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Title

Relapse prevention group therapy via video-conferencing for substance use disorder: protocol for a multicentre randomised controlled trial in Indonesia

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Abstract

Background: Substance use disorder (SUD) is a leading contributor to the global burden of disease. In Indonesia, treatment availability falls below the expected coverage for people with SUD needing care. An effective therapeutic option for SUD with potential for widespread implementation is urgently needed, yet evidence-based data in the country is scarce. Here, we developed a cognitive behavioural therapy (CBT)-based group telemedicine model and proposed to investigate the effectiveness and implementability for providers, in a multicentre randomised controlled trial (RCT).

Methods: Participants will be recruited from the communities across Indonesia. Recruitment will be done through the social networks of eight sites: three hospitals, two primary healthcare centres, and three rehabilitation centres. The intervention is a relapse prevention program called Indo-DARPP, a newly-developed 12-week module based on CBT and motivational interviewing constructed in the Indonesian context. The program is delivered in a group therapy via video-conferencing—intervention will be given in addition to treatment as usual. Control comparison is treatment as usual only. A total of 160 participants will be randomly divided by half into the intervention and control group. The primary outcome is the increase of percent days of abstinence from the primarily used substance in the past 30 days. Secondary outcomes include addiction severity, quality of life, motivation to change, psychiatric symptoms, cognitive function, and stress coping mechanisms. Assessments will be done at baseline (week 0), post-treatment (week 13), and follow-up (week 24). Retention, participant satisfaction, and cost-effectiveness will be assessed as implementation outcomes.

Ethics and dissemination: The study protocol was reviewed and approved by the Ethics Committees in Universitas Indonesia and Kyoto University. Provided positive outcomes, the

treatment program will be advocated to the Indonesian government for adoption as a healthcare-based approach to tackle substance use epidemic in the country.

Trial registration number: UMIN000042186

Keywords: *substance use disorder, telemedicine, online therapy, cognitive behavioural therapy, relapse prevention, motivational interviewing, low- and middle- income country*

Strengths and limitations of this study

- The proposed study will be the first to establish high-quality evidence for a cognitive behavioural therapy (CBT)-based relapse prevention program for substance use disorder (SUD) in Indonesia.
- Telemedicine enables far-reaching nationwide participation, connecting participants with providers in major cities, which in this study will include providers from three different levels of health care: tertiary hospitals, primary healthcare centres, and rehabilitation centres.
- A successful outcome may produce a new SUD treatment module in Indonesia and pave way for adoption into the national guideline.
- Study limitations include risk of recall and social desirability bias, heterogeneous control condition, and possible variability in treatment provision.

Introduction

Substance use disorder (SUD) is a condition characterised by the inability to control the use of psychoactive substances, i.e., alcohol and psychotropic drugs, which disrupts daily living. SUD remains a major and growing health problem worldwide. According to the Global Burden of Disease (GBD) survey in 2016, SUD globally contributes to 131 million disability-adjusted life years (DALY), or 5.5% of all DALYs,[1] and this number has been increasing since the 1990s.[2] While substance use itself is more widespread in high-income countries (HICs), low- and middle-income countries (LMICs) are disproportionately burdened. Absolute mortality rate due to SUD was greatest in LMICs with large populations,[3] and people with economic disadvantage are more likely to develop SUD.[4] Most importantly, substantial treatment gaps exist in limited-resource settings, where the number of people with SUD in need of health care far exceeds the availability of treatment services[5–7]—merely 1% of people with SUD in LMICs received treatment above the minimal standard.[8]

In Indonesia, the world's third most populous LMIC, the national SUD prevalence was estimated at 1.8% or 3.3 million people, with the most used substance being marijuana (68%), followed by amphetamine-type stimulants (ATS, 42%), opioids (38%) and sedatives (35%).[9,10] Its strategic intercontinental location contributes to the country's infamous reputation as a marijuana exporter and drug trafficking hub.[11] While there is an 80% decrease of injecting drug use (IDU) from 2002 to 2016,[10] an increasing use of psychoactive medications out of prescription has been noted, particularly benzodiazepines.[12] Similar to other Muslim majority countries,[13] alcohol consumption is comparatively low in Indonesia—prevalence estimate of alcohol use disorder was 0.8% in 2016, much lower than the overall rate in Southeast Asia (3.9%).[14] New psychoactive substances (NPS) has also entered the country in the last decade.[15] The current COVID-19

pandemic may also further complicate the SUD situation in Indonesia, as observed elsewhere.[16] In unpublished data from our co-author (KS), since the start of pandemic in early April 2020, there has been an increase in both drug and alcohol use in Indonesia of up to 2.5%. Higher drug use might be influenced by lockdown isolation, socio-economic issues due to unemployment, and heavier mental burden.

The treatment gap for mental health care is evident in Indonesia, where only 0.5% of people with SUD are connected with treatment and rehabilitative care.[17] Health providers and facilities are severely lacking; in a nation of 267 million people, only 773 psychiatrists (0.32 per 100,000 people) are employed—second lowest in Southeast Asia[18]—across hospitals with psychiatric care, half of which are located within the capital island of Java.[19] In terms of government-run primary healthcare centres (abbreviated as *Puskesmas* in Indonesian), out of all Puskesmas (~1,700 nationwide), only a fifth actively provide mental health care.[19,20] Current treatment options for SUD include one-on-one supportive psychotherapy, symptomatic pharmacotherapy, peer counselling, and opioid substitution. Methadone maintenance therapy (MMT) is available in Puskesmas since 2006, but coverage remains low: only 5% in a 2012 study[21] due to methadone cost, reliance on subsidisation, lack of program sustainability,[22] and the tendency to incarcerate patients under the 'war on drugs' policy.[21,23] Three-months retention rate of MMT was only 60-74%.[24,25] Psychiatric comorbidities were also common in MMT users and quality of life was evidently lower,[26] indicating the need for a more comprehensive mental health care approach.

Behavioural therapies in many forms are commonly applied for SUD, most popular of which is cognitive behavioural therapy (CBT). Strong evidence backs the efficacy of CBT for SUD treatment. A meta-analysis gave a moderate overall effect size (d = 0.45), with outcomes ranging from the self-report abstinence, drug-free urine at treatment exit, to increased retention in

therapy.[27,28] CBT strategies include: (a) contingency management (CM)[29] which introduces reward for abstinence, (b) motivational interviewing (MI) which explores and resolves ambivalence,[30] (c) relapse prevention (RP) which helps participants to identify high-risk triggers and prevent craving, or (d) combinations thereof.[31] Therapy could be delivered individually or in groups; the latter evidently increased adherence and self-disclosure, as well as decreased the time needed by providers to treat a participant by 40%.[32,33] CBT (particularly MI and RP) is relatively low-cost and can be delivered by non-specialists, making it beneficial in resource-limited settings.[34,35] In regard to LMICs, while an ample amount of RCTs have supported CBT efficacy to reduce alcohol use,[36,37] evidence for drug use disorders is limited. Only five RCTs have been published so far,[38–42] in which three of them were inpatient-based, even though SUD management mandates sustainable outpatient care in community settings.

Telemedicine has the potential to elevate SUD treatment coverage in Indonesia. Internet communication overcomes the geographical barriers of the Indonesian archipelago, and saves time as well as transportation cost for both patients and providers, either in remote areas where health services are thinly spread,[43] or major cities with heavy traffic such as Jakarta.[44] Privacy is better ensured; visiting clinics may disclose SUD diagnosis, which is one of the most stigmatised health conditions.[45] Synchronous telemedicine via live video feed connects participants in real-time, improving rapport and potentially adherence, relative to asynchronous telemedicine (e.g., text message or web application). Video-conferencing has been effectively used in SUD treatment,[46–51] but recent systematic reviews[52–57] have revealed three lacking points: (1) previous reports merely focused on alcohol and opioid use,[46,49–51] (2) group therapy was investigated by only one small-scale pilot RCT,[50] and (3) no studies were done in LMICs. The use of internet devices has been rapidly expanding in LMICs, including Indonesia. Smartphone users accounted for 74% of the

Indonesian population in 2019, possibly reaching 89% by 2025.[67] Furthermore, the COVID-19 pandemic has elevated telemedicine from an accessory to a necessity, including for psychiatric care.[68] Its accessibility and acceptance among SUD patients, as shown in a recent survey,[70] may potentially sustain telemedicine as the 'new normal' even in the post-pandemic world.[69,71]

Given the above challenges and opportunities, we propose a clinical trial to evaluate a relapse prevention telemedicine program for SUD in Indonesia. We have developed a new treatment module called *Indonesia Drug Addiction Relapse Prevention Program* (Indo-DARPP), which is a 12-week CBT-based group therapy. The primary objective is to evaluate the effectiveness of Indo-DARPP delivered via video conference (tele-Indo-DARPP), added to treatment as usual (TAU), to increase abstinence from primarily-used substances, compared to TAU only. Secondary objectives are to assess the effectiveness of the program toward changes in quality of life, motivation to change, psychological symptoms, cognitive function, and coping mechanisms. Retention, participant satisfaction, and group cohesion will be assessed as implementation outcomes, and cost-effectiveness analyses will be conducted to inform health policy investment.

METHODS

Trial design

This trial is a parallel-group, two-arm, assessor-blinded, multicentre superiority randomised controlled trial. The protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (**Supplementary file 1)**. We design the study as a pragmatic type 1 hybrid effectiveness-implementation trial,[72] which allows

concurrent investigation of intervention effectiveness as well as implementation in clinical practice, focusing on the former. After intake screening, participants will undergo baseline assessment (T1) and randomly allocated in a 1:1 ratio either to the intervention arm receiving tele-Indo-DARPP in addition to TAU, or control arm receiving TAU only. Treatment will be done for 12 weeks, followed by post-treatment assessment (T2) in week 13, and follow-up assessment (T3) in week 24 (**Figure 1**).

[**Figure 1** approximately here.]

Participants and settings

Participants will be recruited from the community across Indonesia via social networks of eight sites: two primary health centres (Puskesmas), three referral hospitals, and three drug rehabilitation services (**Table 1**). These facility types constitute the community-based treatment model for SUD in Indonesia,[73] encompassing patients with various characteristics in motivation for behavioural change, substance use history, comorbidities, and current stage in treatment. Recruitment will be done via online advertisement (i.e., social networking services, group chat, website) and direct approach to current and former clients through outpatient services, in a consecutive sampling.

Puskesmas provides general primary care, pharmacotherapy for cases without any complications, and MMT. Referral hospitals provide psychotherapy, pharmacotherapy, opioid substitution therapy using buprenorphine/naloxone, and specialised care for cases with complications, such as severe psychiatric disorder. Rehabilitation services provide long-term

psychosocial care, typically in a mutual-aid group form. Selection of sites was based on feasibility, client demographic, recruitment potential, and availability of providers. While recruited participants may not be under treatment in the aforementioned sites at the time, facilitators for tele-Indo-DARPP will be the staffs of respective sites: general practitioners in Puskesmas, psychiatrists in referral hospitals, and counsellors in rehabilitation centres.

[**Table 1** approximately here.]

Inclusion criteria will be those who: 1) aged 18-65 years old; 2) are diagnosed as having substance use disorder based on DSM-5; 3) have used primarily-used substance for at least one day in the past one year; 4) have access to electronic devices (i.e., smartphone, mobile tablet, personal computer) with internet connection; and 5) are proficient in Indonesian. Exclusion criteria will be those who: 1) have severe comorbidity that hinder informed consent or group therapy participation; and 2) currently hospitalised or are using residential care.

Recruitment

Patients eligibility will be assessed by collaborating staff at respective sites. For those who have never been diagnosed as having SUD, addiction psychiatrists will conduct clinical assessments via video call. Oral and written informed consent will be given to those eligible. For urine tests, explanations will be given immediately after post-treatment (T2) assessment, as anticipation for urine tests may influence substance use behaviour. Consent to urine test or absence thereof will not affect study participation.

Randomisation and blinding

Participants will be randomly allocated to either an intervention (tele-Indo-DARPP + TAU) or a control (TAU only) arm, with stratification by study site. Each site will conduct two waves of recruitment with 10 participants in each wave. After the first wave at each site, we will randomly allocate 5 participants to either intervention or control group. Recruitment will be continued until another 10 participants (second wave) joined, and random allocation will be done similarly. Allocation will be done using computer-generated random numbers by a researcher who will be blinded to participants' information, except for ID. Data will be collected by researchers who are blinded to the allocation arm of each participant.

Development of Indo-DARPP

Indo-DARPP was based on the Serigaya Methamphetamine Relapse Prevention Program (SMARPP), a face-to-face group CBT-based intervention in Japan developed by a co-author (TM),[74] which itself is based on the Matrix Model developed in the US.[75] Efficacy of SMARPP in increasing abstinence duration, motivation to change, and participation in self-help groups have been reported.[76–78] SMARPP has been widely implemented as a psychotherapy for SUD not only in psychiatric clinics but also primary healthcare, rehabilitation, and probation offices in Japan, covered by the national insurance scheme. SMARPP has excellent scalability via the use of a workbook, and can be delivered by non-specialists who have received a brief training.

Contents of Indo-DARPP are based on the RP model, where participants are guided to learn high-risk situations for substance use and coping strategies. The program also incorporates

elements of MI and psychoeducation on substances, SUD, and its common comorbidities. While CM could also be added, it increases cost and may not be effective in the longer term,[79] and thus, MI and RP approaches will be utilised in this study. Adaptations from SMARPP were done via focus group discussions involving Japanese researchers, Indonesia-based psychiatrists, general practitioners, and peer counsellors, all of whom have extensive experience ranging 4-20 years in the addiction field. Substances discussed in the module are amphetamine-type stimulants, benzodiazepines and other prescribed medicines, opioids, marijuana, NPS, and alcohol. Indo-DARPP is designed to be delivered in a small group format using workbook, and sessions will be provided by one facilitator and one co-facilitator who is a peer counsellor with lived experiences of SUD.

A pilot test was held at Site 1, recruiting nine SUD patients into a 12-week tele-Indo-DARPP, to check the content acceptability and feasibility of the online delivery format. Further adjustments were made based on the pilot results and patient feedback.

Intervention via video conference: tele-Indo-DARPP

Tele-Indo-DARPP will be implemented in group therapy with a maximum of five patients, in a weekly 2-hour session for 12 weeks, delivered using the online video-conferencing application Zoom. URLs for video conferences will be informed weekly by the research team to the private Whatsapp group chat consisting of five Indo-DARPP participants plus two providers, which will be created after randomisation. Each Indo-DARPP session consists of three parts: (1) "check-in", where participants share history of substance use and craving in the past week, and analyse high-risk situations and coping actions taken; (2) "today's topic", where providers guide discussion of specific workbook chapters and participants fill in exercises, and (3) "check-out", where providers

give summary and invite feedback, and participants anticipate triggers and coping strategies for the following week.

Providers of tele-Indo-DARPP

At least two persons from each site will serve as facilitators, who meet the following criteria: psychiatrist with at least 1-year experience in treating SUD patients, or healthcare provider with at least 2-year experience in providing care for SUD patients, or peer counsellor with at least 2-year involvement in any organisation providing services for people with SUD. The roles of facilitators are to (1) lead and moderate Indo-DARPP sessions, (2) elaborate on chapter contents, (3) manage participants to follow rules, (4) establish safe and warm environment, (5) provide consultation including out-of-session, and (6) contact absent participants to encourage attendance.

Similarly, at least two persons from each site will serve as co-facilitators for the tele-Indo-DARPP, described as peer counsellors who have also experienced SUD and recovered, with at least 6-month involvement in any organisations providing services for people with SUD. The role of co-facilitator is to (1) share personal experiences relevant to discussion topics, (2) assist facilitators in ensuring a safe and warm environment, (3) provide general support to the Indo-DARPP process, and (4) provide counsel, including out-of-session.

Training and supervision

Prior to recruitment, all providers received a full-day training of trainers (TOT) online session on basic knowledge of SUD treatment, Indo-DARPP contents, video demonstration, hands-on role play, discussion on difficult cases, tele-Indo-DARPP, and study-related quality

control. Workbooks and manuals were handed to all providers, and close communication with the research team will be kept via WhatsApp group chat throughout the research period. To maintain treatment fidelity and quality control, during actual tele-Indo-DARPP sessions, addiction psychiatrists from the research team (KS and EH) will randomly select and observe at least one session at each site and review the providers using a structured checklist.

Control condition

Participants who received treatment before the study will continue to receive treatment as usual, regardless of group allocation. TAU was chosen as the control condition because the Indo-DARPP is expected to complement the existing treatment services for SUD in every level of care. TAU differs according to the service location (**Table 1**). Individual psychotherapy is typically conducted via in-person short consultation (~15 minutes) with clinical psychiatrists. Pharmacotherapy is given to alleviate symptoms, e.g., anxiolytics for anxiety. Patients undergoing MMT visit the site almost every day to receive their daily doses, while patients undergoing substitution therapy with buprenorphine with naloxone visit every week. All participants will be able to continue any outpatient pharmacological treatment (e.g., MMT, antidepressants) and psychotherapy (e.g., twelve-step group sessions).

Primary outcome

Abstinence from primarily used substance

The primary outcome is the percent days of abstinence from the primarily used substance during the past 30 days. Percent days of abstinence has been shown to be sensitive to the effects of CBT

and are good predictors of SUD treatment follow-up.[80] Use of primarily used substance each day (yes/no) for 30 days will be retrospectively interviewed using the timeline followback (TLFB) method (**Table 2**), which has good validity and high test-retest reliability in measuring substance consumption.[81,82] The participants will be asked to recount every week, to reduce the risk of recall bias. The primarily used substance is defined as the substance causing the most problems for participants and drives them to seek care, at T1. For validation purposes, urine samples will be collected at T2 to test the presence of the primarily used substance. Thresholds for a positive result are >100 ng/ml for ethyl glucuronide (for alcohol use), >300 ng/ml for amphetamine-type stimulant (i.e., d-methamphetamine and MDMA), >100 ng/ml for diacetyl morphine (heroine), cocaine, and benzodiazepine, >50 ng/ml for synthetic cannabis (K2), and > 25 ng/ml for tetrahydrocannabinol (marijuana).

[**Table 2** approximately here.]

Secondary outcomes

Addiction severity

The Addiction Severity Index (ASI) is the most widely used measure in the field of addiction.[83] Internal consistency, test-retest reliability, and scale independence of ASI to measure substance use have long been established.[84,85] The Treatnet ASI version 3.0 by the United Nations Office on Drugs and Crime (UNODC) will be used; the scale is available in Indonesian, and one addiction treatment centre in Indonesia was included in its development trial.[86]

Health-related quality of life

The five-level version of the five-dimensional EuroQoL (EQ-5D)[87,88] will be used to assess health-related quality of life (HRQoL), which has been done before among SUD patients with confirmed construct validity.[90,91] The total utility score will be obtained using the already established value set in Indonesia.[89]

Motivation to change

Motivation to change will be assessed by the Action subscale the University of Rhode Island Change Assessment (URICA).[92] URICA has been shown to have good validity, where higher scores indicate that the person has committed to develop positive behavioural changes (Diclemente and County, 2000; Diclemente et al., 2004).[93]

Coping strategies

Types of engaged stress coping will be assessed by the Brief Coping Orientations to Problems Experienced (Brief COPE),[94] which is commonly used for SUD patients.[95] A higher score indicates that the person has adopted the coping type more frequently.

Psychiatric symptoms

Psychiatric symptoms will be evaluated by the Symptom Checklist 90-R (SCL-90-R).[96] The Global Severity Index (GSI) will be used, which is feasible to measure psychiatric symptoms among SUD patients.[97]

Cognitive function

Cognitive function will be assessed by the Rey Auditory Verbal Learning Test (RAVLT),[98] which is useful to diagnose cognitive impairment as well as post-treatment improvement in SUD patients.[99,100]

Implementation outcomes

Retention in treatment

Participants will be coded as 'retained in treatment' if they had therapeutic contacts—including attending tele-Indo-DARPP and visiting any outpatient clinic for TAU—in at least 75% of the planned contacts during the past 3 months.

Treatment satisfaction

Client Satisfaction Questionnaire-3 (CSQ-3)[101] is commonly used for treatment programs, including for SUD.[102]

Group cohesion

Group Therapy Experience Scale (GTES) will be used to measure the level of group cohesion and self-disclosure in group therapy, as implementation outcomes of tele-Indo-DARPP.[103]

Indo-DARPP attendance

Attendance to each session will be recorded by the facilitator.

Cost effectiveness

Cost-effectiveness will be assessed from a patient, provider, and societal perspective. Cost data will be calculated by multiplying the quantity of utilised resources by unit price. Data on quantity and unit price will be obtained from within the trial, or estimated from relevant data sources. For effectiveness data, both clinical and economic indexes will be used. The clinical index is abstinence from primarily used substance in the past 30 days, which will be converted into abstinent year. The economic index is quality-adjusted life year (QALY) calculated from the utility score of EQ-5D.

Feedback interviews

Semi-structured interviews will be done with both participants and providers to assess the following: satisfaction with content quality, comprehensibility, technical experience regarding video-conferencing, comfortableness, module practicability, and participants' perception on the credibility of providers. Interviews will be audio-recorded under the interviewees' consent.

Participant characteristics

The following data will be obtained via a self-administered questionnaire: age, gender, approximate residential location, marital status, household co-habitants, ethnicity, religion, highest education level, employment status, individual and household income, type of internet device used, frequency of video calls in the past year, age of first drug use, primarily used substance, inpatient history or incarceration in the past month, type of treatments received, treatment locations in the past three months, status of current outpatient care (voluntary or involuntary, legal or non-legal), and transportation time and cost from own residence to the outpatient location.

Data collection procedure

Researchers blinded to the treatment allocation will collect data at three different time points: at baseline (week 0, T1), the week after the completion of treatment (week 13, T2), and three months after the completion of treatment (week 24, T3) using self-answered questionnaire and one-on-one interview. As for the primary outcome, the participants will be asked to recall weekly using the TLFB, and thus, an assessment period of approximately 4 weeks will be added after each assessment time point. Urine specimens will be collected only at T2, at the final 2 weeks within the TLFB assessment period. Assessment schedule is shown in **Table 2** and **Figure 2**.

[**Figure 2** approximately here.]

Sample size

Sample size was calculated for the primary outcome to detect a medium effect size of d = 0.59, which is based on a previous study examining the efficacy of telemedicine for people with SUD in an LIMC.[65] Using α = 0.05 and power = 0.80, a simple t-test requires n = 46 per arm. We estimated the design effect of clustering within Indo-DARPP group, using the formula, $D = 1 + (m - 1)\,\rho$, [104] assuming intraclass correlation within Indo-DARPP groups or $\rho = 0.05$, and group size or $m = 5$, which yielded the design effect or $D = 1.2$. Multiplying the result of simple calculation by the design effect, the minimal number of participants in data analysis was 56 per arm. Assuming attrition proportion = 26%,[105] the sample size for enrolment was set as 76 per arm, or 152 in total. We will recruit 10 participants for each wave at a site, thus the number was rounded up to 160 participants.

Statistical analysis

A detailed statistical analysis plan will be developed by a statistician who is blinded to patients' allocation, prior to data analysis. Baseline data description and main analyses will be conducted on an intention-to-treat basis, i.e., participants' data will be handled according to their initially assigned arms, regardless of actual received treatment. Analyses will be conducted with a significance level of 5% in the two-sided test, using Stata/SE 16.1.

Consideration for correlated outcome data

Correlation within sites for a control arm will be ignored, as the TAU within one site varies per patient and some participants may not receive any treatment. For an intervention arm, correlation within each Indo-DARPP group due to the nature of group therapy should be accounted for. We will define a new variable termed 'clustering group identification (CID)', where the control arm will be coded as a unique CID for each person, while the intervention arm will be coded based on the tele-Indo-DARPP group they were in, i.e., the same CID for five participants.

Main analysis

Primary endpoint will be set at T2. The mean of the outcome changes from T1 to T2 will be compared between the intervention and control arms using a linear model. To investigate the durability of the treatment effect, outcome changes from T1 to T3 will also be compared between both arms. We will account for the aforementioned correlations by clustering data, based on CID in the generalised estimation equations (GEE). To help interpret effect size, Cohen's *d* between arms will be calculated.

Missing values

A complete case analysis will be done, which will only include participants with no missing values in the variables of interest. Sensitivity analysis for missing values will be conducted by either inverse probability weighted GEE[106] or multiple imputation.

Subgroup analysis

The effect of intervention will be investigated by subgroups, as the observed effect may vary depending on specific population. The participants will be divided by the types of primarily used substance, gender, previous and current utilisation of other SUD treatment, high and low

values in clinical characteristics at T1, e.g., percent days of abstinence, ASI drug use composite score, URICA readiness score, and cognitive function.

Implementation evaluation

Chi-squared tests and *t*-tests will be done to compare retention in treatment and treatment satisfaction between the arms, exclusively for participants who were already receiving SUD treatment at T1. Group cohesion and Indo-DARPP attendance will be descriptively reported by mean and standard deviation. For cost-effectiveness analysis, the incremental cost-effectiveness ratios (ICERs) will be calculated, which will yield costs per QALY and abstinent year. Feedback interviews will be transcribed and thematic analysis will be conducted.

Compensations

Participants in both the control and intervention groups will receive 300,000 IDR (≈ 21.3 USD) to compensate for their transportation to treatment sites for TAU throughout the 12 weeks, and also 98,000 IDR (≈ 7.0 USD) for every time they complete an online video assessment as compensation for internet data and 2-hour data collection. Specific to the intervention group, participants will receive internet mobile data equivalent to 50,000 IDR (≈ 3.5 USD) before the first session of tele-Indo-DARPP, and receive the same amount of mobile data every time they attended four sessions of tele-Indo-DARPP. As all monetary amounts were set at the approximate cost, the amounts are intended purely for compensation and not as reward, as in contingency management. For providers, compensation amounted to 170,000 IDR (≈ 12.1 USD) and 150,000 IDR (≈ 10.7 USD) will be given for each tele-Indo-DARPP session to facilitator and co-facilitator, respectively.

Data monitoring

Data on adverse events including hospitalisation, arrest, and death will be collected from the participants' treating psychiatrist or medical staff. In addition, participants will be interviewed at T2 on whether they experience any subjective harmful effect (e.g., withdrawal syndrome, increased cravings) after joining Indo-DARPP. An independent data monitoring committee will not be convened, as the study involves short-term non-invasive psychotherapeutic intervention. No interim analysis is planned due to the short duration of intervention. Completeness and accuracy of data collection will be checked by Japanese co-investigators, and there will be no auditing process by independent investigators.

Data publication

Deidentified results of the study will be published in scientific publication, and reported to relevant government body in Indonesia to advocate adoption of the treatment module.

Ethical consideration

This study protocol (version 2.0, May 2020) was approved by the Research Ethical Committee of Faculty of Medicine, Universitas Indonesia (approval number: KET-1175/2019), the Ethics Committee of Graduate School and Faculty of Medicine, Kyoto University (approval number: C1483). The study protocol was registered at the University Hospital Medical Information Network clinical trial registry (UMIN-CTR) (registry number: UMIN000042186).

Consent process will be conducted carefully to ensure that all potential participants fully understand research objectives, procedures, risks, benefits, costs, and alternatives. It will be emphasised that study participation is voluntary and consent can be withdrawn at any time before research publication. We will allocate participants to treatment arms only when written informed

consents for participation are obtained. Likewise, urine specimens will only be collected if written informed consents for urine collection are obtained. Participants will not receive any adverse influence in deciding study participation and/or urine collection. Personal data will be protected by separating study data from participants' identifiable information. To quickly respond to adverse events arising when outpatient visits are not possible, a dedicated phone number and a WhatsApp account for the study will be opened to ease communication to the research team. Participants will be instructed to text or call when experiencing any adverse events. Importantly, written agreement will be obtained from participants to never share others' information to any third party. This regulation will be enforced in both during and outside tele-Indo-DARPP sessions, in any medium, including video conference and group chat.

Discussion

Up until the time of writing, nine RCTs from LMICs have reported the effectiveness of digital delivery of interventions for SUD. Utilised formats were telephone calls,[58–61] webpages,[62–64] and mobile applications,[65,66] however, and no study in LMICs has so far investigated the effectiveness of video-conference-based psychotherapy. The latter may facilitate honest, interactive discussions on personal substance use and cravings, founded on better rapport between providers and patients,[107] all of which is integral for CBT for SUD. One meta-analysis concluded that web-based mental health interventions had better retention rate and treatment outcomes when therapists were synchronously involved.[108]

The proposed study has several strengths. This is the first RCT to investigate the effectiveness of video-conference based psychotherapy in any LMIC, as well as the first study to establish quality evidence on psychotherapy for SUD in Indonesia. Recruitment will be done

throughout multiple levels of care, i.e., tertiary (referral hospitals), primary (Puskesmas) and community (rehabilitation centres). The latter have extensive reach encompassing all major Indonesian islands, and advertising will be done via online social media, facilitating recruitment from across the nation. While CBT effectiveness is the primary outcome, the study allows elucidation of real-world implementation and cost-effectiveness in a hybrid effectiveness-implementation design.[72] This is particularly true in Puskesmas, where the providers will be general practitioners, and in rehabilitation centres, where the providers will be peer counsellors. This pragmatic RCT aims to mimic the usual clinical practice, and we hope that the result may be used to inform decision-making by patients, providers, and policymakers.[109]

Several limitations can also be presumed. While urine drug tests will be done for objective validation, all data from participants will be self-reported and prone to recall and social desirability bias. As the study will include people who use various substances, in multiple sites where TAU differs, and possibly people who are not receiving any treatment, the control condition will be heterogeneous. Variability in the providers' background may create inconsistency in CBT delivery, even though TOT and treatment manuals were introduced as an effort to standardise care. Treatment delivery via online video-conferencing might have poor generalizability toward people with low internet literacy, as well as people in low socio-economic strata who could not afford smartphones—although entry-level Android-based smartphones (less than ~80 USD) are available nationwide in Indonesia.

Efforts to establish evidence-based treatment for SUD should be scaled up in Indonesia and LMICs in general, where effectiveness data is sparse. The proposed study may present high-quality evidence, and a successful outcome may birth a new SUD treatment module in Indonesia, paving way for the adoption of Indo-DARPP into the national guideline. We hope that our efforts

may further promote a comprehensive, healthcare-centric approach—as opposed to repressive anti-drug policies—to tackle the substance use epidemic in the country.

Figure legends

Figure 1. Study flowchart for each site. A total of 20 participants will be recruited through the social network of each site. After 10 participants have been recruited in the first wave, randomisation will be done to allocate participants into two groups: intervention (Indo-DARPP + TAU) and control (TAU only), with 5 participants in each group. Recruitment will be continued until another 10 participants (second wave) joined before randomisation and allocation, similar as before. Treatment period will be 12 weeks. Assessments will be done 3 times: T1 (Week 0) during baseline or before randomisation, T2 (Week 13-16) during post-assessment or 1-4 weeks after treatment period ends, and T3 (Week 24) during 3 months after treatment ends.

Figure 2. Planned trial schedule across all 8 research sites. Staggered schedules were designed to spread the workload of providers in regard to Indo-DARPP intervention, as well as research staff in regard to assessments. After training of providers, all sites were given approximately 1-2 months to recruit at least 20 participants. Sites with relatively higher potential to recruit faster, i.e., those with higher rate of patient turnover, were selected ahead in the schedule. Each site will have 2 waves of recruitment and treatment period.

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Author contributions

CY, KS, and YO conceptualised the study. CY, KS, EH, and YO are the main developers of the Indo-DARPP module, designed study methodology, invited and coordinated site investigators, conducted training of providers, wrote the protocol, reviewed and edited the final manuscript. EB, VR, PA, and AP helped in module development, study design, training of providers, and sites coordination. TS provided biostatistical and epidemiological supervision. TM provided the original SMARPP module and clinical input and perspectives to improve study quality. RS supervised the study and procured grant. CY and RS are the principal investigators of the grants. All authors have read and approved the final manuscript.

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Competing interests

The authors declare no competing interest.

Patient and public involvement

Patients' feedback during the pilot study was incorporated into the Indo-DARPP module design. Apart from that, patients and/or the public were not involved in the conduct, reporting, or dissemination plans of this study.

Patient consent for publication

Not required.

Ethics approval and trial registration

This study protocol was approved by the Research Ethical Committee of Faculty of Medicine, Universitas Indonesia (approval number: KET-1175/2019), and the Ethics Committee of Graduate School and Faculty of Medicine, Kyoto University (approval number: C1483). The study protocol was registered at the University Hospital Medical Information Network clinical trial registry (UMIN-CTR) (registry number: UMIN000042186).

Availability of data and materials

The full protocol and datasets of the planned study will be available from the corresponding author on reasonable request.

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Table 1. Recruitment sites in this study

Name	Location	Type	Treatment as usual	Most reported primarily used substance
Cipto Mangunkusumo Hospital	Jakarta	Tertiary national general hospital	Individual psychotherapy, symptomatic pharmacotherapy	Benzodiazepine
Aceh Mental Hospital	Aceh	Tertiary provincial mental hospital	Individual psychotherapy, symptomatic pharmacotherapy	Methamphetamine
Duren Sawit Regional Hospital	Jakarta	Tertiary regional general hospital	Individual psychotherapy, symptomatic pharmacotherapy, opioid substitution therapy (buprenorphine, naloxone)	Opioid
Karisma Foundation	Jakarta	Rehabilitation center	Individual and group peer counselling	Methamphetamine, opioid
Kapeta Foundation	Banten	Rehabilitation center	Individual and group peer counselling	Methamphetamine, benzodiazepine, synthetic cannabinoids
Kios Atma Jaya	Jakarta	Rehabilitation center and regional HIV clinic	Individual psychotherapy, group peer counselling, outreach program	Opioid
Puskesmas Jatinegara	Jakarta	Primary health care	Counselling, symptomatic pharmacotherapy, methadone maintenance therapy	Heroin
Puskesmas Gambir	Jakarta	Primary health care	Counselling, symptomatic pharmacotherapy, methadone maintenance therapy	Heroin

Counselling focuses on education and giving advice.
Symptomatic pharmacotherapy gives medication for helping patients with specific psychopathologies.
Psychotherapy aims to help a person identify and change troubling emotions, thoughts, and behaviour.

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Table 2. Outcome and measurement

Outcome	Measurement	Data for analysis	Type and score range	Hypothesis for intervention (vs control)	Assessment time point		
					T1	T2	T3
Primary outcome							
Abstinence from primary substance	Timeline followback (TLFB) for the past 30 days	Number of days being abstinent from primary substance divided by 30 (%).	Continuous, 0 (no use) to 100 (used every day).	Higher	✓ □	✓□ [a]	✓ □
Secondary outcomes							
Addiction severity	Addiction Severity Index (ASI)	7 composite scores: medical, employment, alcohol use, drug use, legal, family/social, and psychiatric status. Each composite score calculated using standard formula.	Continuous, 0 (no problems) to 1 (severe problems).	Lower	✓ □	✓□	✓ □
Health-related quality of life	EuroQol-5D (EQ-5D-5L)	Health utility score, calculated from 5 items on mobility, self-care, usual activities, pain/discomfort and anxiety/depression, using Indonesian value set.	Continuous, -0.865 (impaired health) to 1 (full health).	Higher	✓ □	✓□	✓ □
Motivation to change	University of Rhode Island Change Assessment (URICA)	Action stage subscale, sum of 8 items.	Continuous, 8 (not active in behavioural change) to 40 (highly active in behavioural change).	Higher	✓ □	✓□	✓ □
Coping strategies	Brief-Coping Orientation to Problems Experienced (Brief COPE)	3 subscales: problem-focused, emotion-focused, and dysfunctional coping. Sum of 6, 10, 12 items, respectively.	Continuous, problem-focused 6 to 24, emotion-focused 10 to 40, dysfunctional 12 to 48.	Lower in dysfunctional, higher in the others	✓ □	✓□	✓ □
Psychiatric symptoms	Symptom Checklist-90 Revised (SCL-90-R)	Global Severity Index (GSI), average of 90 items.	Continuous, 0 (no symptoms) to 4 (severe symptoms).	Lower	✓ □	✓□	✓ □
Cognitive function	Rey Auditory Verbal Learning Test (RAVLT)	3 test results; immediate, learning, and recalling.	Continuous, 0 (low functioning) to 15 (high functioning).	Higher	✓ □	✓□	✓ □
Implementation outcomes							
Retention in treatment	Self-reporting for the past 3 months	Coded as 'retained' if they had therapeutic contacts in at least 75% of the planned number of therapeutic contacts.	Categorical, 'retained' = 1, 'not retained' = 0.	More 'retained'		✓□	✓ □
Treatment satisfaction	Client Satisfaction Questionnaire-3 (CSQ-3)	Sum of 3 items.	Continuous, 4 (not satisfied) to 12 (satisfied).	Higher		✓□	
Group cohesion	Group Therapy Experience Scale (GTES)	Sum of 16 items.	Continuous, 16 (poor cohesion) to 80 (great cohesion).	Not applicable: measured only in intervention arm		✓□	

[a] Objective validation by urine drug test for 8 substances: alcohol, amphetamine, morphine, cannabinoids, methamphetamine, benzodiazepine, cocaine, synthetic cannabinoids

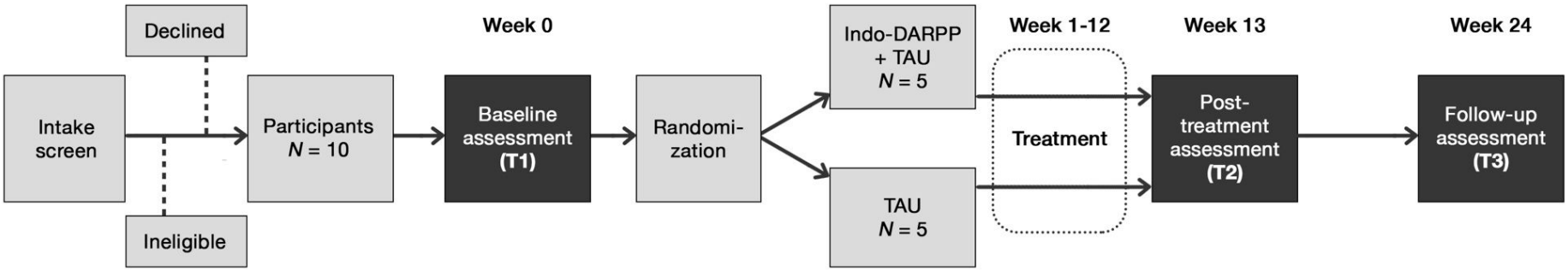

Figure 1. Study flowchart for each site. A total of 20 participants will be recruited through the social network of each site. After 10 participants have been recruited to constitute one wave, randomisation will be done to allocate participants into two groups: intervention (Indo-DARPP + TAU) and control (TAU only), with 5 participants in each group. Recruitment will be continued until another 10 participants (second wave) joined before randomisation and allocation similar as before. Treatment period will be 12 weeks. Assessments will be done 3 times: T1 (Week 0) during baseline or before randomisation, T2 (Week 13-16) during post-assessment or 1-4 weeks after treatment period ends, and T3 (Week 24) during 3 months after treatment ends.

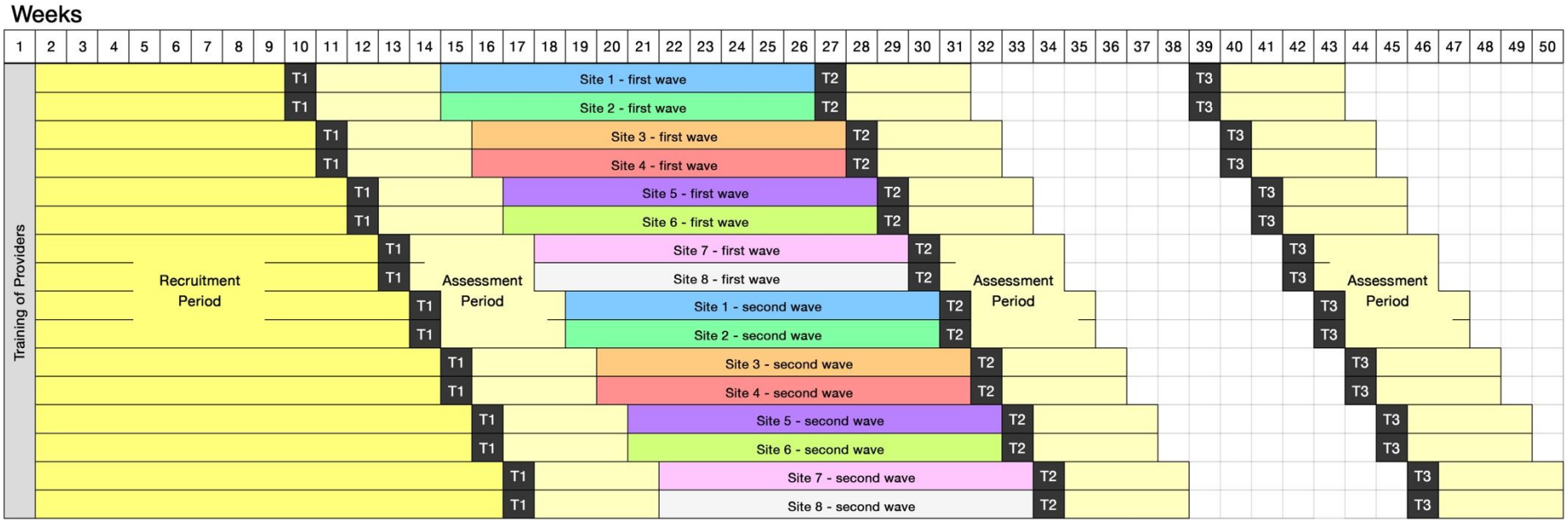

Figure 2. Planned trial schedule across all 8 research sites. Staggered schedules were designed to spread the workload of providers in regard to Indo-DARPP intervention, as well as research staff in regard to assessments. After training of providers, all sites were given approximately 1-2 months to recruit at least 20 participants. Sites with relatively higher potential to recruit faster, i.e., those with higher rate of patient turnover, were selected ahead in the schedule. Each site will have 2 waves of recruitment and treatment period.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4, 23
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a, trial already registered as described in 2a.
Protocol version	#3	Date and version identifier	23
Funding	#4	Sources and types of financial, material, and other support	26-27
Roles and	#5a	Names, affiliations, and roles of protocol	26

responsibilities: contributorship		contributors	
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a, no trial sponsor.
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a, no involvement of funders in the study design.
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a, no direct intervention in the study design by the host universities.
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-9
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	15
Objectives	#7	Specific objectives or hypotheses	9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9-10

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10-11
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	22-23
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	22-23
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	15
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome.	15-19

		Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10, 19, 26
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	20
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Allocation:	#16c	Who will generate the allocation sequence,	12

implementation		who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12, 19
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a, only assessors are blinded
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-19
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	19, 22-23
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the	23

		protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	20-22
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21-22
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	23, DMC will not be convened as the intervention involves a short-term psychotherapy with known minimal risk.
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	23, interim analysis is not planned due to the short duration of intervention.
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	22-23
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	23, there will be no auditing process by independent investigators.

Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	23, 28
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	23
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	23
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	23
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	23
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	27
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	28
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15, CBT intervention will be made available for control group after the end of the study.

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	23
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	26-27
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	28

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	11, 23
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	16

Notes:

- 2b: n/a, trial already registered as described in 2a.
- 5b: n/a, no trial sponsor.
- 5c: n/a, no involvement of funders in the study design.
- 5d: n/a, no direct intervention in the study design by the host universities.
- 17b: n/a, only assessors are blinded
- 21a: 23, DMC will not be convened as the intervention involves a short-term psychotherapy with known minimal risk.
- 21b: 23, interim analysis is not planned due to the short duration of intervention.

- 23: 23, there will be no auditing process by independent investigators.
- 30: 15, CBT intervention will be made available for control group after the end of the study. The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 15. February 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Relapse prevention group therapy via video-conferencing for substance use disorder: protocol for a multicentre randomised controlled trial in Indonesia

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Title

Relapse prevention group therapy via video-conferencing for substance use disorder: protocol for a multicentre randomised controlled trial in Indonesia

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Abstract: 261 words

Main text: 5,598 words

Abstract

Background: Substance use disorder (SUD) is a leading contributor to the global burden of disease. In Indonesia, formal treatment availability falls below the targeted coverage for people with SUD needing care. A standardised and scalable therapeutic option for SUD with potential for widespread implementation is needed, yet evidence-based data in the country is scarce. Here, we developed a cognitive behavioural therapy (CBT)-based group telemedicine model and proposed to investigate the effectiveness and implementability for providers, in a multicentre randomised controlled trial (RCT).

Methods: Participants will be recruited from the communities across Indonesia. Recruitment will be done through the social networks of eight sites: three hospitals, two primary healthcare centres, and three rehabilitation centres. The intervention is a relapse prevention program called Indo-DARPP, a newly-developed 12-week module based on CBT and motivational interviewing constructed in the Indonesian context. The program is delivered by healthcare providers and peer counsellors in a group therapy via video-conferencing—intervention will be given in addition to treatment as usual. Control comparison is treatment as usual only. A total of 220 participants will be randomly divided by half into the intervention and control group. The primary outcome is the increase of percent days of abstinence from the primarily used substance in the past 28 days. Secondary outcomes include addiction severity, quality of life, motivation to change, psychiatric symptoms, cognitive function, coping, and internalised stigma. Assessments will be done at baseline (week 0), post-treatment (week 13), three, and twelve months after the treatment completion (week 24 and 60). Retention, participant satisfaction, and cost-effectiveness will be assessed as implementation outcomes.

Ethics and dissemination: The study protocol was reviewed and approved by the Ethics Committees in Universitas Indonesia and Kyoto University. Results will be disseminated into academic journals and international conferences. Provided positive outcomes, the treatment program will be advocated to the Indonesian government for adoption as a formal healthcare-based approach for SUD..

Trial registration number: UMIN000042186

Keywords: *substance use disorder, telemedicine, cognitive behavioural therapy, relapse prevention, motivational interviewing, Indonesia, peer counsellor*

Strengths and limitations of this study

- The proposed study will be the first to establish high-quality evidence for a cognitive behavioural therapy (CBT)-based relapse prevention program for substance use disorder (SUD) in Indonesia.
- Telemedicine enables far-reaching nationwide participation, connecting participants with providers in major cities, which in this study will include providers from three different levels of health care: tertiary hospitals, primary healthcare centres, and rehabilitation centres.
- A successful outcome may produce a new SUD treatment module in Indonesia and pave the way for adoption into the national guideline.
- Study limitations include risk of recall and social desirability bias, heterogeneous control condition, and possible variability in treatment provision.

Introduction

Substance use disorder (SUD) is a condition characterised by the inability to control the use of psychoactive substances, i.e., alcohol and psychotropic drugs, which disrupts daily living. SUD remains a major and growing health problem worldwide. According to the Global Burden of Disease (GBD) survey in 2016, SUD globally contributes to 131 million disability-adjusted life years (DALY), or 5.5% of all DALYs,[1] and this number has been increasing since the 1990s.[2] While substance use itself is more widespread in high-income countries (HICs), low- and middle-income countries (LMICs) are disproportionately burdened. Absolute mortality rate due to SUD was greatest in LMICs with large populations,[3] and people with economic disadvantage are more likely to develop SUD.[4] The Movement for Global Mental Health and the World Health Organization both have described substantial treatment gaps in LMICs, where the number of people with SUD in need of health care far exceeds the availability of formal treatment services.[5–7] While this does not take traditional care into account, indeed, merely 1% of people with SUD in LMICs received treatment standardised by the government.[8]

In Indonesia, the world's third most populous LMIC, the national SUD prevalence was estimated by the national government at 1.8% or 3.3 million people, with the most used substance being marijuana (68%), followed by amphetamine-type stimulants (ATS, 42%), opioids (38%) and sedatives (35%).[9,10] Its strategic intercontinental location contributes to the country's infamous reputation as a marijuana exporter and drug trafficking hub.[11] While there is an 80% decrease of injecting drug use (IDU) from 2002 to 2016,[10] an increasing use of psychoactive medications out of prescription has been noted, particularly benzodiazepines.[12] Similar to other Muslim majority countries,[13] alcohol consumption is comparatively low in Indonesia—prevalence estimate of alcohol use disorder was 0.8% in 2016, much lower than the overall rate in Southeast Asia

(3.9%).[14] New psychoactive substances (NPS) has also entered the country in the last decade.[15] The current COVID-19 pandemic may also further complicate the SUD situation in Indonesia, as observed elsewhere.[16] In unpublished data from our co-author (KS), since the start of pandemic in early April 2020, there has been an increase in both drug and alcohol use in Indonesia of up to 2.5%. Higher drug use might be influenced by lockdown isolation, socio-economic issues due to unemployment, and heavier mental burden.

In Indonesia, formal mental health providers and facilities are severely lacking; in a nation of 267 million people, only 773 psychiatrists (0.32 per 100,000 people) are employed—second lowest in Southeast Asia[17]—across hospitals with psychiatric care, half of which are located within the capital island of Java.[18] In terms of government-run primary healthcare centres (abbreviated as *Puskesmas* in Indonesian), out of all Puskesmas (~1,700 nationwide), only a fifth actively provide mental health care.[18,19] Current formal treatment options for SUD include one-on-one supportive psychotherapy, symptomatic pharmacotherapy, peer counselling, and opioid substitution. Methadone maintenance therapy (MMT) is available in Puskesmas since 2006, but coverage remains low: only 5% in a 2012 study[20] due to methadone cost, reliance on subsidisation, lack of program sustainability,[21] and the tendency to incarcerate patients under the 'war on drugs' policy.[20,22] Three-months retention rate of MMT was only 60-74%.[23,24] Psychiatric comorbidities were also common in MMT users and quality of life was evidently lower.[25] Most concerningly, insufficient formal treatment coverage and the lack of standardised care for SUD prompted policymakers to enact punitive criminalization practices—even more evident by the current Indonesian administration—in place of a comprehensive mental health care approach.[26,27]

Behavioural therapies in many forms are commonly applied for SUD, most popular of which is cognitive behavioural therapy (CBT). Strong evidence backs the efficacy of CBT for

SUD treatment. A meta-analysis gave a moderate overall effect size (d = 0.45), with outcomes ranging from the self-report abstinence, drug-free urine at treatment exit, to increased retention in therapy.[28,29] CBT strategies include: (a) contingency management (CM)[30] which introduces reward for abstinence, (b) motivational interviewing (MI) which explores and resolves ambivalence,[31,32] (c) relapse prevention (RP) which helps participants to identify high-risk triggers and prevent craving, or (d) combinations thereof.[33] Therapy could be delivered individually or in groups; the latter evidently increased adherence and self-disclosure, as well as decreased the time needed by providers to treat a participant by 40%.[34,35] CBT (particularly MI and RP) is relatively low-cost and can be delivered by non-specialists, making it beneficial in resource-limited settings.[36,37] In regard to LMICs, while an ample amount of RCTs have supported CBT efficacy to reduce alcohol use,[38,39] evidence for drug use disorders is limited. Only five RCTs have been published so far,[40–44] in which three of them were inpatient-based, even though SUD management mandates sustainable outpatient care in community settings.

Telemedicine has the potential to elevate SUD treatment coverage in Indonesia. Internet communication overcomes the geographical barriers of the Indonesian archipelago, and saves time as well as transportation cost for both patients and providers, either in remote areas where health services are thinly spread,[45] or major cities with heavy traffic such as Jakarta.[46] Privacy is better ensured; visiting clinics may disclose SUD diagnosis, which is one of the most stigmatised health conditions.[47] Synchronous telemedicine via live video feed connects participants in real-time, improving rapport and potentially adherence, relative to asynchronous telemedicine (e.g., text message or web application). Video-conferencing has been effectively used in SUD treatment,[48–53] but recent systematic reviews[54–59] have revealed three lacking points: (1) previous reports merely focused on alcohol and opioid use,[48,51–53] (2) group therapy was investigated by only one small-

scale pilot RCT,[52] and (3) no studies were done in LMICs. The use of internet devices has been rapidly expanding in LMICs, including Indonesia. Smartphone users accounted for 74% of the Indonesian population in 2019, possibly reaching 89% by 2025.[60] Furthermore, the COVID-19 pandemic has elevated telemedicine from an accessory to a necessity, including for psychiatric care.[61] Its accessibility and acceptance among SUD patients, as shown in a recent survey,[62] may potentially sustain telemedicine as the 'new normal' even in the post-pandemic world.[63,64]

Given the above challenges and opportunities, we propose a clinical trial to evaluate a relapse prevention telemedicine program for SUD in Indonesia. We have developed a new treatment module called *Indonesia Drug Addiction Relapse Prevention Program* (Indo-DARPP), which is a 12-week CBT-based group therapy. The primary objective is to evaluate the effectiveness of Indo-DARPP delivered via video conference (tele-Indo-DARPP), added to treatment as usual (TAU), to increase abstinence from primarily-used substances, compared to TAU only. Secondary objectives are to assess the effectiveness of the program toward changes in quality of life, motivation to change, psychological symptoms, cognitive function, coping, and internalised stigma. Retention, participant satisfaction, and group cohesion will be assessed as implementation outcomes, and cost-effectiveness analyses will be conducted to inform health policy investment.

METHODS

Trial design

This trial is a parallel-group, two-arm, assessor-blinded, multicentre superiority randomised controlled trial. The protocol adheres to the Standard Protocol Items:

Recommendations for Interventional Trials (SPIRIT) checklist (**Supplementary file 1)**. We design the study as a pragmatic type 1 hybrid effectiveness-implementation trial,[65] which allows concurrent investigation of intervention effectiveness as well as implementation in clinical practice, focusing on the former. After intake screening, participants will undergo baseline assessment (T1) and randomly allocated in a 1:1 ratio either to the intervention arm receiving tele-Indo-DARPP in addition to TAU, or control arm receiving TAU only. Treatment will be done for 12 weeks, followed by post-treatment assessment (T2) in week 13, and follow-up assessment (T3) in week 24 (**Figure 1**).

[**Figure 1** approximately here.]

Participants and settings

Participants will be recruited from the community across Indonesia via social networks of eight sites: two primary health centres (Puskesmas), three referral hospitals, and three drug rehabilitation services (**Table 1**). These facility types constitute the community-based treatment model for SUD in Indonesia,[66] encompassing patients with various characteristics in motivation for behavioural change, substance use history, comorbidities, and current stage in treatment. Recruitment will be done via online advertisement (i.e., social networking services, group chat, website) and direct approach to current and former clients through outpatient services, in a consecutive sampling. Although all facilities are located in urban settings, the recruitment process will include online social media of each site, whose coverage is nationwide particularly for the

rehabilitation centers, and we expect recruitment of participants from anywhere in Indonesia and not limited to the physical scope of each site.

Puskesmas provides general primary care, pharmacotherapy for cases without any complications, and MMT. Referral hospitals provide psychotherapy, pharmacotherapy, opioid substitution therapy using buprenorphine/naloxone, and specialised care for cases with complications, such as severe psychiatric disorder. Rehabilitation services provide long-term psychosocial care, typically in a mutual-aid group form. Selection of sites was based on feasibility, client demographic, recruitment potential, and availability of providers. While recruited participants may not be under treatment in the aforementioned sites at the time, facilitators for tele-Indo-DARPP will be the staff of respective sites: general practitioners in Puskesmas, psychiatrists in referral hospitals, and counsellors in rehabilitation centres.

[**Table 1** approximately here.]

Inclusion criteria will be those who: 1) aged 18-65 years old; 2) are diagnosed as having substance use disorder based on DSM-5; 3) have used primarily-used substance for at least one day in the past one year; 4) have access to electronic devices (i.e., smartphone, mobile tablet, personal computer) with internet connection; and 5) are proficient in Indonesian. Exclusion criteria will be those who: 1) have severe comorbidity that hinder informed consent or group therapy participation; and 2) currently hospitalised or are using residential care.

We set a broad inclusion criteria, i.e. substance use in the past one year, for two reasons. First, proportional hazard models showed that the probability of relapse remains high before

achieving one year of abstinence, and only declined substantially after 16 months [67,68]. Thus, it is clinically important to examine treatment efficacy on people who have not achieved one-year abstinence. [68] Second, in this pragmatic effectiveness study, [69] we design eligibility criteria to more closely represent a population seen in real-world Indonesian clinical practice. Indeed, patients treated at the collaborating clinical sites include people who have been abstinent for more than one month, but still experience cravings and tendency to relapse.

Recruitment

Patients eligibility will be assessed by collaborating staff at respective sites. For those who have never been diagnosed as having SUD, addiction psychiatrists will conduct clinical assessments via video call. Oral and written informed consent will be given to those eligible. The consent form in English is provided in **Supplementary file 2**. For urine tests, explanations will be given immediately after post-treatment (T2) assessment, as anticipation for urine tests may influence substance use behaviour. Consent to urine test or absence thereof will not affect study participation.

Randomisation and blinding

Participants will be randomly allocated to either an intervention (tele-Indo-DARPP + TAU) or a control (TAU only) arm, with stratification by study site. Each site will conduct two waves of recruitment with 10 participants in each wave. After the first wave at each site, we will randomly allocate 5 participants to either intervention or control group. All participants in a given tele-Indo-DARPP group will be from the same recruitment site. Recruitment will be continued

until another 10 participants (second wave) joined, and random allocation will be done similarly. Allocation will be done using computer-generated random numbers by a researcher who will be blinded to participants' information, except for ID. Data will be collected by researchers who are blinded to the allocation arm of each participant. Participants and treatment providers are not blinded as the intervention is a psychotherapy.

Development of Indo-DARPP

Indo-DARPP was based on the Serigaya Methamphetamine Relapse Prevention Program (SMARPP), a face-to-face group CBT-based intervention in Japan developed by a co-author (TM),[70] which itself is based on the Matrix Model developed in the US.[71] Efficacy of SMARPP in increasing abstinence duration, motivation to change, and participation in self-help groups have been reported.[72–74] SMARPP has been widely implemented as a psychotherapy for SUD not only in psychiatric clinics but also primary healthcare, rehabilitation, and probation offices in Japan, covered by the national insurance scheme. SMARPP has excellent scalability via the use of a workbook, and can be delivered by non-specialists who have received a brief training.

Contents of Indo-DARPP are based on the RP model, where participants are guided to learn high-risk situations for substance use and coping strategies. The program also incorporates elements of MI and psychoeducation on substances, SUD, and its common comorbidities. While CM could also be added, it increases cost and may not be effective in the longer term,[75] and thus, MI and RP approaches will be utilised in this study. Adaptations from SMARPP were done via focus group discussions involving Japanese researchers, Indonesia-based psychiatrists, general practitioners, and peer counsellors, all of whom have extensive experience ranging 4-20 years in the addiction field. Substances discussed in the module are amphetamine-type stimulants,

benzodiazepines and other prescribed medicines, opioids, marijuana, NPS, and alcohol. Indo-DARPP is designed to be delivered in a small group format using a workbook (see **Supplementary file 3** for table of contents of the workbook), and sessions will be provided by one facilitator and one co-facilitator who is a peer counsellor with lived experiences of SUD.

A pilot test was held at Site 1, recruiting nine SUD patients into a 12-week tele-Indo-DARPP, to check the content acceptability and feasibility of the online delivery format. Further adjustments were made based on the pilot results and patient feedback.

Intervention via video conference: tele-Indo-DARPP

Tele-Indo-DARPP will be implemented in group therapy with a maximum of five patients, in a weekly 2-hour session for 12 weeks, delivered using the online video-conferencing application Zoom. URLs for video conferences will be informed weekly by the research team to five Indo-DARPP participants and two providers via online group chat for participants who agreed to share their contacts. Those who declined to share will be notified via personal messages. Each Indo-DARPP session consists of three parts: (1) "check-in", where participants share history of substance use and craving in the past week, and analyse high-risk situations and coping actions taken; (2) "today's topic", where providers guide discussion of specific workbook chapters and participants fill in exercises, and (3) "check-out", where providers give summary and invite feedback, and participants anticipate triggers and coping strategies for the following week.

Providers of tele-Indo-DARPP

At least two persons from each site will serve as facilitators, who meet the following criteria: psychiatrist with at least 1-year experience in treating SUD patients, or healthcare provider with at least 2-year experience in providing care for SUD patients, or peer counsellor with at least 2-year involvement in any organisation providing services for people with SUD. The roles of facilitators are to (1) lead and moderate Indo-DARPP sessions, (2) elaborate on chapter contents, (3) manage participants to follow rules, (4) establish safe and warm environment, (5) provide consultation including out-of-session, and (6) contact absent participants to encourage attendance.

Similarly, at least two persons from each site will serve as co-facilitators for the tele-Indo-DARPP, described as peer counsellors who have also experienced SUD and recovered, with at least 6-month involvement in any organisations providing services for people with SUD. The role of co-facilitator is to (1) share personal experiences relevant to discussion topics, (2) assist facilitators in ensuring a safe and warm environment, (3) provide general support to the Indo-DARPP process, and (4) provide counsel, including out-of-session.

Training and supervision

Prior to recruitment, all providers will receive two full-day training online sessions on basic knowledge of SUD treatment, Indo-DARPP contents, video demonstration, hands-on role play, discussion on difficult cases, tele-Indo-DARPP, and study-related quality control. Workbooks and manuals were handed to all providers, and close communication with the research team will be kept via WhatsApp group chat throughout the research period. To maintain treatment fidelity and quality control, during actual tele-Indo-DARPP sessions, addiction psychiatrists from the research team (KS and EH) will randomly select and observe at least two sessions per Indo-DARPP group,

meaning at each wave at each site thus constituting 16.7% of the all sessions, and review the providers using a structured checklist.

Control condition

Participants who received treatment before the study will continue to receive treatment as usual, regardless of group allocation. TAU was chosen as the control condition because the Indo-DARPP is expected to complement the existing treatment services for SUD in every level of care. TAU differs according to the service location (**Table 1**). Individual psychotherapy is typically conducted via in-person short consultation (~15 minutes) with clinical psychiatrists. Pharmacotherapy is given to alleviate symptoms, e.g., anxiolytics for anxiety. Patients undergoing MMT visit the site almost every day to receive their daily doses, while patients undergoing substitution therapy with buprenorphine with naloxone visit every week. All participants will be able to continue any outpatient pharmacological treatment (e.g., MMT, antidepressants) and psychotherapy (e.g., twelve-step group sessions).

Primary outcome

Abstinence from primarily used substance

The primary outcome is the percent days of abstinence from the primarily used substance during the past 28 days. Percent days of abstinence has been shown to be sensitive to the effects of CBT and are good predictors of SUD treatment follow-up.[76] Use of primarily used substance each day (yes/no) for 28 days will be retrospectively interviewed on a weekly-basis using the timeline followback (TLFB) method (**Table 2**), which has good validity and high test-retest

reliability in measuring substance consumption.[77,78] The participants will be asked to recount every week, to reduce the risk of recall bias. The primarily used substance is defined as the substance causing the most problems for participants and drives them to seek care, at T1.

We will collect urine samples to test the presence of the primarily used substance once at T2. Thresholds for a positive result are >100 ng/ml for ethyl glucuronide (for alcohol use), >300 ng/ml for amphetamine-type stimulant (i.e., d-methamphetamine and MDMA), >100 ng/ml for diacetyl morphine (heroine), cocaine, and benzodiazepine, >50 ng/ml for synthetic cannabis (K2), and > 25 ng/ml for tetrahydrocannabinol (marijuana). Urine tests in this study will only serve to corroborate the data of self-reported substance use at the primary endpoint (T2), and not as an objective surrogate of all self-reported substance use data at every time point. This was planned to improve feasibility for participants and minimise drop-out due to the burden of data collection (urine test needs in-person assessment, unlike all other measurements in this study), especially among participants who reside in remote areas deemed most benefited from online therapy.

[**Table 2** approximately here.]

Secondary outcomes

Addiction severity

The Addiction Severity Index (ASI) is the most widely used measure in the field of addiction.[79] Internal consistency, test-retest reliability, and scale independence of ASI to measure substance use have long been established.[80,81] The Treatnet ASI version 3.0 by the United Nations Office on Drugs and Crime (UNODC) will be used; the scale is available in Indonesian, and one addiction treatment centre in Indonesia was included in its development trial.[82]

Health-related quality of life

The five-level version of the five-dimensional EuroQoL (EQ-5D)[83,84] will be used to assess health-related quality of life (HRQoL), which has been done before among SUD patients with confirmed construct validity.[85,86] The total utility score will be obtained using the already established value set in Indonesia.[87]

Motivation to change

Motivation to change will be assessed by the Action subscale the University of Rhode Island Change Assessment (URICA).[88] URICA has been shown to have good validity, where higher scores indicate that the person has committed to develop positive behavioural changes (Diclemente and County, 2000; Diclemente et al., 2004).[89]

Coping

Types of engaged stress coping will be assessed by the Brief Coping Orientations to Problems Experienced (Brief COPE),[90] which is commonly used for SUD patients.[91] A higher score indicates that the person has adopted the coping type more frequently.

Psychiatric symptoms

Psychiatric symptoms will be evaluated by the Symptom Checklist 90-R (SCL-90-R).[92] The Global Severity Index (GSI) will be used, which is feasible to measure psychiatric symptoms among SUD patients.[93]

Cognitive function

Cognitive function will be assessed by the Rey Auditory Verbal Learning Test (RAVLT),[94] which is useful to diagnose cognitive impairment as well as post-treatment improvement in SUD patients.[95,96]

Internalised stigma

Internalised stigma will be assessed by the Internalized Stigma of Mental Illness (ISMI) scale.[97] The term 'mental illness' in the statements will be replaced with 'substance addiction.'

Implementation outcomes

Retention in treatment

Participants will be coded as 'retained in treatment' if they had therapeutic contacts—including attending tele-Indo-DARPP and visiting any outpatient clinic for TAU—in at least 75% of the planned contacts during the past 3 months.

Treatment satisfaction

Client Satisfaction Questionnaire-3 (CSQ-3)[98] is commonly used for treatment programs, including for SUD.[99]

Group cohesion

Group Therapy Experience Scale (GTES) will be used to measure the level of group cohesion and self-disclosure in group therapy, as implementation outcomes of tele-Indo-DARPP.[100]

Indo-DARPP attendance

Attendance to each session will be recorded by the facilitator.

Cost effectiveness

Cost-effectiveness will be assessed from a patient, provider, and societal perspective. Cost data will be calculated by multiplying the quantity of utilised resources by unit price. Data on quantity and unit price will be obtained from within the trial, or estimated from relevant data sources. For effectiveness data, both clinical and economic indexes will be used. The clinical index is abstinence from primarily used substance in the past 28 days, which will be converted into

abstinent year. The economic index is quality-adjusted life year (QALY) calculated from the utility score of EQ-5D.

Feedback interviews

Semi-structured interviews will be done with both participants and providers to assess the following: satisfaction with content quality, comprehensibility, technical experience regarding video-conferencing, comfortableness, module practicability, and participants' perception on the credibility of providers. Interviews will be audio-recorded under the interviewees' consent.

Participant characteristics

The following data will be obtained via a self-administered questionnaire: age, gender, approximate residential location, marital status, household co-habitants, ethnicity, religion, highest education level, employment status, individual and household income, type of internet device used, frequency of video calls in the past year, age of first drug use, primarily used substance, inpatient history or incarceration in the past month, type of treatments received, treatment locations in the past three months, status of current outpatient care (voluntary or involuntary, legal or non-legal), and transportation time and cost from own residence to the outpatient location.

Data collection procedure

Researchers blinded to the treatment allocation will collect data at three different time points: at baseline (week 0, T1), the week after the completion of treatment (week 13, T2), three months after the completion of treatment (week 24, T3), and twelve months after the completion of treatment (week 60, T4), using self-answered questionnaire and online one-on-one interview. As for the primary outcome, the participants will be asked to recall weekly using the TLFB, and

thus, an assessment period of approximately 4 weeks will be added after each assessment time point. Urine specimens will be collected only at T2, at the final 2 weeks within the TLFB assessment period. Assessment schedule is shown in **Table 2** and **Figure 2**. To facilitate honest disclosure from participants, we will not record any Indo-DARPP video-conferencing sessions throughout the study.

[**Figure 2** approximately here.]

Sample size

Sample size was calculated for the primary outcome to detect a medium effect size of d = 0.50, which is slightly more modest than a previous study examining the efficacy of telemedicine for people with SUD in an LIMC (d = 0.59).[101] Using $\alpha = 0.05$ and power = 0.80, a simple t-test requires n = 64 per arm. We estimated the design effect of clustering within Indo-DARPP group, using the formula, $D = 1 + (m - 1)\ \rho$, [102] assuming intraclass correlation within Indo-DARPP groups or $\rho = 0.05$, and group size or $m = 5$, which yielded the design effect or $D = 1.2$. Multiplying the result of simple calculation by the design effect, the minimal number of participants in data analysis was 77 per arm. Assuming attrition proportion = 30% which is more conservative than a previous similar study (26%),[103] the sample size for enrolment was set as 110 per arm, or 220 in total.

Statistical analysis

A detailed statistical analysis plan will be developed by a statistician who is blinded to patients' allocation, prior to data analysis. Baseline data description and main analyses will be conducted on an intention-to-treat basis, i.e., participants' data will be handled according to their initially assigned arms, regardless of actual received treatment. Analyses will be conducted with a significance level of 5% in the two-sided test, using Stata/SE 16.1.

Consideration for correlated outcome data

Correlation within sites for a control arm will be ignored, as the TAU within one site varies per patient and some participants may not receive any treatment. For an intervention arm, correlation within each Indo-DARPP group due to the nature of group therapy should be accounted for. We will define a new variable termed 'clustering group identification (CID)', where the control arm will be coded as a unique CID for each person, while the intervention arm will be coded based on the tele-Indo-DARPP group they were in, i.e., the same CID for five participants.

Main analysis

Primary endpoint will be set at T2. The mean of the outcome changes from T1 to T2 will be compared between the intervention and control arms using a linear model. To investigate the durability of the treatment effect, outcome changes from T1 to T3 and T4 will also be compared between both arms. We will account for the aforementioned correlations by clustering data, based on CID in the generalised estimation equations (GEE). To help interpret effect size, Cohen's *d* between arms will be calculated.

Missing values

A complete case analysis will be done, which will only include participants with no missing values in the variables of interest. Sensitivity analysis for missing values will be conducted by either inverse probability weighted GEE[104] or multiple imputation.

Subgroup analysis

The effect of intervention will be investigated by subgroups, as the observed effect may vary depending on specific population. The participants will be divided by the types of primarily used substance, gender, previous and current utilisation of other SUD treatment, high and low values in clinical characteristics at T1, e.g., percent days of abstinence, ASI drug use composite score, URICA readiness score, and cognitive function. Specifically, based on previous studies which showed that treatment effectiveness varied depending on baseline severity levels [105,106], we hypothesised that participants assigned to tele-Indo-DARPP with more severe level of substance use at T1 would report more increased abstinent days at T2, T3, and T4.

Implementation evaluation

Chi-squared tests and *t*-tests will be done to compare retention in treatment and treatment satisfaction between the arms, exclusively for participants who were already receiving SUD treatment at T1. Group cohesion and Indo-DARPP attendance will be descriptively reported by mean and standard deviation. For cost-effectiveness analysis, the incremental cost-effectiveness ratios (ICERs) will be calculated, which will yield costs per QALY and abstinent year. Feedback interviews will be transcribed and thematic analysis will be conducted.

Compensations

Participants in both the control and intervention groups will receive 300,000 IDR (≈ 21.3 USD) to compensate for their transportation to treatment sites for TAU throughout the 12 weeks,

and also 98,000 IDR (≈ 7.0 USD) for every time they complete an online video assessment as compensation for internet data and 2-hour data collection. Specific to the intervention group, participants will receive internet mobile data equivalent to 50,000 IDR (≈ 3.5 USD) before the first session of tele-Indo-DARPP, and receive the same amount of mobile data every time they attended four sessions of tele-Indo-DARPP. As all monetary amounts were set at the approximate cost, the amounts are intended purely for compensation and not as reward, as in contingency management. For providers, compensation of 170,000 IDR (≈ 12.1 USD) and 150,000 IDR (≈ 10.7 USD) will be given for each tele-Indo-DARPP session to facilitator and co-facilitator, respectively.

Data monitoring

Data on adverse events including hospitalisation, arrest, and death will be collected from the participants' treating psychiatrist or medical staff. In addition, participants will be interviewed at T2 on whether they experience any subjective harmful effects (e.g., withdrawal syndrome, increased cravings) after joining Indo-DARPP. An independent data monitoring committee will not be convened, as the study involves short-term non-invasive psychotherapeutic intervention. No interim analysis is planned due to the short duration of intervention. Completeness and accuracy of data collection will be checked by Japanese co-investigators, and there will be no auditing process by independent investigators.

Data publication

Deidentified results of the study will be published in scientific publication, and reported to relevant government bodies in Indonesia to advocate adoption of the treatment module.

Ethical consideration and dissemination

This study protocol (version 2.0, May 2020) was approved by the Research Ethical Committee of Faculty of Medicine, Universitas Indonesia (approval number: KET-1175/2019), the Ethics Committee of Graduate School and Faculty of Medicine, Kyoto University (approval number: C1483). The study protocol was registered at the University Hospital Medical Information Network clinical trial registry (UMIN-CTR) (registry number: UMIN000042186).

Consent process will be conducted carefully to ensure that all potential participants fully understand research objectives, procedures, risks, benefits, costs, and alternatives. It will be emphasised that study participation is voluntary and consent can be withdrawn at any time before research publication. We will allocate participants to treatment arms only when written informed consents for participation are obtained. Likewise, urine specimens will only be collected if written informed consents for urine collection are obtained. Participants will not receive any adverse influence in deciding study participation and/or urine collection. Personal data will be protected by separating study data from participants' identifiable information. To quickly respond to adverse events arising when outpatient visits are not possible, a dedicated phone number and a WhatsApp account for the study will be opened to ease communication to the research team. Participants will be instructed to text or call when experiencing any adverse events. Importantly, written agreement will be obtained from participants to never share others' information to any third party. This regulation will be enforced in both during and outside tele-Indo-DARPP sessions, in any medium, including video conference and group chat.

Results of this study will be disseminated into peer-reviewed journals and international academic conferences. Provided positive outcomes, Indo-DARPP will be advocated to the Indonesian government for adoption as a nationwide formal treatment program.

Patient and public involvement

Patients' feedback during the pilot study was incorporated into the Indo-DARPP module design. Apart from that, patients and/or the public were not involved in the conduct, reporting, or dissemination plans of this study.

Discussion

Up until the time of writing, nine RCTs from LMICs have reported the effectiveness of digital delivery of interventions for SUD. Utilised formats were telephone calls,[107–110] webpages,[111–113] and mobile applications,[101,114] however, no study in LMICs has so far investigated the effectiveness of video-conference-based psychotherapy. The latter may facilitate honest, interactive discussions on personal substance use and cravings, founded on better rapport between providers and patients,[115] all of which is integral for CBT for SUD. One meta-analysis concluded that web-based mental health interventions had better retention rate and treatment outcomes when therapists were synchronously involved.[116]

The proposed study has several strengths. This is the first RCT to investigate the effectiveness of video-conference based psychotherapy in any LMIC, as well as the first study to establish quality evidence on psychotherapy for SUD in Indonesia. Recruitment will be done throughout multiple levels of care, i.e., tertiary (referral hospitals), primary (Puskesmas) and community (rehabilitation centres). The latter have extensive reach encompassing all major Indonesian islands, and advertising will be done via online social media, facilitating recruitment from across the nation. While CBT effectiveness is the primary outcome, the study allows elucidation of real-world implementation and cost-effectiveness in a hybrid effectiveness-

implementation design.[65] This is particularly true in Puskesmas, where the providers will be general practitioners, and in rehabilitation centres, where the providers will be peer counsellors. This pragmatic RCT aims to mimic the usual clinical practice, and we hope that the result may be used to inform decision-making by patients, providers, and policymakers.[117]

Several limitations can also be presumed. All data from participants will be self-reported and prone to recall and social desirability bias. Urine tests will be done to corroborate subjective data, but this is not a full validation as it is only done once to represent substance-detectable period within a 28-days period, and only at T2, which in turn was planned to improve feasibility for participants and reduce drop-out risk. Control conditions will be heterogeneous, as the study will include people who use various substances, in multiple sites where TAU differs, and possibly people who are not receiving any treatment. Variability in the providers' background may create inconsistency in CBT delivery, even though training and treatment manuals were introduced as an effort to standardise care. Treatment delivery via online video-conferencing might have poor generalisability toward people with low internet literacy, as well as people in low socio-economic strata who could not afford smartphones—although entry-level Android-based smartphones (less than 100 USD) are available nationwide in Indonesia. Group psychotherapy provided in the Indonesian language would induce low external validity to people with limited proficiency in the language.

Efforts to establish evidence-based treatment for SUD should be scaled up in Indonesia and LMICs in general, where effectiveness data is sparse. The proposed study may present high-quality evidence, and a successful outcome may birth a new SUD treatment module in Indonesia, paving way for the adoption of Indo-DARPP into the national guideline. We hope that our efforts

may further promote a comprehensive, healthcare approach—as opposed to repressive anti-drug policies for the SUD population.

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Author contributions

CY, KS, and YO conceptualised the study. CY, KS, EH, and YO are the main developers of the Indo-DARPP module, designed study methodology, invited and coordinated site investigators, conducted training of providers, wrote the protocol, reviewed and edited the final manuscript. EB, VR, PA, and AP helped in module development, study design, training of providers, and site coordination. TS provided biostatistical and epidemiological supervision. TM provided the original SMARPP module and clinical input and perspectives to improve study quality. RS supervised the whole study and procured grants. CY and RS are the principal investigators of the grants. All authors have read and approved the final manuscript.

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Competing interests

The authors declare no competing interest.

Patient consent for publication

Not required.

Ethics approval and trial registration

This study protocol was approved by the Research Ethical Committee of Faculty of Medicine, Universitas Indonesia (approval number: KET-1175/2019), and the Ethics Committee of Graduate School and Faculty of Medicine, Kyoto University (approval number: C1483). The study protocol was registered at the University Hospital Medical Information Network clinical trial registry (UMIN-CTR) (registry number: UMIN000042186).

Availability of data and materials

The full protocol and datasets of the planned study will be available from the corresponding author on reasonable request.

Figure legends

Figure 1. Study flowchart for each site. A total of 20 or 30 participants will be recruited through the social network of each site. After 10 participants have been recruited to constitute one wave, randomisation will be done to allocate participants into two groups: intervention (Indo-DARPP + TAU) and control (TAU only), with 5 participants in each group. Recruitment will be continued until another 10 or 20 participants (second or third wave) joined before randomisation and

allocation similar as before. Treatment period will be 12 weeks. Assessments will be done four times: T1 (Week 0) during baseline or before randomisation, T2 (Week 13-16) during post-assessment or 1-4 weeks after treatment period ends, T3 (Week 24) at 3 months after treatment ends, and T4 (Week 60) at 12 months after treatment ends.

Figure 2. Planned trial schedule across all 8 research sites. Staggered schedules were designed to spread the workload of providers in regard to Indo-DARPP intervention, as well as research staff in regard to assessments. After training of providers, all sites were given approximately 1-2 months to recruit participants. Sites with relatively higher potential to recruit faster, i.e., those with higher rate of patient turnover, were selected ahead in the schedule. Each site will have 2 or 3 waves of recruitment and treatment periods.

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Table 1. Recruitment sites in this study

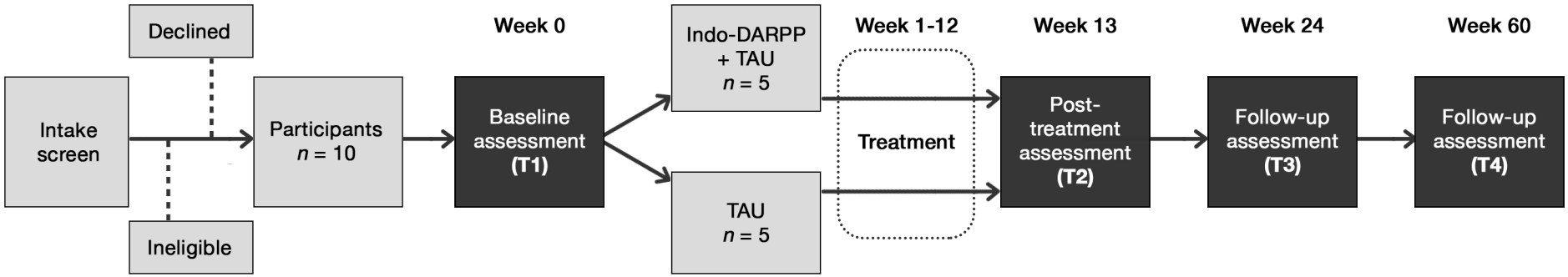
Name	Location	Type	Treatment as usual	Most reported primarily used substance
Cipto Mangunkusumo Hospital	Jakarta	Tertiary national general hospital	Individual psychotherapy, symptomatic pharmacotherapy	Benzodiazepine
Aceh Mental Hospital	Aceh	Tertiary provincial mental hospital	Individual psychotherapy, symptomatic pharmacotherapy	Methamphetamine
Duren Sawit Regional Hospital	Jakarta	Tertiary regional general hospital	Individual psychotherapy, symptomatic pharmacotherapy, opioid substitution therapy (buprenorphine, naloxone)	Opioid
Karisma Foundation	Jakarta	Rehabilitation center	Individual and group peer counselling	Methamphetamine, opioid
Kapeta Foundation	Banten	Rehabilitation center	Individual and group peer counselling	Methamphetamine, benzodiazepine, synthetic cannabinoids
Kios Atma Jaya	Jakarta	Rehabilitation center and regional HIV clinic	Individual psychotherapy, group peer counselling, outreach program	Opioid
Puskesmas Jatinegara	Jakarta	Primary health care	Counselling, symptomatic pharmacotherapy, methadone maintenance therapy	Heroin
Puskesmas Gambir	Jakarta	Primary health care	Counselling, symptomatic pharmacotherapy, methadone maintenance therapy	Heroin

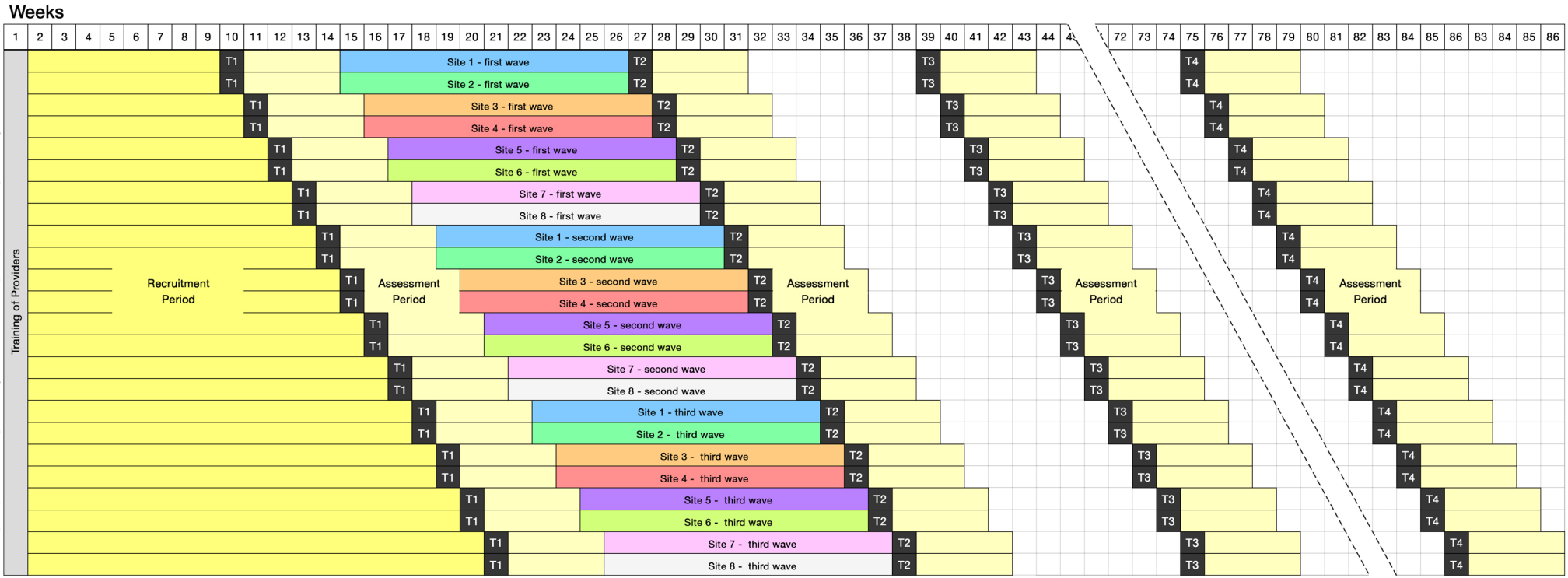
Counselling focuses on education and giving advice.
Symptomatic pharmacotherapy gives medication for helping patients with specific psychopathologies.
Psychotherapy aims to help a person identify and change troubling emotions, thoughts, and behaviour.

Table 2. Outcome and measurement

Outcome	Measurement	Data for analysis	Type and score range	Hypothesis for intervention (vs control)	Assessment time point			
					T1	T2	T3	T4
Primary outcome								
Abstinence from primary substance	Timeline followback (TLFB) for the past 28 days	Number of days being abstinent from primary substance divided by 28 (%).	Continuous, 0 (no use) to 100 (used every day).	Higher	✓ □	✓ □ [a]	✓ □	✓ □
Secondary outcomes								
Addiction severity	Addiction Severity Index (ASI)	7 composite scores: medical, employment, alcohol use, drug use, legal, family/social, and psychiatric status. Each composite score calculated using standard formula.	Continuous, 0 (no problems) to 1 (severe problems).	Lower	✓ □	✓ □	✓ □	✓ □
Health-related quality of life	EuroQol-5D (EQ-5D-5L)	Health utility score, calculated from 5 items on mobility, self-care, usual activities, pain/discomfort and anxiety/depression, using Indonesian value set.	Continuous, -0.865 (impaired health) to 1 (full health).	Higher	✓ □	✓ □	✓ □	✓ □
Motivation to change	University of Rhode Island Change Assessment (URICA)	Action stage subscale, sum of 8 items.	Continuous, 8 (not active in behavioural change) to 40 (highly active in behavioural change).	Higher	✓ □	✓ □	✓ □	✓ □
Coping	Brief-Coping Orientation to Problems Experienced (Brief COPE)	Sum of substance use coping (2 items)	Continuous, 2 (low substance use coping) to 8 (high substance use coping)	Lower	✓ □	✓ □	✓ □	✓ □
Psychiatric symptoms	Symptom Checklist-90 Revised (SCL-90-R)	Global Severity Index (GSI), average of 90 items.	Continuous, 0 (no symptoms) to 4 (severe symptoms).	Lower	✓ □	✓ □	✓ □	✓ □
Cognitive function	Rey Auditory Verbal Learning Test (RAVLT)	3 test results; immediate, learning, and recalling.	Continuous, 0 (low functioning) to 15 (high functioning).	Higher	✓ □	✓ □	✓ □	✓ □
Internalised stigma	Internalized Stigma of Mental Illness (ISMI)	Sum of 4 subscales: alienation, stereotype endorsement, social withdrawal, and stigma resistances.	Continuous, 24 (low internalised stigma) to 96 (high internalised stigma)	Lower	✓ □	✓ □	✓ □	✓ □
Implementation outcomes								
Retention in treatment	Self-reporting for the past 3 months	Coded as 'retained' if they had therapeutic contacts in at least 75% of the planned number of therapeutic contacts.	Categorical, 'retained' = 1, 'not retained' = 0.	More 'retained'		✓ □	✓ □	✓ □
Treatment satisfaction	Client Satisfaction Questionnaire-3 (CSQ-3)	Sum of 3 items.	Continuous, 4 (not satisfied) to 12 (satisfied).	Higher		✓ □		
Group cohesion	Group Therapy Experience Scale (GTES)	Sum of 16 items.	Continuous, 16 (poor cohesion) to 80 (great cohesion).	Not applicable: measured only in intervention arm		✓ □		

[a] Objective validation by urine drug test for 8 substances: alcohol, amphetamine, morphine, cannabinoids, methamphetamine, benzodiazepine, cocaine, synthetic cannabinoids


Declined
Intake screen
Ineligible
Participants n = 10
Week 0
Baseline assessment (T1)
Indo-DARPP + TAU n = 5
TAU n = 5
Week 1-12
Treatment
Week 13
Post-treatment assessment (T2)
Week 24
Follow-up assessment (T3)
Week 60
Follow-up assessment (T4)


Weeks
Training of Providers
Recruitment Period
Assessment Period
Assessment Period
Assessment Period
Assessment Period
Site 1 - first wave
Site 2 - first wave
Site 3 - first wave
Site 4 - first wave
Site 5 - first wave
Site 6 - first wave
Site 7 - first wave
Site 8 - first wave
Site 1 - second wave
Site 2 - second wave
Site 3 - second wave
Site 4 - second wave
Site 5 - second wave
Site 6 - second wave
Site 7 - second wave
Site 8 - second wave
Site 1 - third wave
Site 2 - third wave
Site 3 - third wave
Site 4 - third wave
Site 5 - third wave
Site 6 - third wave
Site 7 - third wave
Site 8 - third wave
T1
T2
T3
T4

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4, 23
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a, trial already registered as described in 2a.
Protocol version	#3	Date and version identifier	23
Funding	#4	Sources and types of financial, material, and other support	26-27
Roles and	#5a	Names, affiliations, and roles of protocol	26

responsibilities: contributorship		contributors	
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a, no trial sponsor.
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a, no involvement of funders in the study design.
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a, no direct intervention in the study design by the host universities.
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-9
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	15
Objectives	#7	Specific objectives or hypotheses	9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9-10

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10-11
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	22-23
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	22-23
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	15
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome.	15-19

		Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10, 19, 26
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	20
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Allocation:	#16c	Who will generate the allocation sequence,	12

implementation		who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12, 19
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a, only assessors are blinded
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-19
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	19, 22-23
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the	23

		protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	20-22
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21-22
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	23, DMC will not be convened as the intervention involves a short-term psychotherapy with known minimal risk.
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	23, interim analysis is not planned due to the short duration of intervention.
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	22-23
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	23, there will be no auditing process by independent investigators.

Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	23, 28
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	23
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	23
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	23
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	23
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	27
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	28
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15, CBT intervention will be made available for control group after the end of the study.

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	23
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	26-27
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	28
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	11, 23
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	16

Notes:

- 2b: n/a, trial already registered as described in 2a.
- 5b: n/a, no trial sponsor.
- 5c: n/a, no involvement of funders in the study design.
- 5d: n/a, no direct intervention in the study design by the host universities.
- 17b: n/a, only assessors are blinded
- 21a: 23, DMC will not be convened as the intervention involves a short-term psychotherapy with known minimal risk.
- 21b: 23, interim analysis is not planned due to the short duration of intervention.

- 23: 23, there will be no auditing process by independent investigators.
- 30: 15, CBT intervention will be made available for control group after the end of the study. The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 15. February 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

Supplementary file 2

Research Participation Consent Form

Title of the Research:

Effectiveness of a cognitive behavioral therapy for drug use disorders in Indonesia: A randomized controlled trial

(Collaboration research between the Faculty of Medicine, University of Indonesia and Kyoto University)

An explanation has been given which includes the following discussion :

1. Research Title
2. Research Clearance
3. Research institutes and researchers
4. Research purposes
5. Research procedure
6. Research period
7. Inclusion Criteria
8. Risks, benefits, and side effects
9. Right to refuse and drop out
10. Voluntary participation and risk of involvement
11. Research data publication
12. How to access research-related materials for participants
13. Privacy of personal data
14. Research data storage
15. Research funds and conflicts of interest
16. Researcher contact list
17. Remuneration for participants
18. General management of drug addiction patients outside of research interventions
19. Follow up management after the research ends
20. Report of the participant's genetic information
21. Compensation for illness related to research and invasive procedures
22. Secondary research data for other institutions
23. Samples and participant information related to invasive procedures
24. Name, position, and affiliation of the person in charge of managing data and information related to research
25. CBT group participant commitments and drop out possibility of research participation

Explanations have been given according to the explanation sheet, and consent has been obtained voluntarily.

Date of consent : _____ / _____ / 20 ___

Researcher's affiliation : _____

Researcher's Name :

Researcher's Signature :

Acknowledged by:

1. Dean of the Faculty Medicine, University Indonesia
2. Director of the *Center for South East Asian Studies, Kyoto University*

Supplementary file 2

CBT-Group Participation Consent Form

I, the undersigned, hereby acknowledge, consent and agree to fulfill the following matters during my participation in CBT group therapy, in order to ensure the safe and secure continuation of the program:

1. I will not divulge information about other participants in the group to external parties without the consent of the parties concerned.
2. I will not record audio, video, or take camera pictures without the permission of the parties concerned and the research team.
3. I will not use drugs during the CBT session.
4. I will not divulge links (URL), ID, and passwords for online meetings in the Zoom application to external parties, without the approval of the research team.
5. I will not harass, say offensive words related to ethnicity,religion and race, or commit acts of violence for any reason to any party related to the research, whether other participants or the research team.

If I infringe the points of the agreement above, I will be given 1 (one) warning. If I do not show any improvement after being warned, or infringe it for the second time, or it is deemed that my participation will interfere with the continuation of CBT therapy in the future, I have no objection to my participation being unilaterally terminated.

I, the undersigned, hereby declare that I have understood the explanation given and agree to my participation in the research mentioned above.in my behavior after being warned, or infringe it for the second time, or it is deemed that my participation will interfere with the continuation of CBT therapy in the future, I have no objection to my participation being unilaterally terminated.

Date of Consent : ____ / _____ / 20 ___

Name : _____

Signature : _____

Supplementary file 2

Urine Test Informed Consent

Title of Research:

Effectiveness of a cognitive behavioral therapy for drug use disorders in Indonesia: A randomized controlled trial

(Collaboration research between the Faculty of Medicine, University of Indonesia and Kyoto University)

An explanation has been given which includes the following discussion:
1. Purpose of the urine sampling
2. Urine test procedure
3. Analysis of urine test results data and maintaining data confidentiality

Explanations have been given according to the explanation sheet, and consent has been obtained voluntarily.

I, the undersigned, declare that I

Agree / do not agree

*please circle one of these options above

…to provide the urine sample to be tested for the research team, and I have acknowledged and understood the purposes, procedures and data analysis as described previously.

Date of consent : ____ / _____ / 20 ___

Name : _____

Signature : _____

Supplementary file 2

Withdrawal of Informed Consent for Urine Test

Title of the research:

Effectiveness of a cognitive behavioral therapy for drug use disorders in Indonesia: A randomized controlled trial

(Collaboration research between the Faculty of Medicine, University of Indonesia and Kyoto University)

I,the undersigned,hereby wish to withdraw my prior consent to participate in the urinary test for this research by signing this form.

Withdrawal Date : ____ / _____ / 20___

Participant's Name : _____

Participant's Signature : _____

Supplementary file 3

Table of contents of Indo-DARPP (English translation)

BMJ Open

Relapse prevention group therapy via video-conferencing for substance use disorder: protocol for a multicentre randomised controlled trial in Indonesia

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-050259.R2
Article Type:	Protocol
Date Submitted by the Author:	10-Aug-2021
Complete List of Authors:	Yamada, Chika; Kyoto University, Department of Environmental Coexistence, Center for Southeast Asian Studies Siste, Kristiana; Universitas Indonesia, Department of Psychiatry, Faculty of Medicine Hanafi, Enjeline; Universitas Indonesia, Department of Psychiatry, Faculty of Medicine, Ophinni, Youdiil; Ragon Institute Beatrice, Evania; Universitas Indonesia, Department of Psychiatry, Faculty of Medicine Rafelia, Vania; Universitas Indonesia, Department of Psychiatry, Faculty of Medicine Alison, Peter; Universitas Indonesia, Department of Psychiatry, Faculty of Medicine Prabowo, Albert; Universitas Indonesia, Department of Psychiatry, Faculty of Medicine Shinozaki, Tomohiro; Tokyo University of Science, Department of Information and Computer Technology Matsumoto, Toshihiko; NCNP, Department of Drug Dependence Research Sakamoto, Ryota; Kyoto University, Department of Environmental Coexistence, Center for Southeast Asian Studies
Primary Subject Heading:	Addiction
Secondary Subject Heading:	Addiction, Global health, Mental health, Evidence based practice
Keywords:	Substance misuse < PSYCHIATRY, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, PSYCHIATRY, Clinical trials < THERAPEUTICS

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Title

Relapse prevention group therapy via video-conferencing for substance use disorder: protocol for a multicentre randomised controlled trial in Indonesia

Author names and affiliations

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Abstract: 300 words

Main text: 5,656 words

Abstract

Background: Substance use disorder (SUD) is a leading contributor to the global burden of disease. In Indonesia, the availability of formal treatment for SUD falls short of the targeted coverage. A standardised therapeutic option for SUD with potential for widespread implementation is required, yet evidence-based data in the country are scarce. In this study, we developed a cognitive behavioural therapy (CBT)-based group telemedicine model, and will investigate effectiveness and implementability in a multicentre randomised controlled trial (RCT).

Methods: A total of 220 participants will be recruited from the social networks of eight sites in Indonesia: three hospitals, two primary healthcare centres, and three rehabilitation centres. The intervention arm will participate in a relapse prevention programme called the Indonesia Drug Addiction Relapse Prevention Programme, a newly developed 12-week module based on CBT and motivational interviewing constructed in the Indonesian context. The programme will be delivered by a healthcare provider and a peer counsellor in a group therapy setting via video-conferencing, as a supplement to participants' usual treatments. The control arm will continue treatment as usual. The primary outcome will be the percentage increase in days of abstinence from the primarily used substance in the past 28 days. Secondary outcomes will include addiction severity, quality of life, motivation to change, psychiatric symptoms, cognitive function, coping, and internalised stigma. Assessments will be performed at baseline (week 0); post-treatment (week 13); and three and 12 months post-treatment completion (weeks 24 and 60). Retention, participant satisfaction, and cost-effectiveness will be assessed as the implementation outcomes.

Ethics and dissemination: The study protocol was reviewed and approved by the Ethics Committees of Universitas Indonesia and Kyoto University. The results will be disseminated via

academic journals and international conferences. Depending on trial outcomes, the treatment programme will be advocated for adoption as a formal healthcare-based approach for SUD.

Trial registration number: UMIN000042186

Keywords: *substance use disorder, telemedicine, cognitive behavioural therapy, relapse prevention, motivational interviewing, Indonesia, peer counsellor*

Strengths and limitations of this study

- The proposed study will be the first to establish high-quality evidence for a cognitive behavioural therapy (CBT)-based relapse prevention programme for substance use disorder (SUD) in Indonesia.
- Telemedicine enables far-reaching, nationwide participation, connecting participants from across the nation with providers in major cities.
- A successful outcome may produce a new SUD treatment module in Indonesia and pave the way for its adoption by national guidelines.
- Study limitations include risk of recall and social desirability bias, heterogeneous control conditions, and possible variability in treatment provision.

Introduction

Substance use disorder (SUD) is characterised by the inability to control the use of psychoactive substances, such as alcohol and psychotropic drugs, which disrupt daily living. SUD remains a significant and growing health problem worldwide. According to the 2016 Global Burden of Disease (GBD) survey, SUD contributed to 131 million disability-adjusted life years (DALYs), or 5.5% of all DALYs,[1] and its prevalence has been increasing since the 1990s.[2] While substance use itself is more widespread in high-income countries (HICs), low- and middle-income countries (LMICs) had disproportionately high SUD mortality rates. The absolute mortality rate due to SUD was greatest in LMICs with large populations,[3] and people with economic disadvantages were more likely to develop SUD.[4] The Movement for Global Mental Health and the World Health Organization have found substantial treatment gaps in LMICs. For instance, the number of individuals with SUD far exceed the availability of formal treatment services.[5–7] While these numbers do not take traditional care into account, it is still concerning that only 1% of individuals with SUD in LMICs have reported receiving government-standardised treatment.[8]

In Indonesia, the world's third most populous LMIC, government statistics have estimated the prevalence of drug use to be 1.8% (3.3 million residents), with the most used substance being marijuana (68%), followed by amphetamine-type stimulants (ATS, 42%), opioids (38%) and sedatives (35%).[9,10] While injecting drug use (IDU) decreased by 80% between 2002 to 2016,[10] unprescribed use of psychoactive medications like benzodiazepines has become significant.[11] Similar to other Muslim majority countries,[12] alcohol consumption is comparatively low in Indonesia, with alcohol use disorder being prevalent only among 0.8% residents in 2016, much lower than the overall rate in Southeast Asia (3.9%).[13] However, new psychoactive substances (NPS) have entered the country in the last decade.[14] Moreover, the COVID-19 pandemic may

further complicate the SUD situation in Indonesia, as has been observed in other countries.[15] For instance, unpublished data from our co-author (KS) revealed that since the pandemic began in early April 2020, both drug and alcohol use have increased in Indonesia by up to 2.5%. Increased drug use might have been influenced by lockdown isolation, socio-economic issues due to unemployment, and severe psychological burden.

In Indonesia, formal mental health providers and facilities are severely lacking; in a nation of 267 million people, only 773 psychiatrists (0.32/100,000 people) are employed—the second lowest proportion in Southeast Asia[16]—across hospitals with psychiatric care, half of which are located in the capital island of Java.[17] Among the ~1700 government-run primary healthcare centres (abbreviated as *Puskesmas* in Indonesian), only a fifth actively provide mental health care.[17,18] Current formal treatment options for SUD include one-on-one supportive psychotherapy, symptomatic pharmacotherapy, peer counselling, and opioid substitution. Methadone maintenance therapy (MMT) has been available in Puskesmas since 2006, but as of 2012, its coverage was only 5%,[19] due to methadone cost, reliance on subsidisation, lack of programme sustainability,[20] and the tendency to incarcerate patients under the 'war on drugs' policy.[19,21] The three-month retention rate of MMT was only 60-74%.[22,23] Psychiatric comorbidities, and lower quality of life, are common among MMT recipients.[24] Most concerningly, insufficient formal treatment coverage and the lack of standardised care for SUD have prompted policymakers to enact punitive criminalisation practices, which are even more stringent under the current administration, instead of a comprehensive mental health care approach.[25,26]

Behavioural therapies in many forms are commonly administered for SUD, the most popular method being cognitive behavioural therapy (CBT). There is strong evidence supporting the efficacy of CBT in treating SUD. A meta-analysis reported a moderate overall effect size (d =

0.45) of CBT treatments, with outcomes such as self-reported abstinence, drug-free urine at treatment exit, and increased retention in therapy.[27,28] CBT strategies include: (a) contingency management (CM),[29] which introduces rewards for abstinence, (b) motivational interviewing (MI), which explores and resolves ambivalence,[30,31] (c) relapse prevention (RP), which helps participants to identify high-risk triggers and prevent cravings, or (d) combinations thereof.[32] Therapy can be delivered individually or in groups; the latter has reportedly increased adherence and self-disclosure, and decreased the treatment duration by 40%.[33,34] CBT (particularly MI and RP) is relatively low-cost and can be delivered by non-specialists, making it adaptable to and beneficial in settings with limited formal mental health professionals.[35,36] In LMICs, while ample RCTs have supported CBT's efficacy in reducing alcohol use,[37,38] evidence for treating drug use disorders is limited, with only five RCTs published so far.[39–43] Among these, three were inpatient-based, even though SUD management mandates sustainable outpatient care in community settings.

Telemedicine has the potential to improve SUD treatment coverage in Indonesia. Internet communication overcomes the geographical barriers of the Indonesian archipelago, and saves time as well as transportation costs for both patients and providers, both in remote areas where health services are sparse,[44] and in major cities with heavy traffic, such as Jakarta.[45] Privacy is also better ensured online as opposed to in visiting clinics, where there is a greater risk of inappropriate disclosure of SUD diagnoses, which is one of the most stigmatised health conditions.[46] Synchronous telemedicine via live video feed connects participants in real-time, improving rapport and potentially adherence, as compared to asynchronous telemedicine (e.g. through text messages or web application). Video-conferencing has been effectively used in SUD treatment[47–52]; however, recent systematic reviews[53–58] have revealed three gaps in research: (1) previous reports have only focused on alcohol and opioid use,[47,50–52] (2) group therapy was investigated by only one small-

scale pilot RCT,[51] and (3) no studies have been conducted in LMICs. This latter gap is particularly relevant because the use of internet devices has been rapidly expanding in LMICs, including Indonesia. Smartphone users accounted for 74% of the Indonesian population in 2019, possibly reaching 89% by 2025.[59] The COVID-19 pandemic has further elevated telemedicine from an accessory to a necessity, including for psychiatric care.[60] Its accessibility and acceptance among SUD patients, as shown in a recent survey,[61] may potentially sustain telemedicine as the 'new normal' even in the post-pandemic world.[62,63]

Given the above challenges and opportunities, we propose a clinical trial to evaluate a relapse prevention telemedicine programme for SUD in Indonesia. We have developed a new 12-week CBT-based group therapy called *the Indonesia Drug Addiction Relapse Prevention Programme* (Indo-DARPP), which will be delivered via video conference (tele-Indo-DARPP). The primary objective will be to evaluate the effectiveness of tele-Indo-DARPP in addition to treatment as usual (TAU) towards increasing abstinence from primarily used substances, as compared to the effectiveness of TAU only. The secondary objectives will be to assess impacts on quality of life, motivation to change, psychological symptoms, cognitive function, coping, and internalised stigma. Retention, participant satisfaction, and group cohesion will be assessed as implementation outcomes, and cost-effectiveness analyses will be conducted to inform health policy investments.

METHODS

Trial design

This trial is a parallel-group, two-arm, assessor-blinded, multicentre randomised controlled trial. The protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (**Supplementary file 1)**. We designed the study as a pragmatic type 1 hybrid effectiveness-implementation trial,[64] which allows concurrent investigation of intervention effectiveness as well as implementation in clinical practice, focusing on the former. After intake screening, participants will undergo baseline assessment (T1) and be randomly allocated in a 1:1 ratio either to the intervention arm receiving tele-Indo-DARPP in addition to TAU, or the control arm receiving TAU only. Treatment will be administered for 12 weeks, followed by a post-treatment assessment (T2) at week 13, and follow-up assessments (T3) at week 24 and (T4) at week 60 (**Figure 1**).

[**Figure 1** here]

Participants and settings

Participants will be recruited across Indonesia via social networks of eight sites: two primary health centres (Puskesmas), three referral hospitals, and three drug rehabilitation services (**Table 1**). These facility types constitute the community-based treatment model for SUD in Indonesia,[65] encompassing patients with diverse motivations for behavioural change, substance use histories, comorbidities, and stages of treatment. Recruitment will be conducted via online advertisements (i.e. on social networking services, group chat, website), and through consecutive sampling by directly approaching current and former clients through outpatient services. Although all targeted facilities are located in urban settings, the recruitment process will include social media

services of each site, particularly rehabilitation centres, which have nationwide coverage. Hence, we expect that participants will be recruited from anywhere in Indonesia, and will not be limited to the physical scope of each site.

The services offered by each type of site vary. Puskesmas provide general primary care, pharmacotherapy for cases without complications, and MMT. Referral hospitals provide psychotherapy, pharmacotherapy, opioid substitution therapy using buprenorphine/naloxone, and specialised care for cases with complications, such as severe psychiatric disorders. Rehabilitation services provide long-term psychosocial care, typically in a mutual-aid group. Sites were selected based on feasibility, client demographics, recruitment potential, and availability of providers. While recruited participants may not be undergoing treatment at these sites at the time, facilitators for tele-Indo-DARPP will be staff members of the respective sites: general practitioners in Puskesmas, psychiatrists in referral hospitals, and counsellors in rehabilitation centres.

[**Insert Table 1** here]

Inclusion criteria will be those who: 1) be aged 18-65 years old; 2) be diagnosed with substance use disorder based on DSM-5; 3) have used primarily used substances for at least one day in the past year; 4) have access to electronic devices (i.e. smartphone, mobile tablet, personal computer) with internet connection; and 5) be proficient in Indonesian. Individuals who 1) have severe comorbidities that hinders informed consent or group therapy participation, and 2) are hospitalised or using residential care, will be excluded.

We set a broad inclusion criterion, i.e., substance use in the past one year, for two reasons. First, proportional hazard models have showed that the probability of relapse remains high before achieving one year of abstinence, and declines substantially only after 16 months. [66,67] Thus, it is clinically important to examine treatment efficacy for people who have not achieved one-year abstinence.[67] Second, in this pragmatic effectiveness study,[68] we designed eligibility criteria to accurately represent the population encountered in real-world Indonesian clinical practice. Indeed, patients treated at the collaborating clinical sites include those who have been abstinent for more than one month but still experience cravings and a tendency to relapse.

Recruitment

Patient eligibility will be assessed by collaborating staff at the respective sites. Addiction psychiatrists will conduct clinical assessments via video calls for those who have never been diagnosed with SUD. The consent form in English is provided in **Supplementary File 2**. For urine tests, explanations will be given immediately after post-treatment (T2) assessment, as anticipation for urine tests may influence substance use behaviour. Consent to urine tests or absence thereof will not affect study participation.

Randomisation and blinding

Depending on the study site, participants will be randomly allocated to either the intervention (tele-Indo-DARPP + TAU) or the control (TAU only) arm. Each site will conduct two or three waves of recruitment, with 10 participants in each wave. For each wave at a site, we will randomly allocate five participants to either the intervention or control arm. All participants in

each tele-Indo-DARPP group will belong to the same recruitment site. Allocation will be performed using computer-generated random numbers by a researcher who will be blinded to the participants' information, except for ID. Data will be collected by researchers who are blinded to participants' study conditions. Participants and treatment providers will not be blinded, as it would not be possible given the psychotherapeutic nature of the intervention.

Development of the Indo-DARPP

The Indo-DARPP is based on the Serigaya Methamphetamine Relapse Prevention Programme (SMARPP), a face-to-face CBT-based group intervention developed by a co-author (TM) in Japan,[69] which itself is based on the Matrix Model developed in the US.[70] It has demonstrated efficacy in increasing abstinence duration, motivation to change, and participation in self-help groups.[71–73] SMARPP is covered by the national insurance scheme and has been widely implemented as a psychotherapy for SUD not only in psychiatric clinics, but also in primary healthcare centres, rehabilitation centres, and probation offices in Japan. SMARPP has excellent scalability as it is delivered through workbooks, and can be facilitated by non-specialists who have received brief training.

The contents of Indo-DARPP are based on the RP model, wherein participants are guided to learn about high-risk situations for substance use, and coping strategies. Elements of MI are incorporated in the earlier parts of the workbook in a form of open questions to assess participants' ambivalence and motivation to change. The programme also includes psychoeducation on substances, SUD, and common comorbidities. While CM could also be added, it increases cost and may not be effective in the longer term;[74] thus, only MI and RP approaches will be utilised in this study. Adaptations from SMARPP were determined via focus group discussions involving

Japanese researchers, and psychiatrists, general practitioners, and peer counsellors based in Indonesia, all of whom have extensive experience ranging from 4 to 20 years in the addiction field. The substances discussed in the module are amphetamine-type stimulants, benzodiazepines, and other prescribed medicines, opioids, marijuana, NPS, and alcohol. Indo-DARPP is designed to be delivered in a small group format using a workbook (see **Supplementary File 3** for the table of contents of the workbook). Sessions will be delivered by one facilitator, and one peer counsellor with lived experiences of SUD as co-facilitator.

A pilot test was conducted at Site 1, with nine SUD patients recruited for a 12-week tele-Indo-DARPP to check content acceptability and feasibility of the online delivery format. Further adjustments were made based on pilot results and patient feedback.

Intervention via video conference: tele-Indo-DARPP

Tele-Indo-DARPP will be delivered as group therapy for 12 weeks in weekly 2-hour sessions over the online video-conferencing application Zoom, with a maximum of five participants. The research team will provide video conference links to participants and two providers. Participants who agree to share their contact information will receive the links on an online group chat, while others will be notified via personal messages. Each Indo-DARPP session consists of three parts: (1) 'check-in', where participants share history of substance use and craving in the past week, and analyse high-risk situations and coping actions taken; (2) 'today's topic', where providers guide discussions of specific workbook chapters and participants complete exercises, and (3) 'check-out', where providers give summary and invite feedback, and participants anticipate triggers and coping strategies for the following week.

Providers of tele-Indo-DARPP

At least two persons from each site will serve as facilitators, who meet either of the following criteria: psychiatrists with at least a year of experience in treating patients with SUD; healthcare providers with at least two years of experience in providing care for patients with SUD; or peer counsellors with at least 2 years of involvement with any organisations providing services for patients with SUD. The roles of facilitators are to: (1) lead and moderate Indo-DARPP sessions; (2) elaborate on chapter contents; (3) manage participants to follow rules; (4) establish a safe and warm environment; (5) provide consultation, including out-of-session; and (6) contact absent participants to encourage attendance.

Similarly, at least two persons from each site will serve as co-facilitators for the tele-Indo-DARPP. Co-facilitators will be peer counsellors who have also experienced SUD and recovered, with at least 6 months of involvement with any organisations providing services for patients with SUD. The role of co-facilitators is to: (1) share personal experiences relevant to discussion topics, (2) assist facilitators in ensuring a safe and warm environment, (3) provide general support to the Indo-DARPP process, and (4) provide counsel, both in and out of sessions.

Training and supervision

Prior to recruitment, all providers will receive two full-day online training sessions on basic knowledge of SUD treatment, Indo-DARPP content, principles of MI (e.g., empathy, reflective listening, empowering affirmations), video demonstrations, hands-on role play, discussion of difficult cases, and study-related quality control. Workbooks and manuals will be handed to all

providers, and close communication with the research team will be maintained via a WhatsApp group chat throughout the research period. To maintain treatment fidelity and quality control, during actual tele-Indo-DARPP sessions, addiction psychiatrists from the research team (KS and EH) will randomly select and observe at least two sessions per Indo-DARPP group. Observations will be conducted at each wave at each site, constituting 16.7% of all sessions, and will be reviewed using a structured checklist.

Control condition

Participants who received treatment before the study will continue to receive treatment as usual, regardless of group allocation. TAU was chosen as the control condition because it is expected to complement the existing treatment services for SUD at every level of care. The TAU differs according to service location (**Table 1**). Individual psychotherapy is typically conducted via in-person short consultations (~15 minutes) with clinical psychiatrists. Pharmacotherapy is used to alleviate symptoms, by prescribing medications such as anxiolytics for conditions such as anxiety. Patients undergoing MMT visit their sites almost every day to receive their daily doses, while patients undergoing substitution therapy with buprenorphine with naloxone visit every week. All participants will be able to continue any outpatient pharmacological treatment (e.g. MMT, antidepressants) and psychotherapy (e.g. twelve-step group sessions).

Primary outcome

Abstinence from primarily used substance

The primary outcome is the percentage of days of abstinence from the primarily used substance, in the past 28 days. Percent days of abstinence have been shown to be sensitive to the effects of CBT and are good predictors of SUD treatment follow-up.[75] Data on the use of primarily used substances each day (measured in a yes/no format) for 28 days will be retrospectively collected on a weekly basis using the timeline follow-up (TLFB) method (**Table 2**), which has good validity and high test-retest reliability in measuring substance consumption.[76,77] The participants will be asked to recount every week to reduce the risk of recall bias. The primarily used substance refers to the most problematic substance for participants, which has driven them to seek care at T1.

Urine samples will be collected to test for the presence of the primarily used substance once at T2. Thresholds for a positive result are >100 ng/ml for ethyl glucuronide (alcohol), >300 ng/ml for amphetamine-type stimulants (i.e. d-methamphetamine and MDMA), >100 ng/ml for diacetyl morphine (heroine), cocaine, and benzodiazepine, >50 ng/ml for synthetic cannabis (K2), and > 25 ng/ml for tetrahydrocannabinol (marijuana). Urine tests in this study will only serve to corroborate the data of self-reported substance use at the primary endpoint (T2), not as an objective substitute of all self-reported substance use data at every time point. This was planned to improve feasibility for participants and minimise drop-out due to the burden of data collection (urine test needs in-person assessment, unlike all other measurements in this study), especially among participants who reside in remote areas who are deemed to benefit the most from online therapy.

[**Table 2** here]

Secondary outcomes

Addiction severity

The Addiction Severity Index (ASI) is the most widely used measure in the field of addiction.[78] Internal consistency, test-retest reliability, and scale independence of ASI to measure substance use have long been established.[79,80] The Treatnet ASI version 3.0 by the United Nations Office on Drugs and Crime (UNODC) will be used; the scale is available in Indonesian, and one addiction treatment centre in Indonesia was included in its development trial.[81]

Health-related quality of life

The five-level version of the five-dimensional EuroQoL (EQ-5D)[82,83] will be used to assess health-related quality of life (HRQoL), which has been used before for SUD patients with confirmed construct validity.[84,85] The total utility score will be obtained using the already established value set in Indonesia.[86]

Motivation to change

Motivation to change will be assessed by the Action subscale of the University of Rhode Island Change Assessment (URICA)[87] which has been shown to have good validity. Higher scores indicate that the person has committed to develop positive behavioural changes.[88]

Coping

Types of engaged stress coping will be assessed by the Brief Coping Orientations to Problems Experienced (Brief COPE),[89] which is commonly used for SUD patients.[90] Higher scores for specific types indicate that patients have adopted them more frequently.

Psychiatric symptoms

Psychiatric symptoms will be evaluated by the Symptom Checklist 90-R (SCL-90-R).[91] The Global Severity Index (GSI) will be used, which is widely used for measuring psychiatric symptoms among SUD patients.[92]

Cognitive function

Cognitive function will be assessed by the Rey Auditory Verbal Learning Test (RAVLT),[93] which is useful for diagnosing cognitive impairment as well as post-treatment improvement in SUD patients.[94,95]

Internalised stigma

Internalised stigma will be assessed using the Internalised Stigma of Mental Illness (ISMI) scale.[96] The term 'mental illness' in the statements will be replaced with 'substance addiction.'

Implementation outcomes

Retention in treatment

Participants will be coded as 'retained in treatment' if they have had therapeutic contact, including attending tele-Indo-DARPP and visiting any outpatient clinic for TAU, in at least 75% of planned contacts in the previous 3 months.

Treatment satisfaction

The Client Satisfaction Questionnaire-3 (CSQ-3)[97] will be used, as it is commonly used for treatment programs, including for SUD.[98]

Group cohesion

The Group Therapy Experience Scale (GTES) will be used to measure the level of group cohesion and self-disclosure in group therapy, as implementation outcomes of tele-Indo-DARPP.[99]

Indo-DARPP attendance

Attendance of each session will be recorded by the facilitator.

Cost effectiveness

Cost-effectiveness will be assessed from patient, provider, and societal perspectives. Cost data will be calculated by multiplying the quantity of utilised resources by the unit price. Data on quantity and unit price will be obtained from within the trial or estimated from relevant data sources. For effectiveness data, both clinical and economic indices will be used. The clinical index will be based on days of abstinence from the primarily used substance in the previous 28 days, which will be converted into years of abstinence. The economic index will be based on the quality-adjusted life year (QALY) calculated from the utility score of the EQ-5D.

Feedback interviews

Semi-structured interviews will be conducted with both participants and providers to assess the following: satisfaction with content quality, comprehensibility, technical experience regarding video-conferencing, comfort, module practicability, language barriers, and participants' perception of the credibility of providers. Interviews will be audio-recorded with the interviewees' consent.

Participant characteristics

The following data will be obtained via a self-administered questionnaire: age, gender, approximate residential location, marital status, household cohabitants, ethnicity, religion, highest education level, employment status, individual and household income, type of Internet device used, frequency of video calls in the past year, age during first instance of drug use, primarily used substance, inpatient history or incarceration in the past month, types of treatments received, treatment locations in the past three months, status of current outpatient care (voluntary or involuntary, legal or non-legal), and transportation time and cost from residence to outpatient locations.

Data collection procedure

Researchers blinded to the treatment allocation will collect data at three different time points: at baseline (week 0, T1), the week after the completion of treatment (week 13, T2), three months after the completion of treatment (week 24, T3), and 12 months after the completion of treatment (week 60, T4), using self-answered questionnaires and online one-on-one interviews. For the primary outcome, participants will be asked to recall weekly drug use using the TLFB; with a period of approximately 4 weeks between each assessment. Urine specimens will be collected only at T2 and at the final 2 weeks within the TLFB assessment period. The assessment schedule is presented in **Table 2** and **Figure 2**. To facilitate honest disclosure from participants, we will not record any Indo-DARPP video-conferencing sessions throughout the study.

[**Figure 2** here]

Sample size

The sample size was calculated for the primary outcome to detect a medium effect size of d = 0.50, which is slightly more modest than that of a previous study examining the efficacy of telemedicine for people with SUD in an LIMC (d = 0.59).[100] Using $\alpha = 0.05$, power = 0.80, a simple t-test requires n = 64 per arm. We estimated the design effect of clustering within the Indo-DARPP group using the formula $D = 1 + (m - 1)\,\rho$, [101] assuming intraclass correlation within Indo-DARPP groups or $\rho = 0.05$, and group size or $m = 5$, which yielded a design effect of $D = 1.2$. We then multiplied n = 64 by $D = 1.2$, which yielded the minimal number of

participants in the data analysis: n = 77 per arm. Assuming an attrition proportion of 30% which is more conservative than a previous similar study (26%),[102] the sample size for enrolment was set as 110 per arm, or 220 in total.

Statistical analysis

A detailed statistical analysis plan will be developed by a statistician who is blinded to the patient allocation prior to data analysis. Baseline data description and main analyses will be conducted on an intention-to-treat basis; that is, participants' data will be handled according to their initially assigned arms, regardless of the actual received treatment. Analyses will be conducted with a significance level of 5% in the two-sided test, using Stata/SE 16.1.

Consideration for correlated outcome data

The correlation within sites for the control arm will be ignored, as the TAU within one site varies per patient and some participants may not receive any treatment. For the intervention arm, the correlation within each Indo-DARPP group due to the nature of group therapy needs to be considered. We define a new variable termed 'clustering group identification' (CID), in which the control arm will be coded as a unique CID for each person, while the intervention arm will be coded based on the tele-Indo-DARPP group, hence assigning the same CID for all five participants.

Main analysis

The primary endpoint has been set at T2. The mean of the outcome changes from T1 to T2 will be compared between the intervention and control arms using a linear model. To investigate the durability of the treatment effect, outcome changes from T1 to T3 and T4 will also be compared between the two arms. We will account for the aforementioned correlations by clustering data

based on CID in the generalised estimation equations (GEE). To help interpret the effect size, Cohen's *d* between the arms will be calculated.

Missing values

A complete case analysis will be performed, which will only include participants with no missing values in the variables of interest. Sensitivity analysis for missing values will be conducted by either inverse probability-weighted GEE[103] or multiple imputation.

Subgroup analysis

Effects of the intervention will be investigated by subgroups, as the observed effect may vary depending on the specific population. Participants will be divided by the types of primarily used substance, gender, previous and current utilisation of other SUD treatment, high and low values in clinical characteristics at T1 (for example, percent days of abstinence, ASI drug use composite score, URICA readiness score, and cognitive function. Specifically, based on previous studies which showed that treatment effectiveness varied depending on baseline severity levels [104,105], we hypothesised that participants assigned to tele-Indo-DARPP with more severe levels of substance use at T1 would report more increase in days of abstinence at T2, T3, and T4.

Implementation evaluation

Chi-squared tests and *t*-tests will be performed to compare retention in treatment and treatment satisfaction between the arms, exclusively for participants who are already receiving SUD treatment at T1. Group cohesion and Indo-DARPP attendance will be descriptively reported by means and standard deviations. For cost-effectiveness analysis, the incremental cost-effectiveness ratios (ICERs) will be calculated, which will yield costs per QALY and abstinent year. Feedback interviews will be transcribed, and thematic analysis will be conducted.

Compensations

Participants in both the control and intervention groups will receive 300,000 IDR (~ 21.3 USD) to compensate for their transportation to treatment sites for TAU throughout the 12 weeks, and 98,000 IDR (≈ 7.0 USD) every time they completed an online video assessment as compensation for internet data and 2-hour data collection. Participants from the intervention group will further receive internet mobile data equivalent to 50,000 IDR (≈ 3.5 USD) before the first session of tele-Indo-DARPP, and subsequently every time they attend four sessions of tele-Indo-DARPP. For providers, compensation of 170,000 IDR (≈ 12.1 USD) and 150,000 IDR (≈ 10.7 USD) will be provided for each tele-Indo-DARPP session to the facilitator and co-facilitator, respectively.

Data monitoring

Data on adverse events, including hospitalisation, arrest, and death, will be collected from the participants' treating psychiatrists or medical staff. In addition, participants will be interviewed at T2 to determine whether they have experienced any subjective harmful effects (e.g. withdrawal syndrome, increased cravings) after joining Indo-DARPP. An independent data monitoring committee will not be convened, as the study involves short-term, non-invasive psychotherapeutic intervention. No interim analysis was planned due to the short duration of the intervention. Completeness and accuracy of data collection will be checked by Japanese co-investigators, and there will be no auditing process by independent investigators.

Data publication

The results of the study will be published in scientific publications and reported to relevant government bodies in Indonesia to advocate adopting the treatment module.

Ethical consideration and dissemination

The study protocol was approved by the Research Ethical Committee of Faculty of Medicine, Universitas Indonesia (approval number: KET-1175/2019) and the Ethics Committee of the Graduate School and Faculty of Medicine, Kyoto University (approval number: C1483). The study protocol was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) (registry number: UMIN000042186).

The consent process will be conducted carefully to ensure that all potential participants fully understand the research objectives, procedures, risks, benefits, costs, and alternatives. It will be emphasised that study participation is voluntary, and consent can be withdrawn at any time before publication. We will allocate participants to treatment arms only when written informed consent for participation is obtained. Likewise, urine specimens will only be collected if written informed consent for urine collection is obtained. Participants will not be influenced when deciding on study participation and/or urine collection. Personal data will be protected by separating the study data from the participants' identifiable information. To quickly respond to adverse events arising when outpatient visits are not possible, a dedicated phone number and WhatsApp account for the study will be opened to ease communication with the research team. Participants will be instructed to text or call when experiencing adverse events. Importantly, written agreement will be obtained from participants to never share others' information with any third party. This regulation will be enforced both during and outside tele-Indo-DARPP sessions, in any medium, including video conference and group chat.

The results of this study will be disseminated via peer-reviewed journals and international academic conferences. Depending on trial outcomes, Indo-DARPP will be advocated to the Indonesian government for adoption as a nationwide formal treatment program.

Patient and public involvement

Patient feedback during the pilot study was incorporated into the Indo-DARPP module design. In addition, patients and/or the public will not be involved in conducting, reporting, or disseminating this study.

Discussion

Till the time of writing, nine RCTs from LMICs had reported the effectiveness of digital delivery of interventions for SUD. The utilised formats were telephone calls,[106–109] webpages,[110–112] and mobile applications.[100,113] However, no study in LMICs has so far investigated the effectiveness of video conference-based psychotherapy. The latter may facilitate honest, interactive discussions on personal substance use and cravings, founded on better rapport between providers and patients,[114] all of which are integral to CBT for SUD. One meta-analysis concluded that web-based mental health interventions had better retention rates and treatment outcomes when therapists were synchronously involved.[115]

This study has several strengths. This will be the first RCT to investigate the effectiveness of video conference-based psychotherapy in any LMIC, as well as the first study to establish quality evidence on psychotherapy for SUD in Indonesia. Recruitment will be done throughout multiple levels of care, that is, tertiary (referral hospitals), primary (Puskesmas), and community

(rehabilitation centres). The latter have extensive reach encompassing all major Indonesian islands, and social media advertising will facilitate recruitment across the nation. While effectiveness of CBT is the primary outcome, the study allows examinations of real-world implementation and cost-effectiveness in a hybrid effectiveness-implementation design.[64] This is particularly true in Puskesmas, where the providers will be general practitioners, and in rehabilitation centres, where the providers will be peer counsellors. This pragmatic RCT aims to mimic usual clinical practice, and we hope that the results may be used to inform decision-making by patients, providers, and policymakers.[116]

This study has several limitations. All data from participants will be self-reported and prone to recall and social desirability bias. Urine tests will be performed to corroborate subjective data, but will not constitute a full validation as they will only be performed once to represent substance-detectable period. This was planned only at T2 to improve feasibility for participants and reduce the risk of drop-outs. Control conditions will be heterogeneous, as the study will include participants who use various substances at multiple sites, where TAU differs or may not even be provided. Variability in the providers' background may create inconsistency in CBT delivery, even though training and treatment manuals will be introduced to standardise care. Treatment delivery via online video-conferencing might have poor generalisability towards people with low Internet literacy, as well as people in low socio-economic strata who cannot afford smartphones, although entry-level Android-based smartphones (less than 100 USD) are available nationwide in Indonesia. Psychotherapy will be provided in Bahasa Indonesia; hence its effectiveness would not be generalisable to people with limited proficiency in the language.

Efforts to establish evidence-based treatment for SUD should be scaled up in Indonesia and LMICs in general, where effectiveness data are sparse. The proposed study may present high-

quality evidence, and a successful outcome may result in a new SUD treatment module in Indonesia, paving the way for the adoption of Indo-DARPP into the national guidelines. We hope that our efforts may further promote a comprehensive healthcare approach, as opposed to repressive anti-drug policies, for the SUD population.

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Author contributions

CY, KS, and YO conceptualised the study. CY, KS, EH, and YO are the main developers of the Indo-DARPP module, designed study methodology, liaised with site investigators, trained the providers, wrote the protocol, and reviewed and edited the final manuscript. EB, VR, PA, and AP helped in module development, study design, training of providers, and site coordination. TS provided statistical and epidemiological supervision. TM provided the original SMARPP module, clinical input, and perspectives to improve study quality. RS supervised the study and provided grant support. CY and RS were the principal investigators of the grant. All authors have read and approved the final manuscript.

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Competing interests

The authors declare no competing interest.

Patient consent for publication

Not required.

Ethics approval and trial registration

This study protocol was approved by the Research Ethical Committee of the Faculty of Medicine, Universitas Indonesia (approval number: KET-1175/2019) and the Ethics Committee of the Graduate School and Faculty of Medicine, Kyoto University (approval number: C1483). The study protocol was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) (registry number: UMIN000042186).

Availability of data and materials

The full protocol and datasets of the planned study will be available from the corresponding author upon reasonable request.

Figure legends

Figure 1. Study flowchart for each site. A total of 20 or 30 participants will be recruited through the social network of each site. After 10 participants have been recruited to constitute one wave,

they will be randomly allocated into two arms: intervention (Indo-DARPP + TAU) and control (TAU only), with 5 participants in each arm. Recruitment will be continued until another 10 or 20 participants (second or third wave) join, in a similar procedure. Treatment period will be 12 weeks. Assessments will be conducted four times: T1 (Week 0) during baseline or before randomisation, T2 (Week 13-16) during post-assessment or 1-4 weeks after treatment period ends, T3 (Week 24) at 3 months after treatment ends, and T4 (Week 60) at 12 months after treatment ends.

Figure 2. Planned trial schedule across all 8 research sites. Staggered schedules were designed to spread the assessment workload of providers and research staff. After training the providers, all sites will be given approximately 1-2 months to recruit participants. Sites with relatively higher potential to recruit faster, i.e., those with higher rates of patient turnover, have been selected first in the schedule. Each site will have two or three waves of recruitment and treatment periods.

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Table 1. Recruitment sites in this study

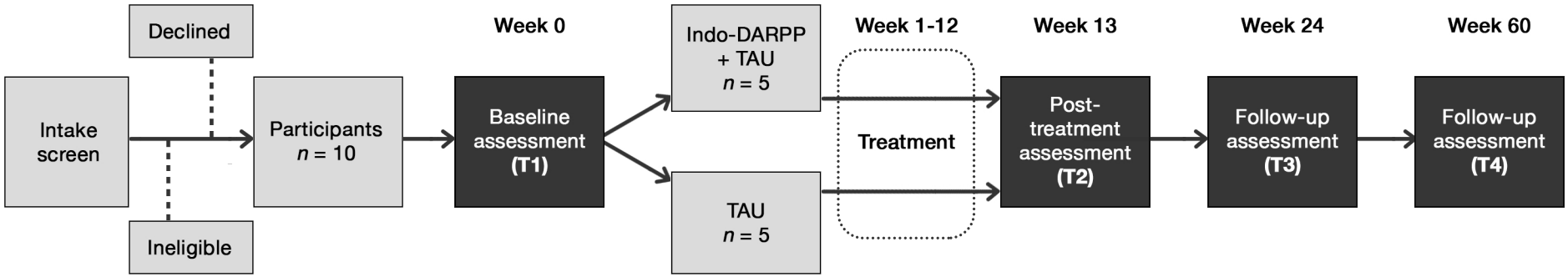
Name	Location	Type	Treatment as usual	Most report
Cipto Mangunkusumo Hospital	Jakarta	Tertiary national general hospital	Individual psychotherapy, symptomatic pharmacotherapy	Benzodiazep
Aceh Mental Hospital	Aceh	Tertiary provincial mental hospital	Individual psychotherapy, symptomatic pharmacotherapy	Methamphet
Duren Sawit Regional Hospital	Jakarta	Tertiary regional general hospital	Individual psychotherapy, symptomatic pharmacotherapy, opioid substitution therapy (buprenorphine, naloxone)	Opioid
Karisma Foundation	Jakarta	Rehabilitation centre	Individual and group peer counselling	Methamphet
Kapeta Foundation	Banten	Rehabilitation centre	Individual and group peer counselling	Methamphet cannabinoids
Kios Atma Jaya	Jakarta	Rehabilitation centre and regional HIV clinic	Individual psychotherapy, group peer counselling, outreach program	Opioid
Puskesmas Jatinegara	Jakarta	Primary health care	Counselling, symptomatic pharmacotherapy, methadone maintenance therapy	Heroin
Puskesmas Gambir	Jakarta	Primary health care	Counselling, symptomatic pharmacotherapy, methadone maintenance therapy	Heroin

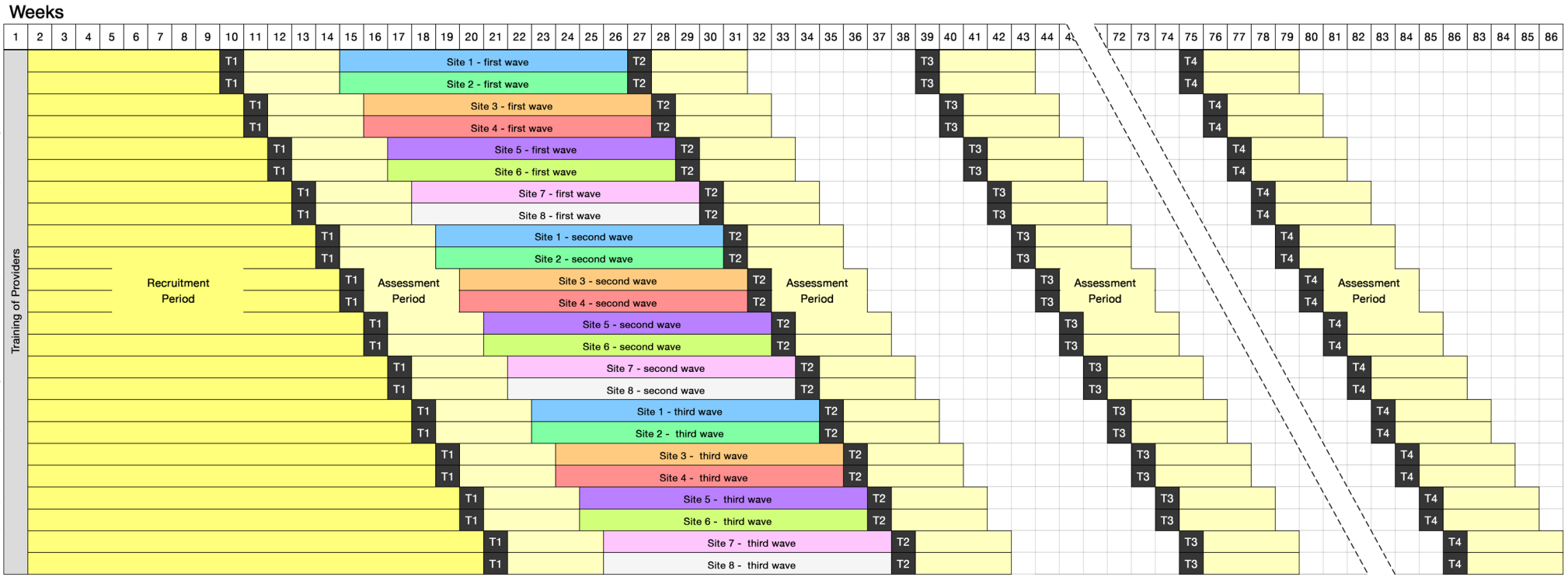
Counselling focuses on education and giving advice.
Symptomatic pharmacotherapy gives medication for helping patients with specific psychopathologies.
Psychotherapy aims to help a person identify and change their emotions, thoughts, and behaviour.

Table 2. Outcome and measurement

Outcome	Measurement	Data for analysis	Type and score range	Hypothesis for intervention (vs control)	Assessment time point			
					T1	T2	T3	T4
Primary outcome								
Abstinence from primary substance	Timeline followback (TLFB) for the past 28 days	Number of days being abstinent from primary substance divided by 28 (%).	Continuous, 0 (no use) to 100 (used every day).	Higher	✓	✓[a]	✓	✓
Secondary outcomes								
Addiction severity	Addiction Severity Index (ASI)	7 composite scores: medical, employment, alcohol use, drug use, legal, family/social, and psychiatric status. Each composite score calculated using standard formula.	Continuous, 0 (no problems) to 1 (severe problems).	Lower	✓	✓	✓	✓
Health-related quality of life	EuroQol-5D (EQ-5D-5L)	Health utility score, calculated from 5 items on mobility, self-care, usual activities, pain/discomfort and anxiety/depression, using Indonesian value set.	Continuous, -0.865 (impaired health) to 1 (full health).	Higher	✓	✓	✓	✓
Motivation to change	University of Rhode Island Change Assessment (URICA)	Action stage subscale, sum of 8 items.	Continuous, 8 (not active in behavioural change) to 40 (highly active in behavioural change).	Higher	✓	✓	✓	✓
Coping	Brief-Coping Orientation to Problems Experienced (Brief COPE)	Sum of substance use coping (2 items)	Continuous, 2 (low substance use coping) to 8 (high substance use coping)	Lower	✓	✓	✓	✓
Psychiatric symptoms	Symptom Checklist-90 Revised (SCL-90-R)	Global Severity Index (GSI), average of 90 items.	Continuous, 0 (no symptoms) to 4 (severe symptoms).	Lower	✓	✓	✓	✓
Cognitive function	Rey Auditory Verbal Learning Test (RAVLT)	3 test results; immediate, learning, and recalling.	Continuous, 0 (low functioning) to 15 (high functioning).	Higher	✓	✓	✓	✓
Internalised stigma	Internalized Stigma of Mental Illness (ISMI)	Sum of 4 subscales: alienation, stereotype endorsement, social withdrawal, and stigma resistances.	Continuous, 24 (low internalised stigma) to 96 (high internalised stigma)	Lower	✓	✓	✓	✓
Implementation outcomes								
Retention in treatment	Self-reporting for the past 3 months	Coded as 'retained' if they had therapeutic contacts in at least 75% of the planned number of therapeutic contacts.	Categorical, 'retained' = 1, 'not retained' = 0.	More 'retained'		✓	✓	✓
Treatment satisfaction	Client Satisfaction Questionnaire-3 (CSQ-3)	Sum of 3 items.	Continuous, 4 (not satisfied) to 12 (satisfied).	Higher		✓		
Group cohesion	Group Therapy Experience Scale (GTES)	Sum of 16 items.	Continuous, 16 (poor cohesion) to 80 (great cohesion).	Not applicable: measured only in intervention arm		✓		

[a] Objective validation by urine drug test for 8 substances: alcohol, amphetamine, morphine, cannabinoids, methamphetamine, benzodiazepine, cocaine, synthetic cannabinoids


Declined
Intake screen
Ineligible
Participants n = 10
Week 0
Baseline assessment (T1)
Indo-DARPP + TAU n = 5
TAU n = 5
Week 1-12
Treatment
Week 13
Post-treatment assessment (T2)
Week 24
Follow-up assessment (T3)
Week 60
Follow-up assessment (T4)


Weeks
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 33 34 35 36 37 38 39 40 41 42 43 44 45 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 83 84 85 86
Training of Providers
Recruitment Period
Assessment Period
Assessment Period
Assessment Period
Assessment Period
Site 1 - first wave
Site 2 - first wave
Site 3 - first wave
Site 4 - first wave
Site 5 - first wave
Site 6 - first wave
Site 7 - first wave
Site 8 - first wave
Site 1 - second wave
Site 2 - second wave
Site 3 - second wave
Site 4 - second wave
Site 5 - second wave
Site 6 - second wave
Site 7 - second wave
Site 8 - second wave
Site 1 - third wave
Site 2 - third wave
Site 3 - third wave
Site 4 - third wave
Site 5 - third wave
Site 6 - third wave
Site 7 - third wave
Site 8 - third wave
T1
T2
T3
T4

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4, 23
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a, trial already registered as described in 2a.
Protocol version	#3	Date and version identifier	23
Funding	#4	Sources and types of financial, material, and other support	26-27
Roles and	#5a	Names, affiliations, and roles of protocol	26

responsibilities: contributorship		contributors	
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a, no trial sponsor.
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a, no involvement of funders in the study design.
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a, no direct intervention in the study design by the host universities.
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-9
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	15
Objectives	#7	Specific objectives or hypotheses	9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9-10

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10-11
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	22-23
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	22-23
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	15
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome.	15-19

		Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10, 19, 26
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	20
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Allocation:	#16c	Who will generate the allocation sequence,	12

implementation		who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12, 19
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a, only assessors are blinded
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-19
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	19, 22-23
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the	23

		protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	20-22
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21-22
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	23, DMC will not be convened as the intervention involves a short-term psychotherapy with known minimal risk.
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	23, interim analysis is not planned due to the short duration of intervention.
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	22-23
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	23, there will be no auditing process by independent investigators.

Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	23, 28
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	23
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	23
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	23
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	23
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	27
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	28
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15, CBT intervention will be made available for control group after the end of the study.

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	23
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	26-27
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	28
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	11, 23
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	16

Notes:

- 2b: n/a, trial already registered as described in 2a.
- 5b: n/a, no trial sponsor.
- 5c: n/a, no involvement of funders in the study design.
- 5d: n/a, no direct intervention in the study design by the host universities.
- 17b: n/a, only assessors are blinded
- 21a: 23, DMC will not be convened as the intervention involves a short-term psychotherapy with known minimal risk.
- 21b: 23, interim analysis is not planned due to the short duration of intervention.

- 23: 23, there will be no auditing process by independent investigators.
- 30: 15, CBT intervention will be made available for control group after the end of the study. The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 15. February 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

Supplementary file 2

Research Participation Consent Form

Title of the Research:

Effectiveness of a cognitive behavioral therapy for drug use disorders in Indonesia: A randomized controlled trial

(Collaboration research between the Faculty of Medicine, University of Indonesia and Kyoto University)

An explanation has been given which includes the following discussion :

1. Research Title
2. Research Clearance
3. Research institutes and researchers
4. Research purposes
5. Research procedure
6. Research period
7. Inclusion Criteria
8. Risks, benefits, and side effects
9. Right to refuse and drop out
10. Voluntary participation and risk of involvement
11. Research data publication
12. How to access research-related materials for participants
13. Privacy of personal data
14. Research data storage
15. Research funds and conflicts of interest
16. Researcher contact list
17. Remuneration for participants
18. General management of drug addiction patients outside of research interventions
19. Follow up management after the research ends
20. Report of the participant's genetic information
21. Compensation for illness related to research and invasive procedures
22. Secondary research data for other institutions
23. Samples and participant information related to invasive procedures
24. Name, position, and affiliation of the person in charge of managing data and information related to research
25. CBT group participant commitments and drop out possibility of research participation

Explanations have been given according to the explanation sheet, and consent has been obtained voluntarily.

Date of consent : _____ / _____ / 20 ___

Researcher's affiliation : _____

Researcher's Name :

Researcher's Signature :

Acknowledged by:

1. Dean of the Faculty Medicine, University Indonesia
2. Director of the *Center for South East Asian Studies, Kyoto University*

Supplementary file 2

CBT-Group Participation Consent Form

I, the undersigned, hereby acknowledge, consent and agree to fulfill the following matters during my participation in CBT group therapy, in order to ensure the safe and secure continuation of the program:

1. I will not divulge information about other participants in the group to external parties without the consent of the parties concerned.
2. I will not record audio, video, or take camera pictures without the permission of the parties concerned and the research team.
3. I will not use drugs during the CBT session.
4. I will not divulge links (URL), ID, and passwords for online meetings in the Zoom application to external parties, without the approval of the research team.
5. I will not harass, say offensive words related to ethnicity,religion and race, or commit acts of violence for any reason to any party related to the research, whether other participants or the research team.

If I infringe the points of the agreement above, I will be given 1 (one) warning. If I do not show any improvement after being warned, or infringe it for the second time, or it is deemed that my participation will interfere with the continuation of CBT therapy in the future, I have no objection to my participation being unilaterally terminated.

I, the undersigned, hereby declare that I have understood the explanation given and agree to my participation in the research mentioned above.in my behavior after being warned, or infringe it for the second time, or it is deemed that my participation will interfere with the continuation of CBT therapy in the future, I have no objection to my participation being unilaterally terminated.

Date of Consent : ____ / _____ / 20 ___

Name : _____

Signature : _____

Supplementary file 2

Urine Test Informed Consent

Title of Research:

Effectiveness of a cognitive behavioral therapy for drug use disorders in Indonesia: A randomized controlled trial

(Collaboration research between the Faculty of Medicine, University of Indonesia and Kyoto University)

An explanation has been given which includes the following discussion:
1. Purpose of the urine sampling
2. Urine test procedure
3. Analysis of urine test results data and maintaining data confidentiality

Explanations have been given according to the explanation sheet, and consent has been obtained voluntarily.

I, the undersigned, declare that I

Agree / do not agree

*please circle one of these options above

…to provide the urine sample to be tested for the research team, and I have acknowledged and understood the purposes, procedures and data analysis as described previously.

Date of consent : ____ / _____ / 20 ___

Name : _____

Signature : _____

Supplementary file 2

Withdrawal of Informed Consent for Urine Test

Title of the research:

Effectiveness of a cognitive behavioral therapy for drug use disorders in Indonesia: A randomized controlled trial

(Collaboration research between the Faculty of Medicine, University of Indonesia and Kyoto University)

I,the undersigned,hereby wish to withdraw my prior consent to participate in the urinary test for this research by signing this form.

Withdrawal Date : ____ / _____ / 20___

Participant's Name : _____

Participant's Signature : _____

Supplementary file 3

Table of contents of Indo-DARPP (English translation)