STATISTICAL ANALYSIS PLAN

Re-Frame: Randomised Controlled Efficacy Trial of a Diversion Programme for Adolescents in Police Custody who Possess Controlled Drugs

University of Kent

Principal investigator: Professor Simon Coulton

YOUTH ENDOWMENT FUND

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Statistical analysis plan

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Project title[1]	Re-Frame: Randomised Controlled Efficacy Trial of a Diversion Programme for Adolescents in Police Custody who Possess Controlled Drugs
Developer (Institution)	With You
Evaluator (Institution)	University of Kent
Principal investigator(s)	Professor Simon Coulton
SAP author(s)	Professor Simon Coulton
Trial design	Two arm, prospective, individually randomised efficacy trial
Trial type	Efficacy
Evaluation setting	Community
Target group	Young people aged 10-17 years inclusive in police custody and in possession of class B or C controlled drugs

Number of participants	370 young people
Primary outcome and data source	Number of offences in the 6 months post-randomisation derived from the Local Police Database (LPD)
Secondary outcome and data source	Self-Reported Delinquency (SRDS), emotional regulation (SDQ), frequency of substance use TLFB, Situational Confidence (SCQ), Motivation to change behaviour (RR), negative and positive expectancy (SUES)

SAP version history

Version	Date	Changes made and reason for revision
1.0	13/03/23	
1.1	08/02/24	Revision to numbers recruited reduced from 438 to 370 Addition of regression equation Addition of method to derive effect size

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Introduction

The trial is a mixed methods prospective, individually randomised efficacy trial with equal probability of being allocated to one of two arms, the Reframe intervention or business as usual.

A pilot evaluation of the Reframe intervention was conducted and recruited 76 participants. In the pilot evaluation we set several a priori parameters that would indicate whether an efficacy study was feasible.

Table 1: Pilot trial progression criteria (green go, amber review, red stop).

Criteria			
Proportion referred who are eligible	70%	50%	40%
Proportion eligible who consent	70%	50%	40%
Proportion eligible who adhere	80%	60%	40%
Proportion followed-up (secondary)	80%	70%	60%

All these criteria were met; 93% of those referred were eligible, 80% of these consented, 92% adhered to all the intervention, 88% were followed-up at month 6, the primary endpoint, and the primary outcome was available for 100% of participants.

The qualitative analysis found the intervention was considered acceptable to all stakeholders, young people, interventionists, and the police. The qualitative analysis found no substantial hindrances to the implementation of the Reframe intervention, but it did highlight some areas where improvements to referral processes could be made. These included raising awareness within the police and streamlining referral pathways.

Interventions

Participants were assessed for initial eligibility by police custody staff. Inclusion criteria included being aged 10-17 years inclusive and being found in possession of class B or C controlled drugs. Young people were excluded if they had been arrested for a sexual or serious violent offence, had a history of four or more previous offences, were in possession of a Class A substance or who had a substance severity that required specialist clinical intervention such as detoxification or medically assisted maintenance. All eligible participants were referred to we Are With You using a secure email system.

Staff at *With You* established whether potential participants were interested in participating in the trial and if they were they provided a paper or email copy of the information sheet and passed their contact details to the trial research staff. Trial research staff contacted the young person and checked they understood the information sheet and answered any queries. If the young person was considered Gillick competent full signed consent was taken. If a young person was not considered Gillick competent signed assent was taken from the young person and formal consent taken from a primary carer.

Immediately after consent the young person completed the baseline outcome measures and was immediately randomised using a remote, independent secure randomisation service to business as usual or intervention. We are with you were informed of the allocation and delivered the treatment.

Intervention Group

Two sessions of Brief Intervention by skilled youth workers. In session one, young people will use a Drug Grid to reflect on how their actions have affected their lives, their family and wider community. The child will have the opportunity to recall their arrest experience and explain how this impacted them. The practitioner will assist the young person in critically reflecting on this event and offer support in relation to trauma or consequences they may feel.

The Drug Grid is a drug education exercise that enables the child to demonstrate current understanding of substances (including medication, legal highs, and image and performance enhancing drugs). As they go through the exercise they will learn about these substances (e.g., depressant or hallucinogen), being led by their own experience and building on their knowledge base. The worker can dispel myths and provide information on the effects of each substance, including the risks of poly use and overdose.

Brief intervention session two is the Drug Triangle delivered one week after session one. Using the Drug Triangle, the child will focus on the substance, mindset and setting that led them to the session. This holistic harm reduction approach ties in with contextual safeguarding, framing the child's situation within a wider context. They will spend time thinking about how this has affected them, their family, school (if applicable), and community. The child will also be encouraged to reflect on the impact on those people and communities that produce drugs. At the end of the session the participant will be advised around their rights in relation to stop and search procedures should they require it in the future as well as assertion techniques and advice relating to the procedure itself.

At the end of the two sessions the young person will have greater clarity about the risks they have taken, the links between substance use, risk-taking behaviour and violent offending and

the potential of criminal proceedings. The short-term aims are that the child will have a greater understanding of their personal needs, increase in confidence to reduce substance use, and a positive shift from precontemplation to action and maintenance in the cycle of change.

Control Group

The young person will receive one session of Advice, Information and Signposting. The child will be offered information about the *With You* substance misuse service in their local area and encouraged to access the service for support if required. Advice, Information and Signposting is a tier 1, universal level of support. It is unstructured and is based on a conversation only.

Design overview

Please ensure all details are in line with the latest version of the protocol.

Trial design, including number of arms		Two arm individually randomised trial
Unit of randomisation		Participant
Stratification variables (if applicable)		Site (Kent, Cornwall, Sefton, Wigan); Age group (10-14, 15-17 years)
Primary outcome	variable	All offences 6 months post-randomisation
	measure (instrument, scale, source)	Local Police Database (LPD)
Secondary outcome(s)	variable(s)	Self-reported offences, emotional regulation, substance use frequency, psychological health and well-being, situational confidence, readiness to change, expectancies.
	measure(s) (instrument, scale, source)	Self-Report Delinquency Scale (SRDS), Strengths and Difficulties Questionnaire (SDQ), Timeline Follow-Back (TLFB28), Warwick-Edinburgh Mental Well-being Scale (WEMWBS), Short Situational Confidence Questionnaire (SCQ-8), Readiness to Change Ruler (RR), Substance Use Expectancy Scale (SUE) at 6 months post-randomisation.
	variable	All offences in 6-months pre-randomisation

Baseline for primary outcome	measure (instrument, scale, source)	Local Police Database (LPD)
Baseline for secondary outcome	**variable**	Self-reported offences, emotional regulation, substance use frequency, psychological health and well-being, situational confidence, readiness to change, expectancies.
	measure (instrument, scale, source)	Self-Report Delinquency Scale (SRDS), Strengths and Difficulties Questionnaire (SDQ), Timeline Follow-Back (TLFB28), Warwick-Edinburgh Mental Well-being Scale (WEMWBS), Short Situational Confidence Questionnaire (SCQ-8), Readiness to Change Ruler (RR), Substance Use Expectancy Scale (SUE) at baseline.

Sample size calculations overview

		Protocol
Minimum Detectable Effect Size (MDES)		0.3
Alpha[2]		0.05
Power		0.8
One-sided or two-sided?		Two-sided
Number of participants	intervention	185
	control	185
	total	370

Sample size calculations were derived using STATA v16. In calculating the sample size, we have used an effect size difference of 0.3, similar to other studies addressing substance use in adolescents (Coulton et al., 2017), which equates to a number needed to treat (NNT) of 6, where delivering the intervention to six young people will result in important reduction in offences in at least one (Furukawa and Leucht, 2011). This equates to a small to medium effect size and any smaller is unlikely to be a meaningful effect on the primary outcome. To detect this effect size, or greater, with 80% power, alpha of 0.05 and a two-sided test requires 350 participants followed-up at 6-months. As the primary outcome is sourced independent of the participant, we expect the follow-up rate at month 6 to be 100. This inflates the required sample to 370, 185 in each group. This number is also sufficient to detect a small to medium effect size difference in the frequency of substance use. In our pilot study the consent rate was quite high, about 80% and the eligibility rate was 88%. In our pilot study we successfully recruited 76 young people, leaving 294 to recruit in the efficacy study. We expect to approach 502 participants over the 12-month recruitment period, just over two per police force per week.

Randomisation and blinding

Individual participants will be randomised according to a schedule provided by Sealed Envelope Ltd, an independent secure health research provider. Allocation strings are developed, encrypted and embedded within a third-party allocation programme. Random permuted blocks of varied length will be used, stratified by site (each site where trial participants are recruited) and age group (10-14; 15-17 years inclusive). Baseline measures will be recorded prior to randomisation and researchers will not be blind to individual randomisation assignment at the 6-month follow-up assessment.

Data quality and management

Methods for generation of trial data will be governed by a trial protocol and will only be undertaken after gaining ethical approval, and statistical analysis governed by an explicit data analysis plan. The PI and members of the research team will be responsible for data verification, validation and quality assurance of data collected.

Only authorised members of the research team will have access to the study data. Personal administrative data will only be processed for the purpose of participant identification and follow-up and will be stored separately from outcome data. All data will be collected after the consent of participants has been obtained and before randomisation and governed by research ethics. All written records will be stored in a secured locked cabinet.

Primary and secondary outcome measures will be captured electronically at the time of data collection. Range and validity checks are integrated into the data capture software and outlying values flagged as invalid at the time of entry. Any data not captured electronically will be subject to double data entry by two independent members of staff. The two entries will be compared, and any discrepancies resolved using the source documents. These data will also be subject to range and validity checks. Data will be linked using a unique anonymised identifier. Audit features will allow for an audit trail to be established for all data entered and modified, including who accessed the data, when and for what purpose.

Data sets will be reviewed for completeness and systematic missing data. The methods detailed in the Statistical Analysis Plan (SAP) will be applied to a clean and validated dataset, following resolution of data queries and database lock. The database will be locked after data validation and quality assurance of the 6-month outcomes has been complete. Data lock will be achieved using a unique encryption key available only to the trial manager and chief investigator. A duplicate dataset, anonymised dataset with allocation blind will be generated for analysis. Unblinding of allocation group will only occur after analysis has been complete and agreed by the research team.

Analysis

The analysis plan was developed a priori before randomisation commenced and all analysis is conducted using STATA 16 SE. In the overall analysis, data from the internal pilot and efficacy study will be combined and analysed blind to group allocation. The efficacy analysis will be conducted and presented in accordance with the CONSORT guidelines (Schulz et al., 2010). The validity of randomisation will be explored by presenting measures of central tendency and estimates of precision for continuous variables, and proportions for categorical variables broken down by allocation arm and stratification factors.

Primary outcome analysis

The primary analysis will be based on the analysis by treatment allocated (ITT) dataset.

This contains all available data for participants who were randomised, regardless of whether they complied with allocation. This dataset will include participants who were withdrawn/withdrew from the trial post-randomisation. These analyses are a lower bound estimate of treatment effects as they represent the effect of offering an intervention, rather than the effect of receiving the intervention.

The primary outcome is the frequency of offences at 6-months post-randomisation. Prior to analysis we will conduct a series of diagnostic tests and assess the underlying assumptions prior to choosing an appropriate and statistically rigorous regression modelling approach. At this stage we propose an Ordinal Least Squares (OLS) regression approach.

Regression models will be adjusted by the baseline number of offences in the six months prior to randomisation and stratification factors; age group and site, as covariates. The regression model specification is detailed in eq. 1.

Eq. 1

$$OFF6_{i,j} = \alpha + \beta_1(allocation)_{i,j} + \beta_2(OFF0)_{i,j} + \beta_3(age)_{i,j} + \beta_4(site)_j + \beta_4(study)_j\ \varepsilon_i$$

Where for participant i within service j; $OFF6$ is the number of offences at month-6, $allocation$ is the allocated group, $OFF0$ is the number of offences in the 6-months prior to baseline score, age the age group (10-14 years/ 15-17 years) , $site$ the site level dummy variables to adjust for site (Kent/ Cornwall/ Sefton/ Lancashire) fixed effects and $study$ the study level (pilot/ efficacy) dummy variable to adjust for study fixed effects and ε_i the individual level error.

Estimates of difference will be generated as a mean difference between the groups and the associated 95% confidence interval.

Secondary outcome analysis

Secondary outcome analysis will be based on the ITT dataset and will be similar to the analysis of the primary outcome. Diagnostic plots for each outcome will be derived and examined to identify the most appropriate regression approach. Where appropriate linear analysis of covariance will be undertaken for continuous normally distributed outcomes, logistic regression with incorporation of covariates for dichotomous variables and fractional covariate regression for proportional outcomes. Covariates will include baseline values for each outcome and stratification factors, site and age group.

Further analyses

Three exploratory analyses will be undertaken.

The mechanism of change will be explored using a mediation model approach and incorporating motivation (RR), self-efficacy (SCQ-8), and expectancy (SUE) at 6-months, adjusted for baseline covariates. Allocated group will be included as an interaction term.

Stepwise regression analysis will be performed to model the relationship between pre-randomisation factors; age, gender, ethnicity, IMD, BFRS, ACEQ, GAD-7, PHQ-9 and observed outcomes at 6 months, separately for the primary outcome and PDA substance use. Interaction terms with allocation arm will be included in the analysis, and a significance level of 0.1 will be used to determine which factors are to be included in the regression model. Pre-randomisation factors will include gender, age, ethnicity, IMD decile, adverse childhood experiences, anxiety and depression and family cohesion. This analysis will be augmented by

an additional analysis including participants in the intervention arm only using the same pre-randomisation factors but also including process measures of adherence, intervention fidelity, therapeutic alliance, interventionist, and interventionist perceptions.

Interim analyses and stopping rules

No interim analyses are planned.

Longitudinal follow-up analyses

Assessments are conducted at baseline and then at six months post-randomisation, the latter being the primary endpoint. Table 2, indicates outcomes assessed at each end-point.

Proposed outcomes at each stage of the evaluation

Outcome	No. of Questions	Baseline	Month 6
Frequency of substance use (Single TLFB item)	1	✓	
Time Line Follow-Back 28-day version[1]	0		✓
Wellbeing (WEBWMS)	14	✓	✓
Quality of Life (EQ5D-5L)	5	✓	✓
Strength & Difficulties (SDQ[2])	25	✓	✓
Self-report Delinquency (SRDS[1,2])		✓	✓
Motivation state to change (RR)	1	✓	✓
Substance Use Expectancy (SUE)	4	✓	✓
Self-efficacy (SCQ-8)	8	✓	✓
Generalised Anxiety Scale (GAD-7)	7	✓	
Depression - Personal Health Questionnaire (PHQ-A)	8	✓	
Adverse Childhood Experiences (ACEQ)	10	✓	
Brief Family Relationships Questionnaire (BFRS)	16	✓	

[1] TLFB28 and SRDS are researcher led questionnaires rather than client self-completed
[2] SRDS and SDQ are YEF Core outcomes

Imbalance at baseline

Rather than just assume the randomisation has worked, we will assess observed balance by comparing the means and distributions of the groups created by randomisation. If they are systematically different across those variables we observe – e.g. always larger / smaller in one group - then that would suggest the randomisation has not been successfully implemented. Baseline equivalence following randomization will be assessed by first looking at allocation by the two stratifying variables, site and age group, and then extending the comparison by key outcomes, mean offences at baseline and mean days using substances at baseline.

Baseline characteristics will be summarised by randomised group. Summary measures for the baseline characteristics of each group will be presented as mean and standard deviation for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables. Following CONSORT when comparing treatment and control groups we will not use statistical tests.

If there is a large imbalance between groups on a specific variable, then that variable will be included in the analysis model. If there are systematic differences across multiple variables that are indicative of failed randomisation then it would be necessary to explore alternative analysis methods to estimate treatment effects, such as instrumental variable models, using treatment allocation as the IV.

Missing data

The proportion of missing data and patterns of missingness will be examined for the primary outcome. Levels of missing data will be reported along with any systematic occurrences of missing data observed in the dataset.

We will explore the mechanism of missing data to establish whether the data can be considered missing completely at random or missing at random. For each treatment arm, participants will be grouped based on their dropout time, and means at baseline and each time will be examined to assess whether there are systematic differences between those who dropped out at specific time points and those who remained in the study.

To avoid loss of efficiency, missing outcome values will be imputed using multiple imputation for chained equations. This approach will only be undertaken if the proportion of missing data is greater than 5% and less than 40%. Where there is less than 5% missing data, the proportion of missing data is considered negligible and missing observations will be excluded. Multiple imputation methods perform less well when the amount of missing data is substantial, if more than 40% of the primary outcome data are missing the assumptions underlying the primary analysis are less plausible. Data will be analysed without imputation and the interpretative limitations of the trial data will be discussed in the results section.

An imputation model, containing all potential prognostic baseline covariates will be used. The number of imputations will be dependent on the amount of missing data, as a minimum the number of imputations will be derived to ensure at least 96% statistical efficiency (RE) according to the formula below (Eq. 2), where λ is the fraction of missing values and M is the number of repetitions.

Eq. 2

$$RE = \left(1 + \frac{\lambda}{M}\right)^{-1}$$

The statistical model and assumptions made in the analysis of the primary outcome will also be implemented in the multiple imputation procedures. If it is suspected data is missing not at random or the pattern of missing data is associated with trial allocation, sensitivity analysis will be performed using a pattern mixture approach with mixed modelling and multiple imputation to compare the sensitivity of conclusions to varying assumptions about the missing value mechanism. All available data from baseline to the time of dropout will be included in the sensitivity analysis using a repeated measures mixed effects model.

Compliance

The compliance analysis will examine treatment effects under different scenarios for compliance using a Complier Average Causal Effects (CACE) approach. The definition of compliance with allocation for this trial is as follows (see Table 2 below): (i) those attending both sessions will be considered 'compliers' in the intervention group (cell A); (ii) those in the control group who did not receive any intervention (cell D) (it is not possible for control participants to access the intervention). In the intervention group, those attending none, or only one session will be considered non-compliers (cell B). All non-compliers in the intervention group are regarded as being 'contaminated'. For the intervention group, there is no option for control participants to access the intervention, so there cannot be non-compliance hence this is n/a (cell C).

Table 2: Compliance/non-compliance according to group allocation versus intervention received

	Actually received…	
Allocated to… ↓	**Intervention**	**Control**
Intervention	*A. Intervention complier* Both intervention sessions.	*B. Intervention non-complier* Only one session attended.

		No sessions attended.
Control	*C. Control non-complier* n/a	*D. Control complier* Control group participant

We will assess treatment effects in the presence of non-compliance, with compliance measured at the individual level and including all those allocated as part of the trial. Our approach for assessing treatment effects under non-compliance will be via the instrumental variable framework (IV). The benefit of using an IV approach is that randomisation is maintained in the analysis, which is crucial for estimating unbiased treatment effects. In summary, with a binary measure of compliance CACE weights the analysis by treatment allocated (ITT) treatment effect by the proportion of compliers (Eq. 3):

EQ. 3

$$\text{CACE} = \text{ITT} / \text{proportion compliant}$$

If the proportion compliant is 1.0 (i.e. perfect compliance) then the CACE estimate is the same as the ITT estimate, but otherwise the impact of this approach is to increase the magnitude of the treatment effect.

CACE uses a two-stage least squares (2SLS). The first stage model uses *intervention received* (T) as the outcome, with random allocation (Z) as the independent variable (Eq. 4):

EQ. 4

$$T = \alpha + Z$$

Based on the stage 1 model, we then calculate predicted values of treatment received ($\hat{T}$) for use in stage 2. The second stage model predicts the substantive outcome (*Y* e.g. number of offences) using the predicted values of treatment received ($\hat{T}$) based on the stage 1 model (Eq. 4):

EQ. 5

$$Y = \alpha + \hat{T} + \varepsilon$$

Levels of confidence and p-values

Unless otherwise specified, estimates will be presented with 95% confidence intervals. Significance tests will be two-tailed, and a significance level of <0.05 will be considered statistically significant. For continuous variables a mean difference between the groups and associated 95% confidence interval will be derived, for proportional outcomes the mean difference will be derived using a marginal effects approach, for dichotomous outcomes a relative risk and associated 95% confidence interval compared to a reference value will be presented. This study has a predefined primary outcome measure, at a specific time point and involves a single comparison between two treatment arms, therefore no adjustment for multiplicity is required. As participant randomisation is conducted within site no adjustment for site cluster effects, over and above inclusion of site as a fixed effect covariate, is required.

Presentation of outcomes

As the sample is large, effect size differences will be calculated using Cohen's d, specified in the following equation (Eq. 6):

EQ. 6

$$\delta = (Y_i - Y_c)/S$$

Where Y_i and Y_c are the regression adjusted means, derived from Eq. 1, for the intervention and control groups respectively and S is the pooled standard deviation.

Effect sizes will be reported with 95% confidence intervals and p-values to reflect statistical uncertainty.

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YOUTH ENDOWMENT FUND

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