLOCK\_4}_{ij}) + \\
& \gamma_8(\text{TASK\_2}_{ij} \times \text{BLOCK\_2}_{ij}) + \gamma_9(\text{TASK\_2}_{ij} \times \text{BLOCK\_3}_{ij}) + \gamma_{10}(\text{TASK\_2}_{ij} \times \text{BLOCK\_4}_{ij}) + \\
& \gamma_{11}(\text{TASK\_3}_{ij} \times \text{BLOCK\_2}_{ij}) + \gamma_{12}(\text{TASK\_3}_{ij} \times \text{BLOCK\_3}_{ij}) + \gamma_{13}(\text{TASK\_3}_{ij} \times \text{BLOCK\_4}_{ij}) + \\
& \gamma_{14}(\text{TASK\_4}_{ij} \times \text{BLOCK\_2}_{ij}) + \gamma_{15}(\text{TASK\_4}_{ij} \times \text{BLOCK\_3}_{ij}) + \gamma_{16}(\text{TASK\_4}_{ij} \times \text{BLOCK\_4}_{ij}) + \\
& \gamma_{17}(\text{TASK\_5}_{ij} \times \text{BLOCK}_{ij}) + \gamma_{18}(\text{TASK\_5}_{ij} \times \text{BLOCK\_3}_{ij}) + \gamma_{19}(\text{TASK\_5}_{ij} \times \text{BLOCK\_4}_{ij}) + \\
& u_{i0} + u_{i1}(\text{TASK\_2}_{ij}) + u_{i2}(\text{TASK\_3}_{ij}) + u_{i3}(\text{TASK\_4}_{ij}) + u_{i4}(\text{TASK\_5}_{ij}) + \\
& u_{0j} + u_{1j}(\text{TASK\_2}_{ij}) + u_{1j}(\text{TASK\_3}_{ij}) + u_{3j}(\text{TASK\_4}_{ij}) + u_{4j}(\text{TASK\_5}_{ij}) + u_{ij},
\end{aligned}
$$

where CORRECT_{ijk} represents the responses of participant i to drug j on task k, γ are fixed effects estimates, and $u_{i.}$ and $u_{.j}$ are participant and drug random effects, respectively. TASK_2 – TASK_5 are effects-coded variables, representing the type of measures used in the ascertainment exercises, and BLOCK_2 – BLOCK_4 are dummy-coded levels of a factorial variable, representing which group of drug products participants were randomly assigned as stimuli. The block main effects and task-by-block interaction terms statistically control for the potential influence that the specific set of 8 drug products used in each block may have on ascertainment. In all, the model has 20 fixed-effects coefficients and 11 random-effects coefficients.

In the final model, we may also include fixed-effects predictors, related to the Level 2 factors: Participant (demographics, health literacy, product familiarity, drug severity score

[1] We adapted this equation from the canonical analytic model for a replicated fully crossed design outlined by Judd, Westfall, & Kenny (2016) in the supplementary appendix to their article.

from the ASI-MV, etc.) or product (category, extended or short release).[2] The main analyses will exclude the drug severity score from the ASI-MV so that data from all participants who complete the study exercises will be included. Exploratory analyses, involving the drug severity scores, will only include the subset of participants who give us permission to link their ASI-MV drug severity scores with study data. These analyses will allow us to examine the influence of patient characteristics (e.g., level of exposure, age, region, etc.) on opioid product ascertainment. We will verify statistical assumptions of the model by numerically and graphically assessing residuals. If models fail to meet parametric assumptions, alternative nonparametric models, such as a nonparametric rank-based mixed models, will be used (Noguchi et al., 2012).

Standard practice in voluntary survey-based research is to allow participants to skip questions if they choose (American Association for Public Opinion Research, 2014). We will include a "Don't know" response option, when applicable. Since participation is voluntary, participants may withdraw from the study at any point if they choose.

Power Analysis

Assuming repeated measures over 96 participants, with each participant answering questions for 8 product names, and 5 types of ascertainment measures per participant and product name in a multilevel design with crossed random effects (i.e., participants and drug products are nested in 4 blocks with 24 participants and 8 products per block), the study will have 80% power at $\alpha = 0.05$ to detect medium-small main effects by type of ascertainment measure ($d = 0.41$) (Westfall, Kenny, & Judd, 2014).[3] The design has considerable flexibility if we need to revise assumptions to include fewer participants. For example, with only 48 participants and all other assumptions held constant, the study would still be sensitive to detect conventionally medium-sized effects ($d = 0.47$).

2.7.4 Analysis of Interview Data

We will use a thematic and iterative approach for analyzing the interview data gathered from all participants who complete the interviews. These will be the same participants as those included in the main analyses, described above. This qualitative method involves identifying, analyzing, and reporting patterns or "themes" within data (Aronson, 1995;

[2] Due to the complexity of the study design, limited sample size, and the number of parameters in the bare-bones analytic model, we will control for potential order effects by design—through randomization—rather than statistically, by including variables that record the order of the tasks as model covariates.

[3] Cohen's *d* is a standardized effect size index defined as the difference between two means divided by the pooled standard deviation of observations within conditions (Cohen, 1988; Judd, West, & Kenny, 2016). Thresholds for interpreting magnitude are conventional, where effects with *d* values of 0.20 to 0.50 are small, 0.50 to 0.80 are medium, and 0.80 or greater are large (Cohen, 1988). Cohen's *d* can be converted to other effect size indices (e.g., *r*, *f*, η^2, OR), using various conversion formulas (Cohen, 1988; Ferguson, 1966; Rosenthal, 1994). For example, $d = 0.41$ is equivalent to $r = 0.20$.

Braun & Clarke, 2006). A first read of the data serves to gain a high-level understanding of participant responses. Further analysis is used to identify key themes that emerge across participants. Two researchers will first examine the data separately and then compare interpretations to identify areas of agreement and resolve any inconsistencies in the findings. Additional exploratory analysis may be performed among the participants who give us permission to link their ASI-MV drug severity scores with study data.

3. Data Collection Procedures

3.1 Site Identification

Inflexxion will identify 4 to 5 substance abuse treatment centers from which to recruit participants undergoing treatment for opioid abuse (target *N* = 100; 20-25 participants per site). These sites will be selected from Inflexxion's client base of addiction treatment centers that license the ASI-MV. We will aim for a mix of sites, with respect to the following criteria:

- Geographic region—We will attempt to include as diverse a range of sites as possible, based on geographic location, when recruiting sites from the ASI-MV user base.
- Urban/rural location—We will attempt to include at least two sites located in nonmetropolitan counties and at least two sites in metropolitan counties (Ingram & Franco, 2014).
- Type of treatment program—We will attempt to include at least two sites with inpatient programs and two with outpatient programs.

Anticipating recruitment challenges, due to the coronavirus pandemic, additional criteria for identifying sites to approach may help to ensure success in reaching recruitment goals. Thus, we may want to consider including:

- Clinics that have both inpatient and outpatient programs at the same facility to allow for recruitment from both programs at one site, if needed.
- Geographic regions that contain more than one site, in case recruitment challenges make it necessary to recruit participants from multiple sites in that region.

We will draft a description of the study and information about what would be required from sites to participate in the study. Inflexxion will contact and inform sites of the study and inquire about participation. At the completion of data collection, Inflexxion will provide sites with compensation for time and effort expended by each site to assist with participant recruitment, scheduling, and data collection.

3.2 Participant Eligibility

Participants will be recruited from sites via convenience sampling. Sites will coordinate participant recruitment and eligibility screening in partnership with RTI. We will aim to recruit approximately 100 participants for this study. We will develop a screener that sites will use to determine whether patients meet the following eligibility criteria:

- Report past 30-day abuse of at least one prescription opioid intended for the treatment of pain (e.g., any prescription opioid which contains hydrocodone, hydromorphone, oxycodone, oxymorphone, morphine, tapentadol)
- Not experiencing cognitive or physical symptoms, due to drug use (e.g., currently high) or the stage of treatment (e.g., withdrawal) that may affect their ability to understand study procedures, provide informed consent, and complete a 45-minute questionnaire
- 18 years of age or older
- Ability to read English
- No prior experience working in a medical or health-related field

Participants who do not meet all of the above criteria will be excluded from the study.

3.3 Procedures

3.3.1 Recruitment and Screening

Participants will be recruited from inpatient and outpatient treatment programs at study sites. Inflexxion will work with participating sites to identify a designated lead staff member (i.e., a site study coordinator) to manage recruitment efforts by providing study information to potential participants, screening, and scheduling study participants. Site study coordinators will be staff members at each of the sites who are experienced in working with this population and the patients at their respective sites.

Potential participants will be contacted by the site study coordinator, who will provide them with information about the study, gauge their interest, and screen them for eligibility. Depending on what is most convenient for the study site, recruitment, screening, and scheduling may be done over the phone or in person. It will likely be more convenient to contact patients in outpatient programs over the phone, while inpatient recruitment and screening may be done primarily in person. Eligible participants will then be scheduled for a 60-minute time slot to complete the study. While participants at inpatient clinics will be provided with a computer and a private room at the clinic facility, outpatient participants will be allowed to choose whether to participate in the study at the treatment center or at home. Participants in outpatient clinics who prefer to participate at the clinic will be encouraged to schedule their study participation to coincide with a planned visit to the clinic, if possible, to avoid the need to schedule an additional visit.

The screener will guide the site study coordinator through the recruitment and screening process. It will include a script for the site study coordinator to follow, including a description of the study, questions for gauging interest and inviting the potential participant to be screened, screening questions, and questions pertaining to scheduling. Eligible individuals who are interested in participating will be scheduled immediately following screening. Participant scheduling will be tracked in an Excel file that will assign a unique ID

number to each participant. The Excel file that site study coordinators share with RTI will include only the participant ID number and screening data and will not include any personally identifiable information (PII), such as participant names and contact information. This participant ID number will be used to link screener data to the main study data.

We will monitor screening data to aim for quotas across sites of at least 15% Black participants and 12% Hispanic participants. These quotas are based on 2019 data from the ASI-MV of past 30-day use of prescription opioids among adults ages 18 and older.

To ensure we reach our proposed target sample size, study sites will aim to overrecruit and schedule an additional 3-5 participants beyond the target number for the site. Recruitment will be adapted at each site, depending on the no-show rate, though this is less likely to be an issue at inpatient facilities. To increase participation rates, study sites can also contact participants the day prior to remind them of their upcoming scheduled study participation.

3.3.2 Consent

The informed consent process will be conducted remotely by an RTI researcher, using web-based video conferencing software at the time of participants' scheduled study participation on a computer in a private room provided by the site or at the participant's home. The consent process will involve two steps. The first step will focus on participation in the study, ending in a voluntary decision about completing the experiment and interview portions of the protocol. In the second step, we will request permission from those who give consent to allow us to link their responses from the ASI-MV assessment completed during intake to their substance abuse treatment program. Participants who do not grant permission for us to access their ASI-MV data will, nonetheless, remain eligible to complete the study, but their data may be excluded from some exploratory analyses, involving drug severity scores gathered through the ASI-MV. We will explain to participants that granting us access to their ASI-MV data is optional and that they can still participate in the study and will receive compensation for their participation, even if they choose not to allow us access to their ASI-MV data.

An RTI researcher will introduce participants to the study and lead them through the consent process, allowing participants to ask questions about the study and the requirements of participation, prior to giving consent. Consent procedures will include informing potential participants of the purpose of the research, who is conducting the research, the voluntary nature of participation and the ability to withdraw from the study at any time, study length and procedures, possible risks to participation, the confidentiality of participant responses, benefits to participation, a token of appreciation participants will receive, and contact information in case participants have questions, following their participation in the study. Consent information provided to participants will be written clearly, using plain language to avoid confusion and misunderstanding.

We will work closely with the IRB and detailed requirements to ensure participants are adequately informed and consent is given voluntarily. One potential risk to participation may be some psychological discomfort or distress from viewing photos of opioid products with which participants have a history of abuse. We will work with study sites to ensure they have a protocol for monitoring and checking for potential negative psychological effects or potential triggering effects of exposure to photos of opioids. If there is evidence of these effects, prior to completion of the study, and participants need to withdraw from the study, we will work with sites to ensure they follow up with participants and have a protocol in place for responding to participants' needs. If incomplete, the participant's data will likely be removed from the study.

We will also develop a protocol for sites to implement in the event that participants show up to participate, while under the influence of drugs or alcohol, in acute withdrawal, or otherwise impaired. Since these individuals may be incapable of giving informed and voluntary consent as well as maintaining focus for the duration of the study, they will either be rescheduled or removed from the study.

3.3.3 Data Collection

Collection Setting

Data collection will occur at participating inpatient and outpatient sites. Eligible participants at these sites will be directed by clinic staff to a private study room at the scheduled time to use a computer provided by the clinic. Clinic staff will help participants join the videoconference call with the RTI researcher.

Participants will first engage in the consent process and, if they consent to participate, continue with the study by completing the online questionnaire. Participant completion of the online questionnaire will be entirely self-guided. However, a clinic staff member will be present and available, either within the room or nearby, to: 1) ensure the participant's privacy during questionnaire completion (i.e., no one else enters the room), 2) discern whether participants may be experiencing any adverse effects from study participation, and 3) troubleshoot any computer or internet connectivity issues that arise.

Data collection with each participant will require approximately 1 hour. Inflexxion will provide study sites with incentives that the site study coordinator will give to participants in appreciation of their time.

We will work with study sites to ensure procedures are in place to reduce the risk of coronavirus transmission and ensure participants are as safe as possible, during study participation. These procedures are not likely to be above and beyond what clinics are already doing to reduce transmission. However, we will include a checklist for study sites to follow, during data collection, to ensure measures, such as the use of face coverings and cleaning of the computer equipment and other high-touch areas, continue to be followed.

Online Questionnaire

Participant data from the experiment will be collected online via a computer-assisted questionnaire. Participants will be guided through a series of randomized exercises, asking them to respond to photographic stimuli as well as answer demographic and background questions.

We will first develop an annotated draft of the study questionnaire, including programming notes, in MS Word for review and revision before programming the interactive version for computer-assisted self-administration. We will program the questionnaire, using Voxco, a Web survey platform. We will then conduct internal usability testing and quality checks (QC) to ensure fidelity, for example, that question wording is accurate; that questions and photos display correctly; and that skip patterns, question randomization, and branching function as intended. We have detailed procedures for conducting a thorough QC of online questionnaires, including rigorous testing of the programmed instrument to ensure all programming logic is correct. Once this initial quality testing is complete, we will provide Inflexxion with a link to the programmed survey to approve.

We will also plan to review the data early in the data collection process to ensure that survey data are being captured as intended.

Cognitive Interviews

After completing the questionnaire, participants will rejoin the videoconference call with the RTI researcher, who will then lead them through a brief interview to explore their decision-making process and understanding of terminology. Interviews will be conducted with the video on so that the participant and researcher can see each other to simulate an in-person conversation. The interviewer will take notes, during the interview. Interviews will also be recorded as a backup in case we need to fill in any gaps in our notes, prior to or during the analysis phase.

4. Summary

This protocol describes the study design and data collection procedures for a repeated measures experiment to examine the accuracy of opioid product identification across five exercises, using different stimuli. Data will be collected via an online questionnaire from around 100 participants at 4 to 5 substance abuse centers. Following the experiment, brief semi-structured interviews will be used to learn about participants' decision-making process, while identifying opioid products. Analysis of these data will contribute to the gap in research, examining the validity of self-report for identifying opioid products and reporting opioid use.

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Appendix A.

Opioid Products from ASI-MV Included in the Experiment

	Product	Active Ingredient Category	Brand / Generic	Short-Acting / Long-Acting	Combination / Single
1.	Lorcet	Hydrocodone	Brand	Short	Combination
2.	Lortab	Hydrocodone	Brand	Short	Combination
3.	Vicodin	Hydrocodone	Brand	Short	Combination
4.	Apadaz	Hydrocodone	Brand	Short	Combination
5.	Zohydro ER	Hydrocodone	Brand	Long	Single
6.	Hysingla ER	Hydrocodone	Brand	Long	Single
7.	Other short-acting Vicodin-type generic	Hydrocodone	Generic	Short	Combination
8.	Percocet	Short-acting combination oxycodone IR	Brand	Short	Combination
9.	Roxicet	Short-acting combination oxycodone IR	Brand	Short	Combination
10.	Other short-acting oxycodone combination	Short-acting combination oxycodone IR	Brand or generic	Short	Combination
11.	Roxicodone	Single-entity oxycodone IR	Brand	Short	Single
12.	Other short-acting oxycodone non-combination IR	Single-entity oxycodone IR	Generic	Short	Single
13.	Actavis oxycodone IR	Single-entity oxycodone IR	Generic	Short	Single
14.	New OxyContin (marked with "OP")	Oxycodone ER	Brand	Long	Single
15.	Xartemis XR	Oxycodone ER	Brand	Long	Combination
16.	Xtampza ER	Oxycodone ER	Brand	Long	Single
17.	Other oxycodone ER	Oxycodone ER	Generic	Long	Single
18.	Dilaudid	Hydromorphone	Brand	Short	Single
19.	Exalgo	Hydromorphone	Brand or generic	Long	Single
20.	Other Dilaudid-type generic	Hydromorphone	Generic	Short	Single
21.	Other generic extended-release hydromorphone	Hydromorphone	Generic	Long	Single
22.	Reformulated Opana ER	Oxymorphone	Brand	Long	Single
23.	Generic extended-release oxymorphone (photo #1)	Oxymorphone	Generic	Long	Single
24.	Generic extended-release oxymorphone (photo #2)	Oxymorphone	Generic	Long	Single
25.	Opana	Oxymorphone	Brand	Short	Single
26.	Nucynta	Tapentadol	Brand	Short	Single
27.	Nucynta ER	Tapentadol	Brand	Long	Single
28.	MS Contin	Morphine	Brand	Long	Single
29.	Kadian	Morphine	Brand	Long	Single
30.	Embeda	Morphine	Brand	Long	Combination
31.	Arymo ER	Morphine	Brand	Long	Single
32.	MorphaBond ER	Morphine	Brand	Long	Single

Appendix B.

Experimental Design: Replicated Fully Crossed Design

There are 32 prescription opioid pain medications included in the ASI-MV that are taken orally in tablet or capsule form. Presenting 32 products as stimuli *to each participant* in a repeated measures design with 5 exercises per product would be too burdensome for participants. To reduce the number of questions that each participant completes, while nonetheless, gathering data on all 32 opioid products across the experiment, we recommend using a replicated fully crossed design (Judd, Westfall, & Kenny, 2016).

Exhibit B1 is a matrix, illustrating the following assumptions:

- 32 opioid products that will be used as stimuli
- Opioid products will be randomly allocated to 4 blocks, each containing 8 drug products per block. This represents the number of stimuli that each participant will see. Participants will also be randomly assigned to the 4 blocks, each containing an equal number of participants (e.g., using permuted block randomization), to ensure a balanced design. Participants will complete all 5 exercises for each of the 8 products in their assigned block (a total of 40 exercises per participant).

Exhibit B1. Example arrangement of opioid product stimuli by block and presentation order.

		Opioid Product																													
B	**P**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**
1	**1**	×	×	×	×	×	×	×	×																								
1	**…**	×	×	×	×	×	×	×	×																								
1	**24**	×	×	×	×	×	×	×	×																								
2	**25**									×	×	×	×	×	×	×	×																
2	**…**									×	×	×	×	×	×	×	×																
2	**48**									×	×	×	×	×	×	×	×																
3	**49**																	×	×	×	×	×	×	×	×								
3	**…**																	×	×	×	×	×	×	×	×								
3	**72**																	×	×	×	×	×	×	×	×								
4	**73**																									×	×	×	×	×	×	×	×
4	**…**																									×	×	×	×	×	×	×	×
4	**96**																									×	×	×	×	×	×	×	×

Note. B = Block; P = Participant. For each opioid product, participant cell values represent opioid products included in the ASI-MV:

1. Opana
2. Kadian
3. Roxicodone
4. Nucynta
5. Generic oxymorphone ER
6. Actavis oxycodone IR
7. Other oxycondone ER
8. Other generic extended-release hydromorphone
9. Reformulated Opana ER
10. Embeda
11. Lorcet
12. Other short-acting oxycondone combo
13. Dilaudid-type generic
14. MS Contin
15. Xartemis XR
16. Zohydro ER
17. Vicodin
18. New OxyContin
19. Apadaz
20. Other short-acting oxycondone non-combination ER
21. Lortab
22. Aryzmo ER
23. Xtampza ER
24. Nucynta ER
25. Hysingla ER
26. Generic extended-release oxymorphone
27. Dilaudid
28. Other short-acting Vicodin-type generic
29. Percocet
30. Roxicet
31. Exalgo
32. MorphaBond ER