iThrive WI – A smartphone intervention for overdose and risk and COVID-19 among people who use drugs

NCT05518461

8/8/2024

PROTOCOL TITLE:

iThrive WI – A smartphone intervention for overdose and risk and COVID-19 among people who use drugs

LEAD RESEARCHER:

Rachel Gicquelais, PhD, MPH
University of Wisconsin - Madison
Departments of Medicine & Population Health Sciences
School of Medicine and Public Health
Warf Office Bldg Office 603
610 Walnut St,
Madison, WI 53726

(410) 212-0787
gicquelais@wisc.edu

CO-INVESTIGATOR:

Ryan Westergaard, MD, PhD, MPH
University of Wisconsin - Madison
Departments of Medicine & Population Health Sciences
5223 UW Medical Foundation Centennial Bldg
1685 Highland Avenue, Madison, WI 53705
608-265-7927
rpw@medicine.wisc.edu

VERSION NUMBER/DATE:

Version 1.0 – 07/06/2022
Version 2.0 – 07/29/2022
Version 3.0 – 08/06/2022
Version 4.0 – 08/24/2022
Version 5.0 – 10/18/2022
Version 6.0 – 05/21/2023
Version 7.0 – 08/08/2024

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	07/29/2022	Addressed comments from pre-review by Jennifer Fenne	Yes
2	08/06/2022	Addressed comments from pre-review by Jennifer Fenne	Yes

3	08/24/2022	Adjusted to reflect a Certificate of Confidentiality has been obtained. Fixed minor typos.	Yes
4	10/18/2022	Updated study team personnel	No
5	5/21/2023	Updated study team personnel	No
6	08/08/2024	Updated data storage location and Dr. Gicquelais position to SMPH	No

Table of Contents

1.0 Study Summary

Study Title	iThrive WI – A mobile health intervention to lower overdose risk and promote COVID-19 vaccine education amongst people who use drugs
Brief Summary	This study will examine if the use of a smartphone application called Thrive4Life Connect can help people who use drugs lower their risk of overdose and learn more about COVID-19 vaccines.
Number of study sites	3 – Vivent Health offices located in the cities of Milwaukee, Eau Claire, and Appleton, WI
Study Design	The mobile health system used in this study, called Thrive4Life Connect, has been developed for use in harm reduction settings by our team with prior funding from the National Institute on Drug Abuse. Thrive4Life Connect is based on the Addiction Comprehensive Health Enhancement Support System (A-CHESS) and facilitates brief, behavioral interventions targeting knowledge gaps, motivation, and social connectedness. This app is being used in another IRB-approved study at UW-Madison (Study ID: 2017-0866). In the proposed study, we will develop new intervention content for assessing and increasing vaccine confidence and lowering overdose risk. We will test the feasibility and preliminary effectiveness using a pilot, pre-post study design with 60 people who have injected drugs in the past week and used opioids in the past 30 days. We will examine feasibility outcomes based on study recruitment, retention, and intervention completion. We will also examine changes in knowledge about COVID-19 and overdose, motivation to reduce risk, and behavioral outcomes including overdose risk behaviors and vaccine uptake to establish preliminary effectiveness.
Primary Objective	To test the feasibility of a mobile health application, Thrive4Life Connect, to deliver an intervention focused on reducing overdose risk and supporting COVID-19 vaccine uptake among people who use drugs in Wisconsin.
Secondary Objective(s)	To understand overdose risk, COVID-19 vaccine uptake, and related attitudes and behaviors before and after the mobile health intervention.

Research Intervention(s)/ Investigational Agent(s)	COVID-19 and overdose-related content contained within Thrive4Life Connect, a mobile health application
Drugs/devices used on study (including any IND/IDE #)	N/A
Study Population	Adults who have used opioids in the past 30 days and injected drugs in the past week, primarily recruiting among clients of Vivent Health
Sample Size	60 people
Study Duration for individual participants	6 months

Study Specific Abbreviations/ Definitions:

HIV	Human immunodeficiency virus
PN	Prevention Navigator
PS	Prevention Specialist
PWID	People who inject drugs
ROI	Rural Opioid Initiative
SSP	Syringe service programs
UW	University of Wisconsin

2.0 Background

2.1 We are now approaching the third year of the COVID-19 pandemic, which collided with a worsening, ongoing overdose epidemic that killed 9,260 people in Wisconsin from 2000-2019 from opioid overdose alone. Consistent with national and state-level trends indicating increases in fatal and nonfatal overdoses,[1,2] overdose mortality in Wisconsin increased by 27% during 2020 relative to 2019[3] Unfortunately, provisional 2021 data suggest it will be the deadliest year for drug overdose deaths in Wisconsin and the US.[3] Beyond exacerbations to overdose mortality, prior studies also suggest that COVID-19 itself has disproportionately impacted people who use drugs, and that low vaccine confidence may continue to drive poor outcomes. Studies have shown that people who use drugs are at increased risk for COVID-19 infection, hospitalization, and death.[4] Regarding vaccination, a survey of people who inject drugs in Wisconsin conducted by our team in March-May 2021 indicated that 50% of respondents were hesitant to be vaccinated for COVID-19, consistent with prior studies.[5]

Our team is well-positioned to support people who inject drugs (PWID), during the collision of a worldwide COVID-19 pandemic and the US overdose epidemic as we have conducted multiple prior studies in collaboration and partnership with Vivent Health, the state's primary network of syringe services programs. Our research will describe how mHealth interventions can reduce overdose and COVID-19 risk at a critical time of climbing overdose mortality in Wisconsin.

2.2 **Preliminary studies - Mobile health Interventions with PWID:** Dr. Westergaard and his research team have conducted several mobile health (mHealth) interventions among individuals with active substance use disorders that provide a strong theoretical basis for the proposed work and highlight our team's ability to use mobile phones to collect rich behavioral health data from this population. Hep-Net, a UW-ICTR-funded pilot study designed to increase readiness to be tested for hepatitis C and respond to an overdose,[6,7] showed the feasibility of a brief, computerized intervention involving individualized goal setting in the syringe services setting. We then studied the benefits of the Addiction Comprehensive Health Enhancement Support System (A-CHESS)[8] within multiple treatment settings, including opioid use disorder treatment[9] and HIV treatment (DP2DA042424).[10] A-CHESS is guided by self-determination theory,[11,12] which identifies three supports for intrinsic motivation for behavior change derived from basic psychosocial needs: relatedness (meaningful relationships with others; a sense of connectedness), competence (ability to deal with challenges), and

autonomy (sense of being in control of one's own behavior and goals). A-CHESS also operationalizes the situated Information-Motivation-Behavioral Skills (sIMB) Model,[13] by providing Information (e.g., available community resources), Motivation (e.g., a weekly survey about health goals), and Behavioral Skills (e.g., messaging with a counselor).

Existing Research Infrastructure to be Leveraged in The Proposed New Research:

WI Rural Opioid Initiative - Formative Phase (UW-Madison IRB Study ID: 2017-0866): The Rural Opioid Initiative is a national, multi-site research consortium funded by NIDA, CDC, SAMHSA, and the Appalachian Regional Commission. The Wisconsin node of the consortium (grant numbers UG3DA044826 and UH3DA044826, R. Westergaard and D. Seal, MPI) is built on an academic-community partnership with Vivent Health. In 2018-19, during the initial, formative (UG3) phase of this study, we enrolled 991 PWID from six rural counties in Wisconsin using the best available methods to ascertain a population-representative, cross-sectional sample of a hard-to-reach population.[14-16] We included individuals aged 15 or above, who injected drugs within the past 30 days, and resided in Brown, Outagamie, La Crosse, Marathon, Douglas, or Eau Claire counties. Through Audio Computer-Assisted Self-Interviews,[17] participants reported sociodemographic characteristics, substance use behaviors, overdose history and risk behaviors, and were tested for HIV, viral hepatitis, and sexually transmitted infections.

WI Rural Opioid Initiative - Intervention Phase (UW-Madison IRB Study ID: 2017-0866): We are currently in the intervention (UH3) phase of the WI Rural Opioid Initiative, which involves a clinical trial of a short-term intervention, "prevention navigation," to increase use of preventive health services and reduce risks from injecting drugs for PWID utilizing syringe services programs. Prevention navigation is based on Project START, an evidence-based, six-session, individualized case management intervention that was found to reduce HIV risk among recently incarcerated men using motivational interviewing techniques and a harm reduction framework.[18,19] Our current trial adapted the Project START model for syringe services program settings. Clients receiving the intervention build skills and set goals to reduce their overdose, HIV, and hepatitis C risk, increase their readiness to engage in addiction and hepatitis C treatment, and address other areas of concern such as smoking and self-stigma. We are currently enrolling PWID in a non-randomized, clinical trial in the same syringe services program offices that participated in the formative phase of the study. Over 12

weeks, intervention recipients complete 4 sessions lasting 50-70 minutes each wherein a "prevention navigator" uses strategies including linkage-to-care case management, peer navigation, motivational enhancement, formative decision making, and harm reduction to help participants develop an individualized risk reduction plan related to their injection drug use. Outcomes at 3 and 6 months among the 270 total intervention participants will be compared with data from 135 control participants, all of whom are recruited from the same sites involved in the formative phase. Analyses will compare two primary outcomes between intervention and control participants: confidence in ability to access addiction treatment services when participants are ready for treatment and engagement in addiction treatment services.

An additional activity supported by the intervention phase of the WI Rural Opioid Initiative is the development of Thrive4Life Connect, a novel harm reduction mHealth application that adapts A-CHESS for PWID accessing syringe services programs at Vivent Health. Thrive4Life Connect is guided by similar theoretical frameworks as A-CHESS (i.e., self-determination theory[11,12] and the sIMB[13]). The Thrive4Life Connect app will be used by all participants to complete study surveys moving forward.

2.3 COVID-19 exacerbated a worsening overdose epidemic,[20-22] resulting in a 27% increase in overdose deaths in Wisconsin in 2020 relative to 2019.[23] Factors hypothesized to contribute to increased overdose mortality during the pandemic include an unsafe illegal drug supply contaminated with illicitly manufactured fentanyl,[24] increasing drug use while alone (i.e., away from potential overdose responders) due to physical distancing,[25] and deteriorating mental health.[26] These data indicate a need for targeted overdose risk reduction efforts to reduce the behavioral health impacts of COVID-19.

2020 and 2021 are the deadliest years for overdose on record nationally and in Wisconsin. Consistent with national trends,[22,24-26] a COVID-19 impact survey conducted by our team among PWID in Wisconsin between March and May, 2021 found that increases in overdose risk behaviors may be driving overdose mortality upwards. In total, 52% of PWID used alone more often (i.e., away from potential overdose bystanders who could respond), 52% were concerned about the safety of the drug supply, 27% overdosed, and >75% reported greater depression, anxiety, and loneliness during the pandemic.

COVID-19 vaccine hesitancy may exacerbate health disparities among PWID. People who use drugs, especially those with an opioid use disorder and racial/ethnic minorities, are at increased risk for COVID-19 infection and poor outcomes (e.g., hospitalization, death).[27] Unfortunately, like other studies,[28] 50% of PWID we recently surveyed were hesitant to be vaccinated for COVID-19. PWID are also under-vaccinated for other infections (e.g., hepatitis A and B[29]) and lack access to preventive services.[30] To address disparities, interventions targeting upstream social determinants of health (i.e., stigma, social isolation, distrust in healthcare, food and housing insecurity) are needed. These may improve use of preventive services and change behaviors that ultimately cause health disparities, including those from COVID-19 and overdose.

3.0 Study Objectives and Endpoints

3.1 The primary objective of this study is to understand the feasibility of using a smartphone application to deliver an intervention focused on overdose and COVID-19. The secondary objective is to understand overdose risk, COVID-19 vaccine uptake, and related attitudes and behaviors before and after the intervention.

3.2 We hypothesize that an intervention to increase COVID-19 vaccination and reduce overdose risk will be feasible to deliver via a smartphone based on intervention completion rates. We also hypothesize that engaging with intervention content may increase knowledge about COVID-19 and overdose and reduce risk behaviors.

3.3 **Study Endpoints:**

- **Baseline:** At the beginning of the study, participants will complete a baseline survey to assess their pre-study overdose and COVID-19 risk behaviors, attitudes, beliefs, and knowledge. These data will be used as a basis to assess change at 3 months and 6 months.

- **3-Months:** After the 12-week Thrive4Life Connect mobile intervention, participants will complete the same survey questions from baseline at 3 months to assess any changes in their overdose and COVID-19 risk behaviors, attitudes, beliefs, and knowledge. We will also examine the percentage of participants who completed intervention content each week, and the percentage of skipped intervention content questions to examine feasibility.

- **6-Months:** 3 months after the 12-week mobile intervention, participants will again complete the same survey at 6 months to assess any changes in their overdose and COVID-19 risk behaviors, attitudes, beliefs, and knowledge. The 6-month survey will help us to

understand whether any behavior changes from 3-months were sustained.

3.4 Participants who express any type of mental or other distress (e.g., thoughts of self-harm, harm to others, reports of child or elder abuse) based on any communications with the study team (e.g., by private message through Thrive4Life Connect, on the Thrive4Life Connect discussion board, via text or phone call with the study team, or any other way) will be engaged by study staff and connected with resources through Vivent Health or other means (e.g., National Suicide Prevention Hotline). The participant will be reminded that they can stop study participation at any time. Participants in significant distress may be removed from the study by research team staff.

4.0 Number of Participants

4.1 This study will include 60 participants in total across 3 Vivent Health syringe services locations in Wisconsin – Milwaukee, Appleton, and Eau Claire.

- Milwaukee: 30 participants
- Appleton: 15 participants
- Eau Claire: 15 participants

4.2 In a prior longitudinal study with Vivent Health (WI Rural Opioid Initiative - Intervention phase), we have experienced up to 50% attrition at 3 months and 6 months. Because of this, we may enroll up to 90 participants in this study.

4.3 Enrolled participants are individuals who complete the baseline survey. Participants who leave the study early (i.e., before completing the 3-month study assessment) may be replaced.

5.0 Inclusion and Exclusion Criteria

5.1 Individuals interested in participating in the study will complete a brief screening survey via REDCap during a visit to a Vivent Health study site. Participants meeting the eligibility criteria described below will be invited to participate in the study and asked to provide multiple types of contact information. The screening survey will ask for participant names, which will be stored confidentially on HIPAA compliant drives, for the duration of study recruitment. The names of ineligible participants and those not interested in participating in the study will be kept and used to ensure that ineligible participants do not screen again.

We will retain screening data at an aggregate level to describe the number of people who screened as eligible or ineligible, as the

percentage eligible will be important in examining the feasibility of the intervention and study. For participants that screen as ineligible, choose to not participate, or do not consent to participating, only their name will be retained from the screening data. As in this study participants are only permitted to screen once, the names of ineligible participants will be kept to ensure they do not screen again. These names will be stored on secure HIPAA-compliant servers at the UW School of Medicine and Public Health as well as HIPAA-compliant Vivent Health Microsoft Teams. All the names of people who screen as ineligible will only be kept for the duration of participant recruitment for this study and will be destroyed after.

If a participant screens as eligible and then schedules an enrollment appointment with the intent to participate (enrollment will occur one week after screening), but then decides to not consent or not participate at that time, their screening data, except for their name, will be destroyed. Only their name will be kept to ensure they do not screen again.

We will retain all screening data for people who consent to participating in the study. For these participants who consent to participating in the full study, screening data will not be deidentified until recruitment and study analyses are complete and banking occurs (described later in this protocol). Once recruitment and analysis procedures are complete for this study, all data collected during screening will be deidentified.

Interested and eligible participants will complete a locator form (which is a part of the screening survey) containing individually identifiable data, including participant name and age, address, and contact information. Individually identifiable data will be stored separately from study-related data collected as part of the screening survey. Ineligible participants or those not interested in participating in the study will not complete the locator form.

5.2 **Inclusion Criteria:** To be considered eligible to participate, clients must meet all the following criteria on the screening survey:

- Be 18 years old or older
- Willing to attend in person study encounters at any of the following Vivent Health locations: Milwaukee, Appleton, and Eau Claire
- Used opioids to get high in the past 30 days
- Injected drugs at least 2 times in the past 7 days
- Express interest in reducing their overdose risk

COVID-19 vaccination status will not be considered when assessing participant eligibility. Information regarding COVID-19 vaccination status will still be collected using the eligibility survey to approximate COVID-19 vaccination rates among our population of interest and to customize content delivered in the study intervention.

5.3 **Exclusion Criteria:** None in addition to the inclusion criteria

If a client initially screens as ineligible to participate in the study, they cannot screen again. Eligibility and screening will continue until a total of 60 participants is reached across the three Vivent Health sites. The distribution of participants between the sites will be as follows: 30 participants in Milwaukee, 15 participants in Eau Claire, and 15 participants in Appleton.

6.0 Special Populations

6.1 ☒ Individuals who are receiving inpatient or outpatient services for mental illness, developmental disability, or alcohol and other drug abuse (AODA).

Justification: Our target study population involves people who inject drugs, who are at risk of overdose, necessitating the inclusion of these individuals in our study. Some of our participants may be in treatment programs, and others may be using drugs but not in treatment. We chose to target this population as our proposed intervention centers around lowering overdose risk, which requires engagement with individuals who engage in overdose risk-related behaviors.

Safeguards: To minimize the risks to people receiving treatment for substance use or who are using substances, participants will be provided with a paper or electronic copy of the informed consent when they initially screen as eligible to participate in the study. The informed consent process will be completed at the enrollment visit by either watching a video of the informed consent highlights then discussing with a Prevention Specialist OR by discussing the key areas of the informed consent with a Prevention Specialist. Vivent Health prevention specialists will be available to answer any questions that participants may have. Participants will be informed that their participation is voluntary, they can stop participating at any time, and they can skip any survey questions they are uncomfortable answering. We will also inform participants that study participation (and stopping study participation) will not affect their access to services at Vivent Health or any treatment they are receiving. We also have a Certificate of Confidentiality to ensure that the research team cannot be forced to disclose information that may identify

participants, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings.

16.0

7.0 Recruitment Methods

7.1 Recruitment will occur out of the following Wisconsin Vivent Health locations: Milwaukee, Eau Claire, and Appleton. Previous participants from other Thrive4Life-related studies may also be included in recruitment efforts. Previous participants from prior studies at Vivent Health will be recruited using the same methods as other prospective participants if they attend an SSP visit at one of the study sites. They may also be recruited via phone call, text message, or other contact methods they shared in Thrive4Life, if they indicated previously that such outreach is acceptable.

7.2 Recruitment will occur out of Wisconsin Vivent Health locations in Milwaukee, Eau Claire, and Appleton.
Prospective participants will be made aware of our study opportunity according to the discretion of Vivent Health Prevention Specialists who identify prospective participants that express interest in lowering their overdose risk.

General flyers providing introductory information about our study may also be handed out to prospective participants or posted at participating Vivent Health locations.

If an individual shows interest in enrolling in our study, they will be made fully aware of the study process and expectations prior to screening for eligibility. Prospective participants will watch a brief overview video discussing the study, read through a one-page flyer that provides a study timeline and expectations, and discuss any remaining questions with Vivent Health Prevention Specialists. If clients still express interest afterwards, they will be given a Vivent Health iPad to complete the eligibility survey.

7.3 Described in section 7.2.

7.4 **Recruitment Materials:**

- General flyer: This flyer will provide introductory information about our study and will encourage interested individuals to ask staff at their local Vivent Health office about this opportunity.
- One-pager and FAQs flyer: This flyer will be provided to individuals who have already expressed interest in participating in our study. This handout will have more specific information about enrollment and picking up the

study-provided iPhone, the study timeline, surveys, compensation, study expectations, and answers to FAQs.
- Overview video: This video will be provided to people who have expressed interest in participating in our study. This video will cover the same information in the one-pager but in a video format. The video will include audio and PowerPoint slides that will provide an overview of study information.

7.5 Participants will receive cash compensation for completing specific study surveys. The maximum value for compensation for one participant in this study will be $150. Participants will also receive an iPhone (model SE) as part of their participation in the study. An unlimited phone service plan will be provided to participants for the duration of their participation in the study (6-7 months). Phone service will end after study completion, but participants will be able to keep their iPhone. If participants lose their iPhone, up to one replacement will be provided after the participant informs Vivent Health and UW research staff of their need for a new phone. Cash compensation and iPhones will be provided to participants in person at their Vivent Health location (Milwaukee, Eau Claire, or Appleton). Venmo, Paypal, or mailing remuneration will be alternative methods for providing compensation to participants as needed (E.g., If a participant moves locations). Compensation will be provided to participants after confirmed completion of the study surveys (see below).

Survey compensation:

- Baseline survey: $20
- First set of daily check-ins: After the baseline survey, three daily check-in surveys will be made available. The completion of one daily check-in will be remunerated at $10, for a total of up to $30 for completing all three check-ins.
- 3-month survey: $20
- Second set of daily check-ins: After the 3-month survey, three daily check-in surveys will be made available. The completion of one daily check-in will be remunerated at correlates to $10 in compensation, for a total of up to $30 for completing all three check-ins.
- 6-month survey: $20
- Third set of daily check-ins: After the 6-month survey, three daily check-in surveys will be made available. The completion of one daily check-in will be remunerated at correlates to $10 in compensation, for a total of up to $30 for completing all three check-ins.

8.0 Consent/Assent Process

8.1 This study will involve individuals who are using drugs, who may also be receiving inpatient or outpatient services for mental illness, developmental disability, or alcohol and other drug abuse (AODA). To minimize the risks to this population, participants will be provided with a paper or electronic copy of the informed consent when they initially screen as eligible to participate in the study. The informed consent process will be completed at the enrollment visit by either watching a video of the informed consent highlights then discussing with a Prevention Specialist OR by discussing the key areas of the informed consent with a Prevention Specialist. Participants will be informed that their participation is voluntary, they can stop participating at any time, and they can skip any survey questions they are uncomfortable answering. After watching the informed consent video or walking through the consent with a Prevention Specialist, participants will be prompted to ask the research team any questions. We also obtained a Certificate of Confidentiality from the National Institutes of Health, which participants will be made aware of.

Walkthrough of Study Informed Consent Process:

Participants will first complete a screening survey to determine their eligibility. This screener will be completed with Prevention Specialists at participating Vivent Health locations. Eligible participants who are interested in participating in the study will be invited to complete a locator form with Prevention Specialists asking for multiple contact methods, which will be utilized for follow-up throughout the study. Participants that express interest in enrolling in the study will be invited back to Vivent Health in one week for an enrollment and informed consent appointment. Participants will be given a paper or electronic copy of the study consent form and asked to review this information in the week before their enrollment appointment.

During the week between the screening encounter and enrollment encounter, study iPhones and Thrive4Life Connect accounts will be activated for the prospective participants. The participant's name and enrollment appointment time will be inputted into a secure Vivent Health Microsoft Teams spreadsheet. This spreadsheet will be used to keep track of participant enrollment appointments and determine when participant iPhones will need to be activated. Participants will be reminded of their enrollment appointment through their preferred contact method from the locator form.

The informed consent process will take place at the enrollment appointment at Vivent Health locations in Milwaukee, Eau Claire, and Appleton. Participants will be provided with detailed

information about study procedures by reading the consent document on paper or electronically. Additional copies of the consent document will be available in the private room at the Vivent Health prevention offices.

Participants will either watch a video of the informed consent highlights then discuss with a Prevention Specialist OR discuss the key areas of the informed consent with a Prevention Specialist. Participants will be able to watch the consent video OR walkthrough the consent with a Prevention Specialist, and review the full text of the consent document. Participants will then be able to provide their electronic agreement to participate in the study on their study iPhone in the Thrive4Life Connect mobile application (by checking a box, rather than signing their name). Participants may also provide verbal consent to participate instead, with documentation of consent being kept on the HIPAA-compliant secure Vivent Health Microsoft Teams. Agreement documentation will also be stored with study data on the Thrive4Life Connect platform. In alternative circumstances, a paper version (no video) of the consent form will be reviewed and provided by research staff at Vivent Health before proceeding with any study procedures. Participants will then be able to affirm participation verbally if needed after reviewing paper consent if, for example, Wi-Fi is down, or another situation arises.

During the informed consent process, participants will be reminded that their participation is voluntary, and they can withdraw at any time during the study. Participants will be notified that the data collected from this study may be banked in a secure location and utilized by researchers for future studies about improving harm reduction.

9.0 Process to Document Consent in Writing

9.1 We are requesting a waiver of written documentation of consent. We will provide participants with a paper or electronic copy of the informed consent information and provide an iPad and headphones so they can watch a video walking them through the informed consent during their in-person enrollment appointment at a participating Vivent Health location. Participants will also be able to talk through the informed consent document with a Prevention Specialist instead of watching the video. During this appointment, participants will be able to ask the Vivent Health Prevention Specialist, who is facilitating their appointment, any questions about the study and consent information. Then, participants will be asked to agree or not agree to participate in this study in the Thrive4Life Connect app (they can also elect to take time to think about it and get back to us at a later date). Therefore, participants will be provided

with consent information via oral, written, and electronic methods.

After consent is verbally affirmed, participants will open their account in Thrive4Life Connect app. The first thing they see will be a screen containing the text from the informed consent document. At the bottom of this screen, there will be a checkbox asking participants to select here if they agree to participate in this study. Participants will be unable to access content in the Thrive4Life Connect app unless they agree to the consent checkbox in the app. The Thrive4Life Connect app is limited in its ability to collect a 'true' signature from participants. Specifically, creating an actual signature (via stylus or finger) is not a functionality that currently exists in the app. Additionally, there is no mechanism to provide a validated electronic signature on Thrive4Life Connect.

The study meets the criteria for a waiver of signed consent through criteria set #1 on HRP-411. The research involves explaining a written script of the informed consent through a pre-recorded video that covers the elements of consent in HRP-314. Participants will also be able to talk through the informed consent document with a Prevention Specialist if they prefer. Prevention Specialists will be provided with a written script of the informed consent as well. Participants will have the opportunity to ask questions and will receive a paper or electronic copy of the consent to review during the video or discussion and afterwards. The research proposed in this study presents no more than minimal risk of harm to prospective subjects. Regarding the risk to participants, the primary risks include being identified as a participant in this study and distress caused by answering questions about sensitive topics, such as substance use. These risks have been minimized by the study team by having a Certificate of Confidentiality, ensuring that participants are encouraged to password-protect their study iPhone, and ensuring participants do not include any identifiable information in their Thrive4Life Connect public usernames. Study data will also be stored on HIPAA compliant servers at the UW School of Medicine and Public Health. Participants are also free to skip questions they are uncomfortable with answering and can reach out to study staff as needed.

This study also involves no procedures for which written consent is normally required outside of the research context, as we ask participants to download an app available through the app store and participate in self-help type activities.

9.2 Participants will be provided with a paper or electronic copy of the informed consent detailing the study procedures, risks, and benefits. They will be asked to review this information during the week

between their screening and enrollment encounters. Then during the enrollment appointment, participants will review the study procedures and informed consent document by either watching a video of the informed consent highlights then discussing with a Prevention Specialist OR by discussing the key areas of the informed consent with a Prevention Specialist. During this process, participants will be encouraged to ask any questions they may have about the study. Agreement to participate in the study will be collected via electronic agreement on the Thrive4Life Connect mobile application. Participants may also provide verbal consent to participate instead, with documentation of consent being kept on the HIPAA-compliant secure Vivent Health Microsoft Teams.

10.0 Setting

10.1 This research will primarily be conducted remotely utilizing a smartphone application, Thrive4Life Connect, and study provided iPhone. Participant recruitment, screening, enrollment, consent, and remuneration will occur in person at Milwaukee, Eau Claire, and Appleton Vivent Health locations. Additionally, participants will be able to come into their local Vivent Health location to ask any questions they may have throughout the study. Data analysis will occur at the UW-Madison School of Medicine and Public Health.

If a participant loses their study-provided iPhone and backup phone, they will be able to complete the study surveys on the online browser version of Thrive4Life Connect. If needed, participants may be able to go to a Milwaukee, Appleton, or Eau Claire Vivent Health location to complete their study surveys on the study iPad.

11.0 Study Intervention

11.1 Participants will be asked to complete a series of intervention modules using the Thrive4Life app on a smartphone provided by the study. These modules are meant to simulate the format and style of the WI Rural Opioid Initiative's in-person interaction with a prevention navigator and are focused on overdose risk and vaccine hesitancy. Participants will answer a series of questions and receive immediate, tailored feedback within the intervention modules based on their responses to module activities and questions. The options and responses to module questions and activities were created collaboratively with Vivent Health staff and by reviewing intervention materials (i.e., worksheets used during the intervention) from our prior study involving in-person prevention navigation intervention sessions.

The FDA Policy for Device Software Functions and Mobile Medical Applications states (in section V.B, page 12) states that mobile health applications that help patients self-manage their disease or conditions without providing specific treatment or treatment suggestions fall under a

category for which FDA intends to exercise enforcement discretion. The Thrive4Life Connect app and our intervention meet this criteria based on prior consultations with Jake Rome at UW-Madison ICTR.

Data from this study are not planned for use and are not being held in support of a future submission to the FDA for approval of the app.

12.0 Study Timelines

12.1 The duration of an individual participant's participation in the study will last approximately 6 months. We aim to enroll all 60 study participants within 8 months. Initial analyses for this study will be completed by the end of the funding period, August 31st, 2023, but may continue beyond that time. We anticipate completing analyses by August 31, 2024.

13.0 Procedures Involved

13.1 We will use a pilot pre-post comparison study with 60 PWID from three Vivent Health syringe services programs in Milwaukee, Eau Claire, and Appleton. Participants will complete baseline surveys, a 12-week intervention and will repeat surveys 3 months and 6 months after baseline. We will primarily examine feasibility outcomes (percentage of participants who complete each component of the 12-week intervention). We will also compare overdose risk behaviors and COVID-19 vaccine confidence at 3 and 6 months to baseline.

13.2 Schedule of Procedures and Study Outline
This study will involve required and optional procedures.

Required activities include:

- Thrive4Life Connect
- Surveys
  - Baseline survey
  - 12 weekly check-in intervention surveys about overdose prevention
  - 3-month survey
  - 9 daily check-in surveys
  - 6-month survey
- Surveys will collect information about: Name, age, gender identity, ZIP code, race and ethnicity, education, marital status, alcohol and drug use, types of health care received, mental health, and other related items.
- Private messaging: Study staff will send participants messages in Thrive4Life Connect to remind participants about when surveys open, send personalized resources, and answer any questions.

- Data linkage to databases like the Wisconsin Immunization Registry, Medicaid, and Wisconsin hospitalization, emergency medical services, and infectious disease surveillance registries.

Optional activities include:

- Interactive modules about COVID-19 vaccines
- Sharing thoughts on discussion boards and private messaging others
- Engaging with online and local resources in the app
- Logs for motivation and thoughts of gratitude
- Using UW-Madison study team contact information.

See the study timeline/flowchart below for a detailed overview of when various activities will occur.

13.3 After recruitment, study participants will be involved in the following procedures: eligibility screening, informed consent and study enrollment, baseline surveys, 12-week intervention session, 3-month follow-up surveys, and 6-month follow-up surveys.

Recruitment, screening for eligibility, and informed consent and enrollment will follow the procedures previously described (See "Recruitment" and "Informed Consent" sections).

During the initial enrollment appointment and after providing informed consent, participants will complete the baseline survey and first of three daily check-ins (ecological momentary assessments). The baseline survey will involve multiple choice questions about overdose and COVID-19 infection and vaccine knowledge, attitudes, and risk behaviors. The daily check-ins will ask clients to report drug use risk behaviors during drug using events in the prior day through Thrive4Life Connect. Participants will be asked to complete two additional daily check-ins about their drug use in the prior day over the course of the week following the enrollment appointment. Participants will be notified through an in-app notification and/or private message that a new survey is available. This event-level data will provide a detailed picture of co-occurring overdose risk behaviors beyond what can be captured in surveys with longer recall periods. We will specifically assess the setting of use and whether the participant was alone, had naloxone nearby, tested drugs for fentanyl, or mixed drug classes.

During the 12-weekly intervention session, participants will complete weekly check-in surveys focused on 1) risk reduction planning tailored to their needs and motivation to change their overdose risk behaviors and COVID-19 vaccination status, and 2) goal setting and outlining steps they will take to achieve their overdose and COVID-19 health goals. All participants will choose goals related to overdose prevention, but choosing goals related to COVID-19 will be an optional activity.

The 3- and 6-month follow-up surveys will collect the same data as the baseline survey and daily check-ins. Three months after beginning the study, participants will complete another survey assessing their overdose and COVID-19 infection and vaccine knowledge, attitudes, and risk behaviors. They will then be asked to complete the second set of three total daily check-ins. This process will be repeated for the 6-month timepoint. A total of nine daily check-ins (ecological momentary assessments) will be completed by each participant over the duration of the study.

Throughout the study, participants will have access to and be encouraged to engage with a list of local resources and information about overdose risk and COVID-19. Participants will be regularly reminded that they can contact project staff if they need referrals or supplies. Discussion boards and private messaging functions within

the Thrive4Life Connect app will also be available to participants. Participants' general usage (i.e., clicks) of resources or pages on the app are tracked within the Thrive4Life Connect app. Actions such as the frequency of participant engagement with resources in the Thrive4Life Connect app, posting on discussion boards, and sending private messages may be analyzed as data for the study. Participant discussion board and private message text will be monitored regularly by specific study staff approved to interact with participants via Thrive4Life Connect data exports to ensure that no illegal or inappropriate activity is occurring in these areas and that participants are not expressing thoughts of harm to themselves or others, or any other signals of distress. All participants and study staff will be able to publicly post and view other discussion board posts. To protect participant confidentiality, participants are encouraged to choose anonymous public usernames (which are viewable by other participants and study staff on discussion boards) and avoid posting identifiable information. All participants and study staff will also be able to utilize the private messaging function. Private messaging will primarily be used by study staff to send participants resources that are specific to their 12 weekly intervention goals. Participants will also be able to message each other and study staff. When messaging with other participants, the same guidelines for discussion boards to ensure confidentiality will apply.

Referrals to community resources (e.g., housing assistance) and sterile injecting supplies or other resources (e.g., naloxone) are provided as part of the regular care that participants may receive at Vivent Health. A majority of the resources available to participants in this study focus on general education that is publicly available online and/or in suggesting topics or supplies that participants may want to ask about as part of their usual care in the future (e.g., picking up a naloxone supply if they don't already have one). Once participants are connected with in-person resources or supplies at Vivent Health locations, that will be considered as part of regular Vivent Health care.

Throughout the study, all resources provided in any survey or in the Thrive4Life Connect app will be continuously updated to reflect the most current information. All resources and any links will be updated as information changes or becomes available.

We may use identifiable information from participants to link their information to databases like the Wisconsin Immunization Registry, Medicaid enrollment and claims data managed by the UW-Institute for Research on Poverty (IRP), and Wisconsin hospitalization data

from the Wisconsin Hospital Association Info Center, emergency medical services from the Wisconsin Ambulance Run Data System, and infectious disease surveillance registries capturing COVID-19, hepatitis C, and HIV infections. The purpose of this linkage is to understand how people who inject drugs use health care resources as well as to gather outcome data such as COVID-19 infection or vaccination status, overdose events, and substance use or other treatment utilization. To accomplish this, we will link multiple datasets using individual identifiers (name, date of birth, address, sex, race, phone number).

The UW-Institute for Research on Poverty (IRP) will assist in constructing the Medicaid study dataset. The IRP has longstanding technical expertise in the construction and secure use of integrated person-level electronic datasets that combine State of Wisconsin administrative data. Specifically, the IRP maintains the Multi-Sample Person File (MSPF) dataset which combines data for the universe of individuals interacting with several WI state agencies, including the Department of Health Services (home of the Medicaid program) and the Department of Corrections, at the person-level dating back to the late 1990's through the present. The MSPF is structured at the person-level, and each individual has a unique ID over time and across state agencies (e.g., a person who is incarcerated in a WI state prison and later enrolled in WI Medicaid) which supports longitudinal analysis. We will provide the UW IRP programming staff with our sample selection criteria (i.e., identifiers listed above for individuals enrolled in the study). They will query the MSPF dataset with these criteria to identify possible linkages to our study. In addition to basic program participation information (e.g., dates of participation), the MSPF includes identifying variables for each unique person including Social Security number, date of birth, name, and the individual's identification number for each state agency that contributes to the MSPF in which s/he receives or has received services. The IRP will submit a finder file with the relevant identification information to each entity that is providing person-level data for the study. Upon receipt of these data, the IRP will then merge data from all sources at the person level, assign a unique, study number to each subject, and remove the personal identifying information used to match data across sources from the analytic dataset that is provided to the investigators. The exchange of data between the IRP and state agencies is governed by the Data Use Agreements between the IRP and the respective agencies and follows a strict data security protocol to protect the confidentiality of individuals. The DUA between the IRP and the WI Medicaid program will be obtained for this study once recruitment has ended.

The remaining dataset owners are housed at the Wisconsin Department of Health Services (DHS) or with affiliated organizations (e.g., WHAIC) for whom DHS provides assistance with linkage projects. The process for gaining approval for linkage projects involves putting together a formal request for review by the DHS Data Governance Board, which we will do upon completing recruitment. After approval from the board is obtained (including a review of proof of IRB approval for this protocol), we will work with the data owners and University HIPAA privacy officers to draft a Data Use Agreement. Once all stakeholders are in agreement on the DUA elements and there is a draft ready, the DUA is routed for institutional signature, which will facilitate getting all of the appropriate persons to review and approve the document. Once DUA approval is obtained, the research team will work with the specific data owners at DHS, who perform the data linkage based on identifiers provided. No study data beyond identifiers will be shared with DHS during this process (e.g., survey data about drug use). DHS data owners will then provide a file on matched encounters back to the research team, which will be identifiable via a unique participant ID number created for the linkage. This unique identifier will allow the research team to link the received DHS datasets back to the original study data (e.g., survey data, Thrive4Life Connect use data).

13.4 **Identifiable Data Elements**: Possible participants will complete a screener and locator form. The screener and locator form will both be administered via one REDCap survey. If a participant screens as eligible, the survey will pause and a Vivent Health prevention specialist will confirm their interest in enrolling. Interested participants will then complete the rest of the survey by providing multiple methods of contact information.

Identifiable Data Element	**Add an X if collecting and storing**
Names (or derivatives such as initials)	X
Dates (except year)	X
Telephone Numbers	X
Geographic subdivisions smaller than a state	X
Email addresses	X

Thrive4Life Connect app account/study ID numbers	X
Social media contact information	X
Information for 2 or more points of contact	X

Other Data Elements:

We will collect the following data directly from participants using survey responses in the Thrive4Life Connect app:

- Overdose and COVID-19 health-related goals
- Substance use and overdose risk, knowledge, attitudes, beliefs, concerns, and behaviors
    - Safer behaviors
    - Risk behaviors
- Overdose perspectives and experiences
- COVID-19 knowledge, attitudes, beliefs, concerns, and behaviors
- General attitudes towards vaccines
- COVID-19 vaccination status and history
- Event-level information about the most recent time a participant used drugs
    - Daily check-ins (ecological momentary assessments)
- Survey completion dates

Source Records:

☒ Data from outside institutions or organizations (specify: Wisconsin Department of Health Services and Medicaid, registries described above)

☒ Other (specify: A-CHESS Thrive4Life Connect mobile app utilization data)

Supplementary data will be collected indirectly from participants based on their activity in the Thrive4Life Connect app:

- Discussion board participation
- In-app private messaging with study staff
- Viewing of in-app resources
- Usage of "My Motivation" and "My Gratitude"
  "My Motivation" and "My Gratitude" are optional activities available in the Thrive4Life Connect app.

  "My Motivation" prompts participants with the following, "Stay motivated by keeping a list of why you want to stay well - and watch your list grow!" This area then provides

participants with an opportunity to curate a personal log of things (text or pictures) that motivate them to meet their goals.

"My Gratitude" prompts participants with the following, "Awareness and appreciation of things you're thankful for may help brighten your day. What are you grateful for?" Participants can then curate a personal list of things (text only) that they are grateful for in "My Gratitude."

13.5 The Thrive4Life Connect mobile application does not require FDA regulation, as per consultation with the Administrative Director of the FDA Regulated Research Oversight Program.

14.0 Comparison of usual care and study procedures

14.1 Clients visiting Vivent Health may choose not to participate in the study. There is no alternative to participating if they choose not to participate.

14.2 Regardless of study participation, clients at Vivent Health can continue to receive their usual prevention services from Vivent Health, including but not limited to obtaining sterile injecting equipment and other supplies, referrals, and hepatitis C and HIV testing.

14.3 Study participants are provided with some overlapping information about overdose prevention, COVID-19, and health and social services via the Thrive4Life Connect smartphone application that could be obtained from staff working at Vivent Health. Specifically, the Thrive4Life Connect app contains a resources section with flyers and information on these topics, which are also available at Vivent Health.

14.4 Research participation will not affect access to Vivent Health prevention services or any other care or treatment the participant is involved in.

15.0 Withdrawal of Participants

15.1 The Thrive4Life Connect application allows participants to share their views, opinions, photos and personal experiences. However, participants are prohibited to post content on the Thrive4Life Connect site that promotes racism, bigotry, hatred, nudity, or physical harm of any kind against any group or individual. If participants use the application in an inappropriate manner, research staff will delete the inappropriate messages and follow up with them. If the behavior continues, research staff may withdraw participants from the study.

Participants expressing severe emotional or mental distress (e.g., by communicating thoughts of harm to self or others) may also be withdrawn from the study by study staff (or by their own choice). Withdrawal decisions will be made jointly by the research team and lead researchers.

If a participant is incarcerated, no research activities would occur during the time of incarceration. Participants can contact the study team when they are released to discuss participating in the study. If participants are under criminal justice supervision and are prohibited from using internet-enabled devices, it is their responsibility to ensure that their study participation is allowable under the terms of their supervision.

15.2 Orderly termination will involve informing the participant that they are being withdrawn from the study. The study team will then have the ability to remove access from the study activities on the Thrive4Life Connect application and to deactivate the data plan on their study-provided smartphone.

15.3 See 15.2.

Participants are able to end their participation in the study at any time. Participants who do not complete the 12-week intervention will still be eligible to complete the 3-month and 6-month paid study surveys. This situation will be considered a partial withdrawal. These partial withdrawals will be reported in the same way, in continuing reviews, as withdrawals. Data may continue to be collected if partially withdrawn participants begin using the Thrive4Life Connect app again and if they decide to still complete the 3-month and 6-month surveys. If participants partially withdraw and their phone service is turned off, they can contact the study team to discuss participation and turning the service back on. All surveys can be completed without phone service using Wi-Fi.

16.0 Data Management and Confidentiality

16.1 To ensure quality control of participant data in the Thrive4Life Connect app, our study team will test the functionality of each survey and all intervention content. This testing procedure will be designed to identify any possible survey bugs, ensure correct memory logic between surveys, and ensure skip logic within surveys.

A majority of the survey questions in this study utilize multiple choice or checkbox options and guided type in boxes with limited

answer ranges. All questions must be answered, but a "Prefer not to answer" option is always available for participants who may be uncomfortable answering certain questions. Instructions are also provided at the beginning of each survey.

Survey data are stored in the Thrive4Life Connect app even if a participant does not complete a survey or forgets to submit their final answers. This function ensures data quality by limiting data loss.

Research staff will periodically review completed surveys to ensure they are functioning properly.

16.2 Steps to secure data:

- ☒ Data will be coded, and the "key" linking identities to codes will be kept separately from the data.
- ☒ Only those listed as key personnel will have access to the "key."

  List of key personnel:
  - Rachel Gicquelais
  - Ryan Westergaard
  - Sarah Uhm
  - Katy Mijal
  - Rebecca Miller
  - Erika Bailey
  - Andrew Hagmeier
  - Jacob Schleicher
  - Dahlia Jones
  - Adam Hanson
  - Carmella Brown
  - Caitlin Conway
  - Theresa Zauner
  - Mikaela Becker
  - Carly Kowitz
  - Catrina Solberg
  - Janelle Moneypenny
  - Kara Lee

- ☒ This study is in part funded by the National Institutes of Health. However, NIH funding only covered the development of the Thrive4Life Connect app platform, and not the development or evaluation of the intervention studied in this project. To ensure confidentiality for participants and because we will collect sensitive information, the research team applied for and received a new Certificate of Confidentiality to protect data from

being requested without the subject's consent as part of a legal proceeding.

16.1 Data storage:

☒ Research Electronic Data Capture (REDCap) *Specify which instance you will be using (e.g., ICTR's, Department of Medicine's)*: Department of Medicine

☒ Other software option that will be stored on departmental server. *Specify the department*: School of Medicine and Public Health HIPAA-compliant servers

☒ Locked filing cabinet or drawer inside a locked room. Specify the building: School of Medicine and Public Health WARF building

☒ Other (describe): HIPAA-compliant Vivent Health Microsoft Teams – Information about study survey completion dates will be collected for each participant. This information will be used to inform whether a specific participant is eligible to pick up their compensation for each survey. Vivent Health personnel will also update the Microsoft Teams to reflect when a participant has picked up their compensation.

☒ Portable devices will be used to access secure web-based data collection sites such as ICTR's REDCap. No data will be stored locally on the device.

16.2 Management of Identifiers:

☒ Identifiers will be destroyed at study closure or at the time of publication.

16.3 Data will be stored on the Thrive4Life Connect mobile application platform, HIPAA-compliant servers at the UW School of Medicine and Public Health , DOM REDCap, and HIPAA-compliant Vivent Health Microsoft Teams, as described above. Because data are collected electronically, separate data storage for each study site is not necessary and will not be used.

The Thrive4Life Connect app was developed based on the UW-Madison Addiction-Comprehensive Health Enhancement Support System (A-CHESS) platform, which has been used in several prior addiction-related studies. Any data stored on a participant's device are stored in an encrypted file and only accessible by that participant, i.e. participants don't have any other participant's data on their phone. These data are only collected after the participant has signed into their account and are removed when the participant signs out of the Thrive4Life Connect A-CHESS based

application. Any data transferred to and from UW-Madison servers are done through an encrypted connection.

Thrive4life Connect utilization data that will be used for study analyses of Thrive4Life Connect app utilization are stored on HIPAA Compliant servers housed at the UW-Madison Division of Information Technology (DoIT). DoIT partners with the UW-Madison Office of Cybersecurity to ensure that our infrastructure meets the necessary security controls.

16.4 Data including identifiers from this study will only be shared with members of the study team at UW-Madison and Vivent Health.

17.0 Provisions to Protect the Privacy Interests of Participants

17.1 Steps to protect participants' privacy interests*:*

☒ Procedures will be performed in a private area where others cannot see the procedures being performed or overhear the conversation between subjects and researchers.

☒ All members of the study team are up to date on their institutional HIPAA training.

We have strict rules to protect participant personal information and protected health information (PHI). We will limit who has access to participant health information, names, addresses, phone numbers, and other identifiable information. We will also store this information securely. We may publish and present what we learn from this study, but none of this information will identify participants directly without permission. Study participants will also be protected by a Certificate of Confidentiality.

Federal or state laws may permit or require us to show information to university or government officials and to study sponsors responsible for monitoring this study. There are some situations when we will not keep information confidential. We will report information about participants to the appropriate authorities in the following circumstances:

- If they tell us they are planning to harm themselves or another person.
- If they tell us something that causes us to believe that a child or vulnerable adult is being abused

17.2 This study involves collecting sensitive information about drug and alcohol use on surveys in the Thrive4Life Connect app. The primary objective of this study is to test a novel mobile health intervention to reduce overdose risk and support vaccine uptake with people who inject drugs in Wisconsin. To assess the effectiveness of this study

and fulfill the study goals, the collection and analysis of this sensitive information is necessary.

17.3 Participants will be able to stop their participation at any time throughout the study. Additionally, participants can refuse to answer any survey question(s) that may make them uncomfortable. Throughout the study, participants will also be encouraged to reach out to the study team if they have any questions. Based on a participant's survey answers, they will also be connected with resources that are specific to their situation. We also obtained a Certificate of Confidentiality for the study and will explain what this means to participants during the informed consent process.

18.0 Sharing of Results

18.1 Results from this study will not be shared directly with participants or others. Individual results will not be reported in participants' health records.

18.2 We will only share results in an aggregate format, and we will not share any data that could be used to identify participants. We will only report summary data to individuals outside the study team. We expect to publish manuscripts based on information gathered in this study, but no participants will be identified in these shared results.

19.0 Data and Specimen Banking

19.1 Data from this pilot study will be banked for future use. Data banking will not be optional. Deidentified data from this study, specifically Thrive4Life Connect survey answers, will be stored on HIPAA compliant secure servers at the UW-Madison School of Medicine and Public Health.

Banked data will be stored indefinitely, but study ID numbers will be removed from data before banking. Banking will occur after all publications for this study are completed and published or after 7 years (whichever comes first).

<u>Members at UW-Madison that can see and use participant information:</u>

- Members of our research team
- Offices and committees responsible for the funding and oversight of research

19.2 Data to be stored:

<u>We will collect the following data directly from participants using survey responses in the Thrive4Life Connect app:</u>

- Overdose and COVID-19 health-related goals

- Substance use and overdose risk, knowledge, attitudes, beliefs, concerns, and behaviors
    - Safer behaviors
    - Risk behaviors
- Overdose perspectives and experiences
- COVID-19 knowledge, attitudes, beliefs, concerns, and behaviors
- General attitudes towards vaccines
- COVID-19 vaccination status and history
- Event-level information about the most recent time a participant used drugs
    - Daily check-ins (ecological momentary assessments)
- Survey completion dates
- Demographic information
- Frequency and distribution of questions where participants chose "Prefer not to answer"

<u>Supplementary data may also be collected indirectly from participants based on their activity in the Thrive4Life Connect app:</u>

- Discussion board participation
- In-app private messaging with study staff
- Viewing of in-app resources
- Usage of "My Motivation" and "My Gratitude"

Information from participants collected from databases like the Wisconsin Immunization Registry, Medicaid, and Wisconsin hospitalization, emergency medical services, and infectious disease surveillance registries.

All data will be deidentified prior to banking.

19.3 To comply with some academic journal requirements, we anticipate needing a procedure to make data available to interested colleagues. Written requests to release deidentified data or specimens may be made to the lead researchers by email. Requests must specify the specific data requested. The lead researcher would then supply a deidentified dataset based on the data requested. No PHI will be shared in a requested dataset.

19.4 Participants will not be able to withdraw their banked data for future research use. All data will be fully anonymized prior to banking. If a participant decides to withdraw from the study, no additional data will be collected from them after that point.

20.0 Study Analysis

20.1 Primary Outcome Null hypothesis (feasibility): the study is feasible based on intervention content completion rates of at least 50%. Alternative hypothesis: fewer than 50% of intervention content is completed.

Secondary outcome null hypothesis #1 (preliminary effectiveness of overdose content): there is no difference in the number of days endorsing overdose risk behaviors per month at baseline vs. 3 months and baseline vs. 6 months. Alternative hypothesis: the frequency of overdose risk behaviors decreased from baseline to 3 months, and baseline to 6 months.

Secondary outcome null hypothesis #2 (preliminary effectiveness of COVID-19 content): there is no difference in proportion of participants who have been vaccinated against COVID-19 at baseline vs. 3 months and baseline vs. 6 months. Alternative hypothesis: the proportion vaccinated will increase from baseline to 3 months, and baseline to 6 months.

20.2 As a pilot feasibility study, the number of participants (n=60) reflects the maximum allowable participants in our budget and study timeframe. A formal sample size calculation was not done.

20.1 All participants who enroll in the study will be included in each analysis.

20.4 The average and variation in percentage of completed intervention modules and in the percentage completing each weekly intervention module over 12 weeks will be calculated and examined descriptively.

We will examine changes in the frequency of endorsing overdose risk behaviors and COVID-19 vaccination based on a descriptive analysis of the baseline, 3 month and 6 month surveys. We may also test for differences using appropriate statistical tests, including paired t-tests, McNemar's test, and models appropriate for count outcomes and repeated measures (Poisson or Negative Binomial Generalized Estimating Equations). As a pilot study, we expect that most analyses will be descriptive rather than inferential in nature.

20.5 We will examine weekly survey and intervention module completion rates. There are no stopping rules for efficacy or safety in this study.

20.6 As a pilot feasibility study, we will examine missingness and survey completion as primary outcomes to assess engagement with intervention content and study feasibility. We may impute or use simple techniques such as last observed carried forward in analyses. We will track reported reasons for missing data such as loss of study phone, incarceration, withdrawal, etc.

21.0 Potential Benefits to Participants

21.1 Participating in this study may be a beneficial way for PWID to get support from other people living with substance use problems. Thrive4Life Connect will also provide participants with information about local resources and harm reduction. The study may also benefit other people in the future by helping us learn more about how a smartphone app can lower overdose risk for people who use drugs.

22.0 Risks to Participants

22.1 Risks:

- Information participants enter into Thrive4Life Connect can be viewed by UW and Vivent Health research team members. They may monitor discussion boards and post information there. Study staff will also reach out to participants via private messaging or other contact methods (texts, phone calls, social media, etc.). Information participants enter into Thrive4Life Connect is not stored on the phone, but this information is stored on the Thrive4Life Connect app.
- When participants set up their Thrive4Life Connect account, they will be asked to create an account username. This username will be listed on discussion board posts and included in a list of participants that can receive private messages. To reduce the risk of being identified, we will require participants to choose a username that will NOT include any identifiable information such as their first name, last name, date of birth, address, etc.
- Other participants can see what is posted to the discussion boards. There is a risk that other participants could identify each other based on the information they provide in their discussion board posts.
- Answering questions on sensitive issues (like drug and alcohol use, mental health, etc.) in surveys may cause anxiety, distress, embarrassment, or feelings of sadness. Participants do not have to answer any questions that they do not want to.
- The Thrive4Life Connect app allows participants to share their views, opinions, photos, and personal experiences. However, <u>participants are NOT allowed</u> to post content on the Thrive4Life Connect app that promotes racism, bigotry, hatred, nudity, or physical harm of any kind against any group or individual. If a participant uses the app in an inappropriate or illegal manner, the research staff will delete the inappropriate content and follow up with them. If the behavior continues, the research staff may withdraw the participant from the study.

- There is a risk that study participants may send or receive private messages including unwanted or inappropriate content. If this happens, we ask that participants report this information to the study team (608-294-7446).
- Information from the internet and/or Thrive4Life Connect discussion boards could be wrong. However, a panel of UW staff review all information on the app, so this risk is unlikely. We will provide tips to help participants figure out whether they can trust the information they receive from these sources.
- There is a risk that participant information could become known to someone not involved in this study. If this happens, it could result in damage to reputation, which could also affect relationships with family and friends, affect employment, or make it harder to get insurance or a job.
- The study team may discover behavior that raises concern about harm to themselves or others. If we see anything that suggests that a participant or others face imminent risk of harm, we will contact appropriate parties to intervene (e.g., your care team and/or police).

22.2 Potential participants may choose not to participate or enroll after learning more about the study. Participants may end their participation at any time and choose not to answer any questions they do not wish to. Participants are not required to use the app discussion board. They must be able to receive private messages or texts from study staff (with survey reminders and weekly intervention content feedback) but are not required to respond. Participants will be shown how to add a password to their study iPhone, and how to disable the function that shows a preview of the content received in messages during study enrollment to protect privacy.

23.0 Provisions to Monitor the Data to Ensure the Safety of Participants

23.1 The study team (lead researchers Dr. Gicquelais and Dr. Westergaard and staff including Ms. Sarah Uhm, Ms. Katy Mijal, and Ms. Mikaela Becker) will be responsible for monitoring the data to ensure the safety of participants. We will review all survey data collected at baseline, 3 months and 6 months for any reports of serious events (i.e., death, life-threatening overdose, hospitalizations lasting 24 hours or more). Data will be monitored on a monthly basis. We will also review any reports of potentially serious events received by participants to the study team via the Thrive4Life Connect app private message function or discussion board on a rolling basis. Given the sample size of only 60 participants and

planned analyses focused on feasibility, we will not be able to statistically examine the safety data to determine whether harm is occurring. We will review adverse events starting with recruitment of the first study participant through 30 days after the last date that the final participant completed their final study procedure (i.e., all 6 months surveys).

The severity of each event will be classified using the following guidelines adapted from the UW-Madison ICTR Trial Template:

Mild (Grade 1)	Events require minimal or no treatment and do not interfere with the subject's daily activities.
Moderate (Grade 2)	Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe (Grade 3)	Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.
Life Threatening (Grade 4)	The subject was at risk of death at the time of the event.
Fatal (Grade 5)	The event caused death.

The relationship of each event to study procedures will be classified using the following guidelines adapted from the UW-Madison ICTR Trial Template:

Definitely Related	Clearly related to the study procedures/intervention and other possible contributing factors can be ruled out.
Probably Related	Likely related to the study procedures/intervention and the influence of other factors is unlikely.
Possibly Related	Possibly related to the study procedures/intervention and there are other factors that could be equally likely.
Unlikely to be related	Doubtfully related to the study procedures/intervention and there is another likely cause.

Unrelated	Clearly not related to the study procedures/intervention and/or evidence exists that the event is definitely related to another cause.

The event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the protocol, the IRB application, or the informed consent document.

In consultation with the lead researchers, a trained member of the study team will be responsible for conducting an evaluation of adverse events or unanticipated problems and shall report these issues and evaluation to the reviewing Institutional Review Board (IRB) in accordance with the Reportable Event Reporting Requirements.

24.0 Economic Burden to Participants

24.1 There are no costs associated with joining or participating in this study.

25.0 Resources Available

Will the research be conducted outside School of Medicine and Public Health or UW Hospitals and Clinics (e.g. the researcher does not have an SMPH research feasibility attestation for this study)?	☒ YES (complete 25.1) ☐ NO (remove text below, but retain this section)

25.1 All recruitment activities will be conducted at Vivent Health offices. Each Vivent Health office included in the study has a brick-and-mortar location in the community that provides prevention services such as HIV and hepatitis C testing and sterile injection supplies. Thus, these locations provide access to our eligible population. We expect to devote up to 1 year to recruit participants. UW-Madison will provide all necessary study supplies to conduct the research. All persons assisting with the research will be listed on our IRB and have completed the appropriate human subjects research trainings. Trainings for the study procedures will be completed prior to starting recruitment and enrollment.

26.0 Multi-Site Research

26.1 This study will involve multiple sites. Three Vivent Health locations will be included in this study: the Milwaukee, Eau Claire, and Appleton Vivent Health locations. To ensure consistency in study operations, all Vivent Health sites will use the same procedures to

enroll participants. At all enrollment appointments, participants will review the study procedures and informed consent document by either watching a video of the informed consent highlights then discussing with a Prevention Specialist OR by discussing the key areas of the informed consent with a Prevention Specialist. The content relayed regarding the study procedures and informed consent will be standardized across all sites, as all participating locations will use the same video or script and paper or electronic consent materials.

HIPAA-compliant Vivent Health Microsoft Teams will be used to store participant screener, locator, and survey completion data. The Vivent Health Microsoft Teams will be accessible to all site locations. Participant information for each site will be stored within the same survey reports for this study.

Prior to beginning enrollment, we will host training sessions for all site locations to provide each location with the most up to date information regarding the study protocol, consent, data management, and other study activities. All research staff who engage in the informed consent process will be up to date on required HIPAA and CITI trainings and listed as personnel on the IRB application.

Because the IRB reliance protocol will not fully be in place at the time of writing IRB review (a Federal Wide Assurance is being completed as soon as possible), Vivent Health personnel will not engage in any research activities until the Vivent Health sites have been formally approved via a change of protocol and a finalized reliance agreement has been executed.

26.2 The UW-Madison study team will consistently communicate with the participating Vivent Health locations to address any modifications to the study. Communication may occur via in-person or virtual meetings, email and phone communications, and Vivent Health Microsoft Teams for any changes related to PHI. The Research Supervisor at Vivent Health, who is a member of the research team and oversees research projects occurring at Vivent Health will also help to disseminate key study protocols, changes, problems, and information about closure of the study throughout the duration of the study.

27.0 References

1. Glober N, Mohler G, Huynh P, et al. Impact of COVID-19 Pandemic on Drug Overdoses in Indianapolis. J Urban Health Bull N Y Acad Med. 2020;97(6):802-807. doi:10.1007/s11524-020-00484-0

2. Khoury D, Preiss A, Geiger P, Anwar M, Conway KP. Increases in Naloxone Administrations by Emergency Medical Services Providers During the COVID-19 Pandemic: Retrospective Time Series Study. JMIR Public Health Surveill. 2021;7(5):e29298. doi:10.2196/29298
3. Ahmad F, Escobedo L, Rossen L, Spencer M, Warner M, Sutton P. Provisional Drug Overdose Death Counts. National Center for Health Statistics; 2021. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm
4. Wang QQ, Kaelber DC, Xu R, Volkow ND. COVID-19 risk and outcomes in patients with substance use disorders: analyses from electronic health records in the United States. Mol Psychiatry. 2021;26(1):30-39. doi:10.1038/s41380-020-00880-7
5. Mellis AM, Kelly BC, Potenza MN, Hulsey JN. Trust in a COVID-19 vaccine among people with substance use disorders. Drug Alcohol Depend. 2021;220:108519. doi:10.1016/j.drugalcdep.2021.108519
6. Westergaard RP, Hull SJ, Merkow A, Stephens LK, Hochstatter KR, Olson-Streed HK, Baker LM, Hess TM. Computerized Tailored Interventions to Enhance Prevention and Screening for Hepatitis C Virus Among People Who Inject Drugs: Protocol for a Randomized Pilot Study. JMIR Res Protoc. 2016 Jan 22;5(1):e15. PMCID: PMC4744331
7. Hochstatter KR, Hull SJ, Sethi AK, Burns ME, Mundt MP, Westergaard RP. Promoting Safe Injection Practices, Substance Use Reduction, Hepatitis C Testing, and Overdose Prevention Among Syringe Service Program Clients Using a Computer-Tailored Intervention: Pilot Randomized Controlled Trial. J Med Internet Res. 2020 Sep 29;22(9):e19703. PMCID: PMC7556373
8. Gustafson DH, McTavish FM, Chih M-Y, Atwood AK, Johnson RA, Boyle MG, Levy MS, Driscoll H, Chisholm SM, Dillenburg L, Isham A, Shah D. A smartphone application to support recovery from alcoholism: a randomized clinical trial. JAMA Psychiatry. 2014 May;71(5):566–572. PMCID: PMC4016167
9. Gustafson DH, Landucci G, McTavish F, Kornfield R, Johnson RA, Mares M-L, Westergaard RP, Quanbeck A, Alagoz E, Pe-Romashko K, Thomas C, Shah D. The effect of bundling medication-assisted treatment for opioid addiction with mHealth: study protocol for a randomized clinical trial. Trials. 2016 12;17(1):592. PMCID: PMC5153683
10. Hochstatter KR, Akhtar WZ, Dietz S, Pe-Romashko K, Gustafson DH, Shah DV, Krechel S, Liebert C, Miller R, El-Bassel N, Westergaard RP. Potential Influences of the COVID-19 Pandemic on Drug Use and HIV Care Among People Living with HIV and Substance Use Disorders: Experience from a Pilot mHealth Intervention. AIDS Behav. 2021 Feb;25(2):354– 359. PMCID: PMC7376523

11. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. Am Psychol. 2000 Jan;55(1):68–78. PMID: 11392867
12. McTavish FM, Chih M-Y, Shah D, Gustafson DH. How Patients Recovering From Alcoholism Use a Smartphone Intervention. J Dual Diagn. 2012;8(4):294–304. PMCID: PMC3541672
13. Rivet Amico K. A situated-Information Motivation Behavioral Skills Model of Care Initiation and Maintenance (sIMB-CIM): an IMB model based approach to understanding and intervening in engagement in care for chronic medical conditions. J Health Psychol. 2011 Oct;16(7):1071–1081. PMID: 21459919
14. Heckathorn DD. Respondent-Driven Sampling: A New Approach to the Study of Hidden Populations. Soc Probl. Oxford Academic; 1997 May 1;44(2):174–199.
15. Heckathorn DD. Respondent-Driven Sampling II: Deriving Valid Population Estimates from Chain-Referral Samples of Hidden Populations. Soc Probl. Oxford Academic; 2002 Feb 1;49(1):11–34.
16. Salganik MJ, Heckathorn DD. 5. Sampling and Estimation in Hidden Populations Using Respondent-Driven Sampling: Sociological Methodology [Internet]. SAGE PublicationsSage CA: Los Angeles, CA; 2016 Jun 24 [cited 2020 Jun 29]; Available from: https://journals-sagepub-com.proxy1.library.jhu.edu/doi/10.1111/j.0081-1750.2004.00152.x
17. Macalino GE, Celentano DD, Latkin C, Strathdee SA, Vlahov D. Risk behaviors by audio computer-assisted self-interviews among HIV-seropositive and HIV-seronegative injection drug users. AIDS Educ Prev. 2002 Oct;14(5):367–378. PMID: 12413183
18. Wolitski RJ. Relative Efficacy of a Multisession Sexual Risk–Reduction Intervention for Young Men Released From Prisons in 4 States. Am J Public Health. 2006 Oct;96(10):1854– 1861. PMCID: PMC1586131
19. CDC Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. Project START: An Individual-level Intervention for People Being Released from a Correctional Facility and Returning to the Community [Internet]. 2020 [cited 2021 May 25]. Available from: https://www.cdc.gov/hiv/research/interventionresearch/rep/packages/start.html
20. Centers for Disease Control and Prevention. Overdose Deaths Accelerating During COVID- 19 [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2021 Feb 23]. Available from: https://www.cdc.gov/media/releases/2020/p1218-overdose-deaths-covid- 19.html
21. UW Health. COVID-19 Pandemic Coincides With Rise of Opioid Overdoses [Internet]. UW Health News and Events. 2020. Available

from: https://www.uwhealth.org/news/covid-19- pandemic-coincides-with-rise-of-opioid-overdoses-w/53462

22. Holland KM, Jones C, Vivolo-Kantor AM, Idaikkadar N, Zwald M, Hoots B, Yard E, D'Inverno A, Swedo E, Chen MS, Petrosky E, Board A, Martinez P, Stone DM, Law R, Coletta MA, Adjemian J, Thomas C, Puddy RW, Peacock G, Dowling NF, Houry D. Trends in US Emergency Department Visits for Mental Health, Overdose, and Violence Outcomes Before and During the COVID-19 Pandemic. JAMA Psychiatry. 2021 Feb 3; PMCID: PMC7859873
23. Ahmad F, Escobedo L, Rossen L, Spencer M, Warner M, Sutton P. Provisional drug overdose death counts [Internet]. National Center for Health Statistics; 2021. Available from: https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm
24. Tyndall M. Safer opioid distribution in response to the COVID-19 pandemic. Int J Drug Policy. 2020 Sep;83:102880. PMCID: PMC7383133
25. Genberg BL, Astemborski J, Piggott DA, Woodson-Adu T, Kirk GD, Mehta SH. The health and social consequences during the initial period of the COVID-19 pandemic among current and former people who inject drugs: A rapid phone survey in Baltimore, Maryland. Drug Alcohol Depend. 2021 Feb 13;221:108584. PMCID: PMC7881742
26. Stack E, Leichtling G, Larsen JE, Gray M, Pope J, Leahy JM, Gelberg L, Seaman A, Korthuis PT. The Impacts of COVID-19 on Mental Health, Substance Use, and Overdose Concerns of People Who Use Drugs in Rural Communities. J Addict Med. 2020 Nov 3; PMID: 33156181
27. Wang QQ, Kaelber DC, Xu R, Volkow ND. COVID-19 risk and outcomes in patients with substance use disorders: analyses from electronic health records in the United States. Molecular Psychiatry. Nature Publishing Group; 2021 Jan;26(1):30–39.
28. Mellis AM, Kelly BC, Potenza MN, Hulsey JN. Trust in a COVID-19 vaccine among people with substance use disorders. Drug Alcohol Depend. 2021 Mar 1;220:108519. PMCID: PMC7797771
29. Koepke R, Sill DN, Akhtar WZ, Mitchell KP, Guilfoyle SM, Westergaard RP, Schauer SL, Vergeront JM. Hepatitis A and Hepatitis B Vaccination Coverage Among Persons Who Inject Drugs and Have Evidence of Hepatitis C Infection. Public Health Rep. 2019 Dec;134(6):651–659. PMCID: PMC6832086
30. Lasser KE, Kim TW, Alford DP, Cabral H, Saitz R, Samet JH. Is unhealthy substance use associated with failure to receive cancer screening and flu vaccination? A retrospective cross-sectional study. BMJ Open. 2011 Apr 7;1(1):e000046. PMCID: PMC3191402

28.0 Appendices

See additional materials included in iThrive WI ARROW IRB application.