CLINICAL STUDY PROTOCOL

A Randomised, Open-Label, Parallel-Group Study Examining Outcomes of Breaking Free Online Computer-Assisted-Therapy plus Standard Treatment versus Standard Treatment Alone in Participants with Substance Use Disorders: A Telehealth Approach

Short Protocol Title:	**BFO vs Standard Treatment in SUD: Telehealth Model**
Product:	Breaking Free Online www.BreakingFreeOnline.com
Sponsor:	Breaking Free Online Limited Innovation Birmingham Campus Faraday Wharf Holt Street Birmingham B7 4BB Registered in England under company number 07441522 +44 (0) 161 834 4647
ISRCTN reference number:	ISRCTN13694016
REC reference number:	**21/NW/0191**
Protocol Version:	**V2.0**
Protocol Date:	**01st April 2021**

PROTOCOL APPROVAL PAGE (SPONSOR)

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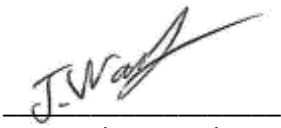
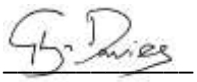
The signatures below constitute approval of this protocol by the signatory and provide the necessary assurance that this study will be conducted according to all stipulations of the protocol.

Dr Sarah Elison-Davies, PhD — 01 April 2021
Chief Investigator (Breaking Free Online) — Date

Lauren Pittard — 01 April 2021
Clinical Trial Coordinator (Breaking Free Online) — Date



Dr Jonathan Ward, — 05 April 2021
Managing Director (Breaking Free Online) — Date



Glyn Davies, — 05 April 2021
Service Development Director (Breaking Free Online) — Date

PROTOCOL ACCEPTANCE FORM (INVESTIGATOR)

Protocol Title:	A Randomised, Open-Label, Parallel-Group Study Examining Outcomes of Breaking Free Online Computer-Assisted-Therapy plus Standard Treatment versus Standard Treatment Alone in Participants with Substance Use Disorders: A Telehealth Approach
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By my signature below, I hereby state that I have read, and agree to abide by, the instructions, conditions, and restrictions of the protocol or protocol amendment referenced above.

_____

Name of Investigator (print)

_____

Name of Investigator (signature) Date

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1. GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
AUD	Alcohol Use Disorder
BCT	Behavioural Change Technique
BFO	Breaking Free Online
CAT	Computer-Assisted Therapy
CBT	Cognitive Behavioural Therapy
CGL	Change Grow Live
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CM	Contingency Management
CSE	Coping Strategy Enhancement
CSEW	Crime Survey for England and Wales
CUD	Cannabis Use Disorder
DSM-V	Diagnostic and Statistical Manual of Mental Disorders 5
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
GCP	Good Clinical Practice
GP	General Practitioner
ICH	International Conference on Harmonization
ISF	Investigator Site File
ITEP	International Treatment Effectiveness Project
ITT	Intention to Treat
LBM	Lifestyle Balance Model
MET	Motivational Enhancement Therapy
MI	Motivational Interviewing
MRC	Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OUD	Opioid Use Disorder

PHQ-4	Patient Health Questionnaire-4
PPE	Personal Protective Equipment
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RPM	Recovery Progression Measure
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDS	Severity of Dependence Scale
SUD	Substance Use Disorder
WHO	World Health Organisation
WHO-QoL	World Health Organisation Quality of Life Scale

2. STUDY SYNOPSIS

Product:	Breaking Free Online (BFO)
Study Title:	A Randomised, Open-Label, Parallel-Group Study Examining Outcomes of Breaking Free Online Computer-Assisted-Therapy plus Standard Treatment versus Standard Treatment Alone in Participants with Substance Use Disorders: A Telehealth Approach
Objectives:	Primary Objective: - To compare the effects of BFO when delivered via a telehealth model as an adjunct to standard treatment versus standard treatment alone on self-reported substance use following treatment completion, and at 3- and 6-months follow-up. Secondary Objectives: - To determine the effect of BFO as an adjunct to standard treatment versus standard treatment alone on the following health outcomes at treatment completion, and at 3- and 6-months follow-up: a) Severity of substance dependence b) Prevalence and severity of concurrent depression and anxiety c) Quality of life d) Biopsychosocial functioning - To assess participant engagement with BFO during the 8 week-treatment period.
Design:	A two-arm, randomised, parallel-group longitudinal study, with standardised psychometric assessments at baseline, after an 8-week treatment period, and 3- and 6-months following treatment completion, of BFO delivered via a telehealth model plus standard treatment versus standard treatment only.
Inclusion Criteria:	1. Aged 18 years or above on the day of consent. 2. Experiencing problem alcohol and/or drug use at time of consent, as determined by Investigator. 3. Problem alcohol or drug use present for ≥ 12 months at time of consent, as self-reported. 4. Willing to comply with an 8-week treatment programme for problem alcohol and/or drug use. 5. Willing to provide outcome measures post-treatment, and at 3- and 6-months follow-up. 6. Able to read, write and communicate in the English language. 7. Able to access an internet enabled device for the duration of the study. 8. Able to access a telephone or video-communication enabled device for the duration of the 8-week treatment period. 9. Willing and able to give informed consent for participation in the study, and capable of understanding and complying with protocol requirements.
Exclusion Criteria:	1. Under 18 years old on the day of consent. 2. Participation in any other alcohol and/or drug related clinical studies within 12 months prior to date of consent. 3. Detention under the Mental Health Act at the time of consent. 4. Clinically significant intellectual or developmental disability which may impair ability to engage with the Breaking Free Online treatment programme and/or complete the necessary assessment measures included in the methodology, as determined by Investigator.

	5. Pregnancy (as self-reported) at the time of consent. 6. Previous use of the Breaking Free Online programme for the purposes of alcohol or drug use intervention.
Treatment groups:	i. BFO programme delivered via telehealth model, plus standard treatment (investigational group). ii. Standard treatment (control group).
Population	Adult service users receiving outpatient treatment for substance use disorders by a mental health NHS Trust in the UK.
Planned Sample size:	To obtain a total of 122 evaluable participants (representing 61 participants per study group), it is estimated that a total of 183 participants will need to be recruited and screened. The sample size may be recalculated after an interim analysis when data for 30 evaluable participants per treatment group are available.
Study duration:	Following a 28-day screening and randomization period, participants will engage with one of the treatment groups for a period of 8-weeks. At 3- and 6-months following treatment completion, participants will be followed-up for standardized psychometric assessment. Therefore, the total estimated duration of each subject's participation will be 10-months.

3. BACKGROUND

3.1 COMPUTER ASSISTED THERAPIES FOR MENTAL HEALTH AND SUBSTANCE USE DISORDERS

Computer-assisted therapies (CAT) provide access to evidence-based therapeutic interventions, such as those provided in cognitive-behavioural therapy (CBT), via the internet. As a treatment modality, CAT has been demonstrated to widen access to treatment and can also be more cost-effective than receiving one-to-one therapy as multiple users can access the therapy at the same time (Carroll & Rounsaville, 2010; Olmstead, Ostrow, & Carroll, 2010). Providing interventions as CAT also ensures treatment fidelity is optimised as techniques with the intervention are delivered by a computer in a highly standardised manner (Carroll, 2013; Carroll & Rounsaville, 2010).

There is a growing evidence-base to support the clinical effectiveness of CAT with this mode of treatment delivery being recommended by NICE (NICE, 2009) for a number of psychological difficulties, such as depression (Cavanagh & Shapiro, 2004) and anxiety disorders (MacGregor, Hayward, Peck, & Wilkes, 2009). Additionally, meta-analyses investigating effectiveness of CAT have found it to be more effective at reducing self-reported and clinically significant levels of anxiety and depression compared to treatment as usual and waiting list groups (Grist & Cavanagh, 2013; Richards & Richardson, 2012; Twomey, O'Reilly, & Byrne, 2015). Alongside the evidence-base for effectiveness of CAT for depression and anxiety disorders, the evidence-base for CAT approaches for substance use disorders (SUD) is also growing (e.g. Bickel, Marsch, Buchhalter, & Badger, 2008; Carroll et al., 2008; Kay-Lambkin, Baker, Kelly, & Lewin, 2011; Kay-Lambkin, Baker, Lewin, & Carr, 2009).

Specifically in relation to SUD, accessing interventions online may help to overcome barriers such as the shame and stigma sometimes associated with accessing in-person drug and alcohol treatment services (Marks, Cavanagh, & Gega, 2007), and can also ensure that access is confidential. Access to treatment can also be widened to those who may ordinarily find it difficult to attend traditional services, such as those with childcare responsibilities or work commitments, those living in rural locations and those with limited mobility such as individuals with disabilities (Elison, Humphreys, Ward, & Davies, 2013; Moore, Fazzino, Garnet, Cutter, & Barry, 2011).

3.2 BREAKING FREE ONLINE

'Breaking Free Online' (BFO: Elison, Davies, & Ward, 2015a; Elison, Davies, & Ward, 2015b), is a tailorable CAT programme designed to support recovery from SUD and concurrent mental health issues. BFO is appropriate for addressing a wide number of substances as it has been designed to a target the biopsychosocial and lifestyle factors that underlie SUDs more generally. The programme has been delivered via UK-based treatment services for the past 10-years, has a growing evidence-base (e.g. Elison, Davies, et al., 2015a; Elison, Ward, et al., 2017), and since 2019 has been delivered as standard treatment in both Canadian community and US correctional treatment settings. BFO can be delivered as a self-directed 'self-help' programme or as a structured one-to-one or groupwork programme where sessions are facilitated by a practitioner.

When an individual first uses BFO, they complete an assessment of their substance use and dependence, and their wider biopsychosocial functioning. Included in this assessment is the 'Recovery Progression Measure' (RPM: Elison, Davies, & Ward, 2016; Elison, Dugdale, Ward, & Davies, 2017), which measures baseline levels of functioning across six biopsychosocial domains. BFO then uses these data to populate a six-domain model (see Figure 1), the 'Lifestyle Balance Model' (LBM: Davies, Elison, Ward, & Laudet, 2015). The LBM acts as a clinical formulation to help the user understand the specific issues and domains of functioning that may be implicated in their substance misuse and provides access to the clinical content of the programme.

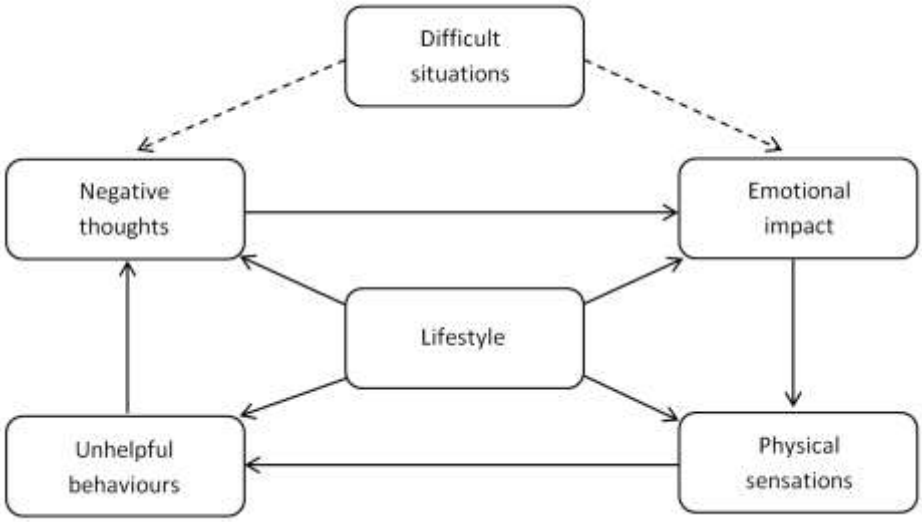

Figure 1: The Lifestyle Balance Model

Based on RPM scores, each of the domains of the LBM are coloured either green, amber, or red, indicating respectively, 'little', 'moderate' or 'significant' impairment. Tailoring advice then guides the user to concentrate on completing clinical content of the programme that is able to address the domains of their functioning in the LBM where they may be experiencing the greatest levels of impairment (amber and red domains of the LBM). Individuals are able to address these domains of functioning by completing 12 core evidence-based clinical intervention strategies, or 'behavioural change techniques', (BCTs: Michie et al., 2013) that are included in BFO that have been demonstrated to be effective in reducing substance use and improving mental health and broader biopsychosocial functioning. These BCTs are informed by therapeutic approaches such as CBT (Beck, Wright, Newman, & Liese, 2011), relapse prevention (Marlatt & Donovan, 2005), mindfulness (Marlatt, Bowen, Chawla, & Witkiewitz, 2010), and motivational enhancement (Miller & Rose, 2015), amongst others. Table 1 provides a full description of the individual BCTs in BFO, the purpose of each of these BCTs, and the therapeutic approaches informing these BCTs.

3.2.1 THE PUBLISHED BFO EVIDENCE-BASE: IMPLEMENTATION AND EFFICACY OF THE PROGRAMME

For the past eight years, a research programme has been underway to evaluate BFO, both in terms of exploring processes of implementation of the programme within health and social care systems, and in terms of examining the efficacy of the clinical content. The Medical Research Council (MRC)

framework for evaluating complex interventions has been used to structure this research programme – the first iteration of this framework was published 20-years ago (MRC, 2000) but has recently been updated (MRC, 2019). The MRC framework describes the importance of using multiple methodologies when developing and evaluating such interventions (Craig et al., 2008) – by employing multiple methodologies, multiple forms of data are generated, which may be located upon a 'hierarchy of evidence' (e.g. Borgerson, 2009; Evans, 2003; Goldenberg, 2009). Additionally, the MRC framework also emphasises the importance of examining not just clinical effectiveness, but barriers and facilitators of implementation in order maximise engagement, and mechanisms of action in order to understand how individual components of complex interventions exert their effects (Moore et al., 2015). The following section summarises the outcomes from this MRC-structured BFO research programme.

Qualitative research exploring the barriers and facilitators of implementation of BFO:

In order to optimise benefits from introduction of BFO into the existing treatment system, multiple qualitative studies have been conducted with all stakeholders to gain insights into how BFO could most effectively be implemented. 'Diffusion of Innovation' theory (Rogers, 2002) was used to conceptualise initial adoption of BFO throughout a number of UK community-based services with 18 service users and staff (Elison, Ward, Davies, & Moody, 2014). The study revealed a number of barriers to diffusion, including lack of IT resources and insufficient time for staff to familiarise themselves with the programme. A number of facilitators were also identified in this study, including the role of volunteers and peer mentors in supporting service users to use BFO.

To examine how the extent to which BFO had become a normalised treatment option in community-based services, a second qualitative study was conducted with 25 members of staff (Dugdale, Elison, Davies, Ward, & Dalton, 2016), with 'Normalisation Process Theory' (May et al., 2007; Murray et al., 2010) used to conceptualise findings. Some staff reported they still preferred traditional, face-to-face interventions, as they felt more familiar with these kinds of offline interventions, although participants reported that they recognised the benefits of BFO and the role peer mentors could play in supporting service users to use the programme.

A third qualitative study was conducted with 18 peer mentors working in community-based (Dugdale, Elison, Ward, Davies, & Dalton, 2016) to further explore the role of peer mentor delivery of BFO, with the 'Transtheoretical Model' (Prochaska, 2013) being used to understand peer mentors' recovery journeys, from their time as service users, through to becoming peer mentors. Interviews revealed that peer mentors perceived that their delivery of BFO facilitated their own recovery maintenance and acted as a means to continue accessing psychosocial techniques to maintain their own recovery, as well as helping them to support service users to gain optimal benefit from the clinical content of the programme.

Quantitative outcomes research examining efficacy of BFO:

Multiple quantitative studies have been published examining efficacy of the BFO programme, through the use of data captured automatically on the BFO backend database. Using a simple pre-test post-test design, these studies have consistently demonstrated significant reductions in substance use,

severity of substance dependence, and improvements in mental health, quality of life and biopsychosocial functioning (all $p < .0001$). The first of these studies was conducted using data from 34 service users engaging with BFO via community-based substance misuse services (Elison et al., 2013), with subsequent studies examining outcomes for 393 individuals using a range of different substances (Elison, Davies, et al., 2015a) and 300 individuals using BFO to address their alcohol misuse (Elison, Davies, et al., 2015b). These outcomes have also been replicated in studies with individuals engaging with BFO via eTherapy 'dual diagnosis' mental health services that provide support to individuals with SUD and comorbid mental health issues. The first of these included a sample of 47 individuals accessing BFO alongside biweekly telephone support from a Psychological Wellbeing Practitioner (PWP) (Elison, Ward, Davies, Lidbetter, et al., 2014) and the second a larger sample of 117 individuals (Elison, Ward, et al., 2017). Similar findings have also been obtained in studies examining outcomes for individuals engaging with BFO in prisons – the first of these studies reported positive outcomes for 85 males engaging with the programme via prison substance misuse services (Elison, Weston, Davies, Dugdale, & Ward, 2015), with these findings being replicated in a larger sample of 341 males serving sentences in UK prisons (Davies et al., 2017).

Research examining the mechanisms of action of BFO:

As the MRC framework emphasises the importance of not only understanding whether a complex intervention is effective, but also of understanding how such an intervention exerts its effects, a number of studies examining the mechanisms of action of BFO have also been conducted. The first of these included both clinical outcomes data and programme engagement data from 2311 individuals accessing BFO via UK-based community services (Elison, Jones, Ward, Dugdale, & Davies, 2017). Significant improvements (all $p < .0001$, effect sizes range .19 - .60) were identified from baseline to post-treatment (substance use, substance dependence, mental health, quality of life and biopsychosocial functioning). A 'dosage effect' was also identified, with the number of BCTs in the programme completed being positively associated with all outcomes and also that completion of specific BCTs was associated with specific outcomes. In addition, the primacy of cognitions was also revealed, with completion of a cognitive restructuring BCT being associated with improvements across all outcomes.

A further mechanisms of action study was conducted with 5792 service users engaging with BFO at 'Change Grow Live' (CGL), the largest substance misuse treatment provider in the UK (Elison-Davies et al., 2020). All service users completed a baseline assessment, and 1489 service users completed a post-treatment assessment. Service users who did not complete a post-treatment assessment were found to have more severe mental health and biopsychosocial impairment at baseline. For those service users who did provide post-treatment data, there were significant improvements in between from baseline to post-treatment assessment in substance use and dependence, mental health, quality of life and biopsychosocial functioning. Outcomes were associated with baseline service user characteristics including substance use and dependence, biopsychosocial impairment, age and BFO engagement. Outcomes were also significantly positively associated with the number of techniques in BFO completed, indicating a dose-response.

Mechanisms of action studies have also been conducted with specific substance-using populations. For example, a study was conducted with 1937 individuals engaging with BFO for alcohol use disorder

(AUD), with this study seeking to understand the how baseline participant characteristics and treatment goal preference (abstinence of reduction/moderation) might influence treatment outcomes (Ward, Elison-Davies, Davies, Dugdale, & Jones, 2019). Participants who chose complete abstinence as a treatment goal were more likely to be abstinent at baseline and to have received previous treatment than participants who chose reduction/moderation as a goal. Participants who preferred reduction/moderation also demonstrated better biopsychosocial functioning and lower alcohol dependence at baseline than those who preferred abstinence. Lower biopsychosocial impairment, lower alcohol dependence, and lower alcohol consumption at baseline were associated with a higher likelihood of achieving treatment goals.

Mechanisms of action of BFO for 1830 individuals using the programme to address cannabis use disorder has also recently been conducted (Elison-Davies, Wardell, Quilty, Ward, & Davies, 2021). Data revealed moderate-severe depression/anxiety in half the sample and elevated severity of cannabis dependence scores in over a third. Women demonstrated greater clinical complexity at baseline than men. Baseline mental health and biopsychosocial functioning were also associated with whether participants completed a follow-up assessment. Among 460 participants who completed a follow-up assessment, intervention engagement (i.e., BCT completion) was positively associated with self-reported quality of life and biopsychosocial functioning at follow-up, and for these individuals, significant improvements from baseline to follow-up were found in substance use and dependence, mental health, quality of life and biopsychosocial functioning (all $p < .0001$, effect sizes range .30 - .48).

Alongside the mechanisms of action research with individuals with AUD and cannabis use disorder (CUD), a further mechanisms of action study has been conducted with 1107 individuals with opioid use disorder (OUD) who have engaged with BFO (Elison-Davies, Märtens, Yau, Davies, & Ward, 2021). This study demonstrated significant improvements from baseline to post-treatment measures in opioid use, opioid dependence, mental health issues, quality of life and biopsychosocial functioning (all $p < .0001$, effect sizes range .17 - .50). A number of baseline participant characteristics, including severity of opioid use dependence, mental health and biopsychosocial functioning were also found to be associated with post-treatment measures (all $p < .0001$). An aggregated consensus measure of baseline clinical impairment was found to be associated with changes in opioid use and post-treatment biopsychosocial functioning measures, with those participants with greater baseline clinical impairment demonstrating a greater magnitude of improvement from baseline to post-treatment than those with lower clinical impairment.

BFO studies currently underway:

In order to complete the hierarchy of evidence for BFO, a number of randomised controlled trials (RCTs) are currently underway. These include a two-arm trial examining the effectiveness of BFO alongside standard treatment for male service users serving sentences in a Category D prison in North-West England (Elison-Davies et al., 2018). Participants in this study engage with BFO via the 'Virtual Campus', a secure online learning resource delivered across prisons in England Wales – BFO sessions are delivered as group CAT sessions by trained facilitators in the computer suite located within the prison education department. Participant recruitment started in 2019 but in early 2020 was put on hold due to Ministry of Justice imposed COVID-19 restrictions – recruitment will recommence as soon

as it is safe for these restrictions to be lifted. In addition, a Canadian Institutes for Health Research (CIHR) funded study is currently in set-up in Toronto. This is a three-arm RCT examining the effectiveness of BFO plus standard treatment when BFO is delivered as CAT by trained Peer Supporters with lived experience of SUD. The methodology for this RCT has been revised as a result of the COVID-19 pandemic, meaning that though BFO was originally to be delivered by Peer Supporters via in-person appointments with participants, BFO sessions will now be delivered via a 'virtual care' model, whereby Peer Supporters will support participants via videoconferencing software such as Zoom. Further RCTs at both male and female correctional facilities in the USA are also planned for 2021, with these studies being facilitated by the fact that in many US prisons and jails, service users are provided with in-cell tablet computers that will allow them to engage with BFO despite Department of Justice imposed COVID-19 restrictions.

Table 1. The 'behavioral change techniques' (BCTs) contained within Breaking Free Online

Content in Breaking Free Online	Description of strategy	Therapeutic approaches underpinning strategies	BCT taxonomy (V1) techniques (number in taxonomy)
Baseline and progress check assessments	Monitor behaviour to provide feedback about progress towards goals; Encourage new behaviours via positive feedback	Goal setting; self-monitoring	Self-monitoring of behaviour (2.3); Feedback on outcome(s) of behaviour (2.7)
Lifestyle Balance Model	Generic formulation; Idiosyncratic formulation; Personalized feedback; Case formulation – understand the links between situations, thoughts, emotions, behaviours, physical sensations, and lifestyle	Node-link mapping (International Treatment Effectiveness Project (ITEP); Cognitive-behavioural therapy (CBT)	Information about antecedents (4.2); Information about health consequences (5.1); Salience of consequences (5.2); Information about social and environmental consequences (5.3); Information about emotional consequences (5.6)
Difficult situations domain of LBM	Assessment; Self-monitoring; Standardized measures; Psycho-education on impact of problematic situations; Intervention to help people in distress access support; Recognize–avoid–cope; Relapse prevention for coping with environmental/situational/emotional triggers; Creating action plans on how to avoid or cope in high risk situations	All structured therapeutic approaches; Psychoeducation; Guided self-help; Relapse prevention; Refusal skills	Social support (unspecified) (3.1); Reduce negative emotions (11.2); Problem solving (1.2); Action planning (1.4); Instruction on how to perform the behaviour (4.1); Behavioural practice/rehearsal (8.1); Behaviour substitution (8.2); Avoidance/reducing exposure to cues for the behaviour (12.3); Goal setting (behaviour) (1.1); Problem solving (1.2); Action planning (1.4)
Negative thoughts domain of LBM	Psychoeducation on impact on negative thoughts; Mind traps; Cognitive restructuring; Challenge thoughts that may be unhelpful	Psychoeducation; Guided self-help; International Treatment Effectiveness Project (ITEP); Cognitive-behavioural therapy (CBT)	Information about antecedents (4.2); Information about health consequences (5.1); Salience of consequences (5.2); Information about social and environmental consequences (5.3); Information about emotional consequences (5.6); Re-attribution (4.3); Framing-reframing (13.2)

Emotions domain of LBM	Psychoeducation on impact on emotions; Attention narrowing; Attention switching; Emotional regulation; Recognize/understand/normalize emotions; Developing more appropriate coping strategies	Psychoeducation; Guided self-help; Coping strategy enhancement (CSE); Mindfulness-based cognitive therapy	Information about antecedents (4.2); Information about health consequences (5.1); Salience of consequences (5.2); Information about social and environmental consequences (5.3); Information about emotional consequences (5.6); Behavioural practice/rehearsal (8.1); Reduce negative emotions (11.2); Problem solving (1.2); Social support (unspecified) (3.1); Behavioural practice/rehearsal (8.1); Distraction (12.4)
Physical sensations domain of LBM	Psychoeducation on impact of physical sensations; Urge surfing; Body scanning; Relapse prevention-based techniques	Psychoeducation; Guided self-help; Mindfulness-based cognitive therapy	Information about antecedents (4.2); Information about health consequences (5.1); Salience of consequences (5.2); Information about social and environmental consequences (5.3); Information about emotional consequences (5.6); Instruction on how to perform a behaviour (4.1); Behavioural practice/rehearsal (8.1); Reduce negative emotions (11.2)
Unhelpful behaviours domain of LBM	Psychoeducation on impact of destructive behaviours; Activity scheduling; Behavioural activation; Encourage new behaviours via positive feedback; Increase activity to increase energy levels and relieve boredom	Psychoeducation; Guided self-help; Cognitive-behavioural therapy (CBT)	Information about antecedents (4.2); Information about health consequences (5.1); Salience of consequences (5.2); Information about social and environmental consequences (5.3); Information about emotional consequences (5.6); Non-specific reward (10.3); Non-specific incentive (10.6); Reward approximation (14.4); Rewarding completion (14.5); Goal setting (behaviour) (1.1); Action planning (1.4)
Lifestyle domain of LBM	Psychoeducation on impact of lifestyle; Creating SMART goals for recovery; Goalsetting Increase treatment engagement and retention. Increase readiness to change behaviour	Psychoeducation; Guided self-help; Motivational enhancement therapy (MET); Implementation intentions	Goal setting (behaviour) (1.1); Problem solving (1.2); Goal setting (outcome) (1.3); Action planning (1.4); Non-specific reward (10.3); Focus on past success (15.3); Action planning (1.4)

3.3 STUDY RATIONALE

One very significant barrier to treatment that many individuals with SUD have faced in 2020 has been the impact of worldwide societal lockdowns that have been initiated in an attempt to curb the transmission of 'severe acute respiratory syndrome coronavirus-2' (SAR-CoV-2), or 'COVID-19'. The COVID-19 pandemic has severely disrupted life for people around the world and to date, has been associated with over one million deaths worldwide (World Health Organization, 2020). The impact of COVID-19 on the health of the human population is expected to extend far beyond the impact it exerts on those directly infected by it. Indirect effects are already being identified as a result of the fact that healthcare systems around the world have been forced to drastically reduce their in-person services, in order to be able to conform to social distancing measures imposed by governments to reduce transmission rates (Douglas, Katikireddi, Taulbut, McKee, & McCartney, 2020).

Individuals with SUD may be particularly vulnerable to the effects of the pandemic (Jemberie et al., 2020). Many have underlying physical health conditions that put them at an elevated risk of becoming seriously ill if they contract COVID-19, e.g., some have pre-existing respiratory conditions such as bronchitis and others may have compromised immune systems. Social isolation has also increased the vulnerability of individuals with SUD, due to the fact that they have been unable to access the in-person treatment services and mutual aid groups that are so vital to their ongoing recovery, because many of these in-person sources of support have been restricted during the lockdown period. When this is coupled with the extra anxiety, uncertainty, isolation and stress the pandemic has caused so many people to feel, this combination of factors has the potential to put in jeopardy the recovery of any individual with SUD, especially those who may have concurrent mental health difficulties.

In-person mental health and addiction services face an uncertain future, given an effective COVID-19 vaccine or treatment is still not available, meaning several more months of varying levels of severity of lockdown. This study therefore aims to examine the effectiveness of BFO when it is delivered alongside the restricted services able to be delivered during this period of pandemic. Specifically, BFO will be delivered alongside bi-weekly telephone support from mental health and addiction support practitioners – this kind of 'telehealth' approach, delivered in combination with a digital CAT intervention, has the potential to provide evidence-based, effective support to individuals in recovery from SUD during a time when they may be particularly vulnerable to relapse.

3.4 OVERALL BENEFIT RISK ASSESSMENT

The 2012 Department of Health report by the UK Chief Medical Officer revealed problematic drug and/or alcohol use to be major public health concerns (Davies, 2012). Alcohol misuse alone has been estimated to cost the NHS £3.5 billion per year (Roberts, Morse, Epstein, Hotopf, Leon, & Drummond, 2019), although the cost of alcohol to society more broadly may be even greater, standing at an estimated £17 – 22 billion annually a decade ago (McManus, Meltzer, Brugha, Bebbington, & Jenkins, 2009). In terms of illicit drugs, the most recent Crime Survey for England and Wales (CSEW) estimates that between 2018 and 2019, 9.4% of 16 – 59 year olds living in the UK had used an illicit drug within the previous 12-months, which translates to approximately 3.2 million people (Office, 2019).

Whilst some of the risks inherent in substance use disorders remain relatively constant, 2020 has seen a rise in several new, unanticipated risks related to drug use. A rapid trend-spotter assessment conducted by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) found that substance use behaviours considered 'less risky' prior to the COVID-19 pandemic, for instance sharing a cannabis joint, now carry substantial and under-researched risks of harm via the transmission of coronavirus (EMCDDA, 2020). A Europol/EMCDDA analysis conducted on the impact of COVID-19 on the drug market also found that disruptions to illicit drug supplies across Europe did not, as anticipated, decrease illicit drug use, but rather prompted greater interest or use of more novel substances (EMCDDA, Europol, 2020) which carry with them their own – often poorly understood - risks and harms. Finally, the EMCDDA trend-spotter assessment also found that many harm reduction and treatment services for individuals who use drugs are offered by community or voluntary groups and are poorly integrated into mainstream healthcare systems. This resulted in these groups being less able to both access vital resources such as personal protective equipment (PPE), and less able also to follow the robust COVID-19 protection measures rolled out across the NHS (EMCDDA, 2020), resulting in increased risk of COVID-19 transmission and harm to service users.

Figures published by the charity Alcohol Change UK also indicate that COVID-19 has had a detrimental effect on drinking habits within the UK, with one in five individuals reporting that their alcohol consumption had increased between the introduction of lockdown measures in March 2020 and completion of the survey in April 2020. When extrapolated to the UK population, this represents 8.6 million adults drinking more frequently when compared to pre-pandemic (Alcohol Change UK, 2020). Alcohol Change UK also reported a 355% increase in traffic to the "Get Help Now" section of their website between March and April 2020, indicating that there has been a substantial increase in individuals seeking assistance to manage their drinking habits as a result of the pandemic (Alcohol Change UK, 2020). The comorbid nature of alcohol use disorders and mental health disorders is well documented, and studies conducted during the pandemic indicate that negative changes in alcohol intake during the early part of 2020 (i.e., an increase in consumption) are associated with greater depression, anxiety and stress severity (Stanton, To, Khalesi, Williams, Alley, Thwaite, Fenning, & Vandelanotte, 2020).

These findings highlight the need for substance use interventions that are able to 1) target novel illicit substance use, which may continue to rise as the pandemic runs its course, 2) be delivered via methodologies that reduce, as much as is reasonable, face to face contact and in-person presentation to services, 3) be rapidly upscaled in order to meet an unprecedented demand in individuals seeking help, and 4) address concurrent mental health difficulties that may arise as a result of, or themselves cause, increased substance use.

As this study represents the first community randomised controlled trial of BFO, adverse event (AE) and severe adverse event (SAE) data is unavailable for reporting. Despite this, the Sponsor has identified that risks to participants arise primarily from both participant expectations and the requirement of participants to address their substance use.

As with any opportunity to trial a new intervention, participants may enter the trial with the hope or expectation that the intervention will help them achieve changes that they have previously been unable to. There is therefore a risk that the participant may become disappointed, frustrated, or angry,

or suffer otherwise adverse psychological events, if this is not the case. The Sponsor will make attempts to mitigate this outcome by not overstating the benefits that people may gain from taking part in the study, and explaining within the participant information sheet that different people may experience different outcomes when utilising interventions for SUD. Although not all participants may benefit from this treatment, it may help identify the psychological techniques that do or do not work for them. Even if there is no discernible improvement for an individual, it can potentially rule out those techniques that will definitively not help them to address their addiction, ultimately resulting in a more focused and effective treatment approach for the individual.

Discussing, addressing, or thinking about the reasons they continue to use alcohol and/or drugs may also cause participants to become upset or distressed, and the possibility for resultant self-harm, or harm to others, is recognised. For the standard treatment arm, these risks will be mitigated by the safeguarding protocols that shall already be in place at the site providing treatment. For participants randomised to the interventional BFO plus standard treatment arm, the same safeguarding measures will be in place, and these individuals shall also receive bi-weekly "recovery check-in" phone calls from staff at their service, which will allow further opportunities to assess the risk of harm to the participant and determine if further action is required. Site personnel involved in this study shall be experienced alcohol and drug workers who routinely handle the difficult situations that may arise when dealing with patients with SUD, and are trained to manage these situations in ways that do not compromise the safety of themselves or the patient.

Based on the evidence base underpinning BFO, the evaluations conducted on the clinical efficacy of the programme so far, the anticipated risks and mitigation strategies for the study, and the clear unmet need for novel digital intervention provision both during and after the COVID-19 pandemic, it is believed that the potential benefits to this clinical study outweigh the potential risks.

3.5 STUDY CONDUCT

This study shall be conducted in compliance with the principles of Good Clinical Practice (GCP), including International Conference on Harmonisation (ICH) Guidelines, in accordance with the most recently ratified version of the Declaration of Helsinki, the principles of the *Data Protection Act 1998*, and the law and the principles of good practice relating to ethics, science, information, health and safety, and finance set out in the *Research Governance Framework for Health and Social Care 2008*. In addition, all applicable local laws, regulations, and regulatory requirements relating the conduct of a clinical trial using human participants shall be adhered to.

The study shall be conducted in accordance with this protocol as well as in compliance with the Sponsor's research policies. The appropriate Research Ethics Committees (RECs) or institutional review boards shall approve the protocol, subsequent amendments, and the study Informed Consent documents prior to commencement of research.

Freely given informed consent shall be obtained from every subject prior to their participation in this clinical trial. The rights, safety, and well-being of participants shall be the most important

consideration throughout the study, and their rights shall prevail over any intended or perceived interests to science and/or society.

Study personnel involved in this trial shall be appropriately qualified by experience, education, or training to perform their respective tasks, and this shall be appropriately documented.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1 STUDY OBJECTIVES

Primary Objective:
To compare the efficacy of BFO when delivered via a telehealth model as an adjunct to standard treatment versus standard treatment alone on self-reported substance use following treatment completion, and at 3- and 6-months follow-up.

Secondary Objectives:
1) To determine the efficacy of BFO as an adjunct to standard treatment versus standard treatment alone on the following health outcomes at treatment completion, and at 3- and 6-months follow-up:

a) Severity of substance dependence
b) Prevalence and severity of concurrent depression and anxiety
c) Quality of life
d) Biopsychosocial functioning

2) To assess participant engagement with BFO during the 8 week-treatment period.

4.2 ENDPOINTS

Primary Efficacy Endpoint:

- Participant self-reported substance use, per questionnaire including questions regarding:

  - Weekly primary substance use (i.e., 'How many days in the past week did you use [primary substance]?', and 'How much [primary substance] did you use each day?')

  - Use and frequency of use of secondary substances (i.e., 'Do you use any other substances in addition to [primary substance]?', 'How many days in the past week did you use [secondary substance]?', and 'How much [secondary substance] did you use each day?')

Secondary Efficacy Endpoints:

All secondary efficacy endpoints shall be evaluated via the use of standardised psychometric assessment measures, as detailed below:

- Severity of substance dependence, per *Severity of Dependence Scale* (SDS: Gossop, Best, Marsden, & Strang, 1997). A 5-item scale measuring severity of substance dependence, e.g. cravings and substance-related cognitions. A score of 7 or over indicates elevated risk of SUD. Both alcohol and drug-specific versions are included in the assessment. Internal reliability: α = .81 - .90; test-retest reliability ICC = .89.

- Prevalence and severity of depression and anxiety, per *Patient Health Questionnaire* (PHQ-4: Kroenke, Spitzer, Williams, & Löwe, 2009). A 4-item scale that measures severity of depression and anxiety. Threshold scores on the PHQ are 0 – 3 no depression anxiety, 3 – 5 'mild', 6 – 8 'moderate' and 9 – 12 'severe'. Internal reliability, α = .81.

- Quality of life, per 5 items (1, 2, 17, 18, 20) from the *World Health Organization Quality of Life measure* (WHOQoL-BREF: Skevington, Lotfy, & O'Connell, 2004). Items selected are those that measure generic general quality of life as opposed to specific aspects of quality of life. Internal reliability of these five items, α = .84.

- Biopsychosocial functioning, per *Recovery Progression Measure* (RPM: Elison et al., 2016; Elison, Dugdale, et al., 2017). A 36-item scale measuring functioning in six biopsychosocial domains functioning that are implicated in all SUDs and recovery from SUDs. Within each of the six RPM domains there are five dichotomous 'yes/no' items measuring the presence or absence of specific biopsychosocial difficulties within that domain, and an 11-point Likert-style scale 'impact scale' assessing overall level of severity of impairment in that domain. Internal consistency, α = .89; test-retest reliability, ICC = .73.

Additional Endpoints

- Participant engagement with BFO, per backend BFO database which captures number of hours participant spends on BFO, the number of BCTs completed within BFO (i.e., how many of the 12 BCTs in the program were completed) and the total number of times each BCT was completed, accounting for the fact each BCT can be completed more than once.

- Where possible, engagement shall also be assessed via qualitative data, collected via semi-structured interviews with both participants and practitioners at the end of the study. These interviews will explore a number of topics, including participants' experiences of substance misuse and previous treatment they might have received. Participants will also be interviewed about their views of the BFO program, how they think it might be improved and any barriers or facilitators of implementation of the programme via a telehealth model. These interviews will be conducted within using videoconference software (e.g. GoToMeeting, Zoom, Microsoft Teams etc.) and will last approximately 30 – 45 minutes.

5. STUDY POPULATION

This study shall enrol adults with SUD receiving treatment from an NHS Trust in the UK, aged over 18 years, with problem alcohol and/or drug use of duration of 12-months or longer. This period of time is in line with DSM-V criteria for substance related disorders (American Psychiatric Association, 2000). Eligibility criteria for this study have been carefully considered to ensure the safety of the participants and the integrity of the study results. Subjects must fully meet all inclusion criteria and none of the exclusion criteria. The Sponsor shall not grant protocol waivers to study eligibility criteria.

Since the study is a parallel-group comparison, equal numbers of participants will be required for each of the groups. The projected sample size will require 61 evaluable participants in each treatment group to achieve enough observed power (assuming an observed power of 0.80 with $\alpha = .05$) with an allowance of 50% attrition at 3- and 6-months follow-up. Therefore, to obtain a total of 122 evaluable participants, it is estimated that a total of 183 participants will need to be recruited and screened. The sample size may be recalculated after an interim analysis when data for 30 evaluable participants per treatment group are available.

5.1 INCLUSION CRITERIA

1. Aged 18 years or above on the day of consent.
2. Experiencing problem alcohol and/or drug use at time of consent, as determined by Investigator.
3. Problem alcohol or drug use present for ≥ 12 months at time of consent, as self-reported.
4. Willing to comply with an 8-week treatment programme for problem alcohol and/or drug use.
5. Willing to provide outcome measures post-treatment, and at 3- and 6-months follow-up.
6. Able to read, write and communicate in the English language.
7. Able to access an internet enabled device for the duration of the study.
8. Able to access a telephone or video-communication enabled device for the duration of the 8-week treatment period.
9. Willing and able to give informed consent for participation in the study, and capable of understanding and complying with protocol requirements.

5.2 EXCLUSION CRITERIA

1. Under 18 years old on the day of consent.
2. Participation in any other alcohol and/or drug related clinical studies within 12 months prior to date of consent.
3. Detention under the Mental Health Act at the time of consent.
4. Clinically significant intellectual or developmental disability which may impair ability to engage with the Breaking Free Online treatment programme and/or complete the necessary assessment measures included in the methodology, as determined by Investigator.

5. Pregnancy (as self-reported) at the time of consent.

6. Previous use of the Breaking Free Online programme for the purposes of alcohol or drug use intervention.

6. STUDY DESIGN

6.1 STUDY DESIGN OVERVIEW

This is a randomised, open-label, parallel-group, longitudinal study of the Breaking Free Online substance use intervention – delivered via a telehealth model - as an adjunct to standard treatment vs standard treatment alone in adult participants with substance use disorder.

Subjects shall be randomised on a 1:1 ratio to either:

i) The intervention arm – BFO, completed in a self-directed manner at home over the course of 8 weeks with bi-weekly "recovery check-in" phone calls from a recovery practitioner or member of the Sponsor research team to support programme use, in addition to standard treatment (as below).

ii) The control arm – standard treatment alone, delivered over 8-weeks. Standard treatment shall be delivered once or twice weekly, depending on the standard of care model utilized by the study site.

6.2 STUDY PROCEDURE

Each participant's course of treatment shall consist of the following periods, as detailed below and displayed in Section 6.7.

6.2.1 PRE-TREATMENT PERIOD (INFORMED CONSENT):

All prospective participants that potentially meet the study criteria will be informed of the study's objectives and requirements before any screening procedures are performed. The investigator or designee shall explain the study thoroughly to the participant using the Participant Information Sheet and Informed Consent Form. If willing to participate in the study, he/she will be requested to provide written consent after being given sufficient time to consider his/her participation and having had the opportunity to ask for further details. The Informed Consent Form will be signed and personally dated by both the participant and the consenting investigator or designee. Due to the COVID-19 restrictions in place at the time of protocol writing, informed consent may be obtained electronically, via videoconferencing software. In these instances, a simple electronic signature shall be obtained from the participant and the researcher obtaining informed consent, in accordance with the MHRA/HRA "Joint Statement on Seeking Consent by Electronic Means". The participant will be provided with a copy of the signed Informed Consent Form and the Participant Information Sheet. The original forms will be retained with the source documents. Informed Consent must be obtained within 28 days prior to treatment commencement.

After consenting to participation in the study, each potential participant shall be allocated a 5-digit Screening Number between 11500 and 11740 that they shall retain through the screening process. The screening number shall be allocated according to the order of recruitment to the study, and should be documented on the study Screening Log, as well as on all study related documentation, by a member of the research team.

6.2.2 PRE-TREATMENT PERIOD (SCREENING):

If written consent is given, each participant will then undergo a full screening assessment for confirmation of study eligibility. Qualifying screening assessments must be performed within 28 days prior to treatment commencement. Subsequent reason(s) for exclusion from the study (if applicable), shall be recorded on the study Screening Log by a member of the research team.

6.2.3 PRE-TREATMENT PERIOD (RANDOMISATION):

Subjects who meet all study eligibility criteria will be randomly assigned in a 1:1 fashion to receive either standard treatment plus adjunct BFO, or standard treatment alone. Randomisation must be performed within 28 days prior to treatment commencement and may take place on the day of screening provided it is performed after eligibility is confirmed.

Prior to study commencement, an independent researcher shall create a Master Randomisation List via the *Research Randomizer* (from the Social Psychology Network- Urbaniak & Plous, 2011), which uses the "Math. Random" method within the JavaScript programming language for web browsers.

In accordance with the Master Randomisation List, the Sponsor's authorised personnel will prepare sequentially numbered opaque sealed envelopes containing both the randomisation number of the subject (a 3-digit number from 001 to 183) and the study group that each participant will be allocated to. These envelopes shall be provided to the study site prior to the commencement of recruitment.

After it has been confirmed that the participant has met all of the necessary inclusion criteria for the study, and none of the exclusion criteria, a member of the research team will assign and open one sealed envelope, containing the type of treatment, with the participant, and this shall be documented in the subject's source data. The participants' randomisation number will be allocated according to the order of randomisation to the study, and shall also be documented on the study Screening Log, as well as on all study related documentation, by a member of the research team.

6.2.4 TREATMENT PERIOD:

For both arms, treatment shall commence no later than 28 days after informed consent has been obtained.

INTERVENTION GROUP

Prior to, but within 4 calendar days of, the first session of standard treatment within the context of the clinical trial, participants randomised to the intervention group will receive a unique access code

to the BFO programme from the investigator or designee. This access code shall be paired to their randomisation number to allow identification of individual participant datasets within BFO without requiring the participant disclose personal identifying information to Sponsor. The investigator or designee shall assist the subject in the set-up of a BFO account, and the participant shall complete the battery baseline of psychometric assessments and substance use questions within the BFO programme. After successful set up of an account and completion of baseline assessment, the investigator or designee shall provide training to the participant on use of the programme.

Within 4 days of baseline assessment completion, the participant shall receive the first session of an 8-week standard treatment for SUD within the trial. This standard treatment shall be determined by the service at which the participant initially presented. Details of, and compliance with, standard treatment shall be recorded in the participant's source data.

Participants in the intervention arm will continue to use BFO alongside standard treatment for SUD for the duration of the 8-week treatment period. During this time, participants should be encouraged to use BFO at least once weekly, for approximately an hour per session, at home in a self-directed capacity.

Approximately 2 weeks after standard treatment commencement in the context of the trial, and bi-weekly thereafter, participants in the intervention arm shall receive 'recovery check-in' phone calls from the investigator or designee, that shall last approximately 15-20 minutes. The content of these 'recovery check-in' phone calls is detailed in Section 7.1.1. These calls shall be appropriately documented in the participant's source data. These calls shall continue throughout the 8-week treatment period and cease at the end of treatment.

Within 3 days following the end of 8-week treatment period and final standard treatment session in the context of the trial, participants in the investigational arm shall be prompted by the investigator or designee to complete the end-of-treatment battery of psychometric assessments and substance use questions, also hosted by SurveyMonkey. Participants will be provided with a link to the applicable survey by the investigator or designee. This survey shall be identical in content to the initial baseline assessment completed prior to treatment.

Participants shall continue to be able to access the BFO programme after the end of the treatment period, however this is not a requirement, and use of the programme outside of the initial 8-week treatment period shall be outside of the scope of this research.

CONTROL GROUP

Prior to, but within 4 calendar days of, the first session of standard treatment within the context of the clinical trial, participants in the control group shall be required to complete a battery of baseline psychometric assessments and substance use questions via a secure online survey, hosted by SurveyMonkey. Participants will be provided with a link to the applicable survey by the investigator or designee. This survey shall be identical in content to the baseline assessment contained within the BFO programme.

Within 4 days of baseline assessment completion, the participant shall receive the first session of an 8-week standard treatment for SUD within the trial. This standard treatment shall be determined by the service at which the participant initially presented. Details of, and compliance with, standard treatment shall be recorded in the participant's source data.

Within 3 days following the end of 8-week treatment period and final standard treatment session in the context of the trial, participants in the control arm shall be prompted by the investigator or designee to complete the end-of-treatment battery of psychometric assessments and substance use questions, also hosted by SurveyMonkey. Participants will be provided with a link to the applicable survey by the investigator or designee. This survey shall be identical in content to the initial baseline assessment completed prior to treatment.

6.2.5 POST-TREATMENT PERIOD (FOLLOW-UP)

At 3-month and 6-month follow up timepoints (defined as 3- and 6-months post treatment *completion* date), participants shall be required to complete a battery of follow up psychometric assessments and substance use questions. Identical in content to the baseline and post-treatment assessments, these assessments shall be completed by all subjects via secure online survey, hosted by SurveyMonkey. Participants will be provided with a link to the applicable survey by the investigator or designee at both 3- and 6-month follow up timepoints.

If any participant fails to return for a scheduled treatment session or fails to complete a follow-up standardised psychometric assessment, attempts should be made to contact the participant to determine the reason, and to perform the study assessment if feasible.

6.3 WITHDRAWAL, DISCONTINUATION, AND END OF TRIAL

6.3.1 PARTICIPANT WITHDRAWAL

Participants will be informed that they have the right to withdraw from the study at any time, without prejudice to the current service they are receiving, and without the need to provide their reasons for ending involvement with the research. Study withdrawal, as well as reasons for withdrawal if provided, shall be recorded in the source data, and the Sponsor shall be informed of the withdrawal as soon as practicable. Data collected from these participants up to the point of withdrawal shall be retained, however no further study procedures or assessments shall be performed, or study data collected, and participants shall be returned to standard care.

Participants also retain the right to withdraw their consent for previously collected data to be used in the final analyses. This revocation of consent should be documented in the source data, and the study site shall inform the Sponsor of this as soon as is practicable, to enable Breaking Free Online Limited authorised personnel to purge from the BFO backend database any data provided by these participants.

6.3.2 EARLY DISCONTINUATION OF PARTICIPANT

A participant must be discontinued from the study should any of the following occur:

- Changes in status of the participant such as he/she no longer meets eligibility requirements for the study, or the site investigator believes that the participant's health will be compromised if they were to continue in the study.
- Major protocol violations (to be discussed with the Sponsor).
- Serious illness or health concern that would prevent the participant from following the treatment conditions in the study, as determined by Investigator.
- Type of incarceration that would not permit the participant to follow the treatment conditions in the study.
- Participant withdraws consent.
- Administrative reasons identified by Sponsor or site that preclude participant involvement (to be discussed with Sponsor).

Following the decision to discontinue a participant who is following treatment, an end-of-treatment standardised psychometric assessment should be performed whenever possible, and the participant shall be returned to standard treatment. Discontinuation of participants, and the reason for discontinuation, shall be documented in the source data and the Sponsor shall be informed as soon as practicable.

All data from participants who have been discontinued from the study will be databased unless the participant does not wish to be included in the database – in this case, the revocation of consent should be documented in the source data, and the study site shall inform the Sponsor of this as soon as is practicable, to enable Breaking Free Online Limited authorised personnel to purge from the BFO backend database any data provided by these participants. In such an eventuality, another participant may need to be enrolled under the same treatment group as a replacement.

6.3.3 END OF TRIAL

The end of the study shall be determined by the last data collected, at 6-month follow-up time point, from the last participant randomised. The REC shall be informed of the end of the study within the required timelines.

The Sponsor reserves the right to stop the study at any time on the basis of new information (e.g. interim analysis), or should the progress be unsatisfactory, should participants experience negative outcomes that may be associated with the new interventions, or for other valid administrative reasons. The Sponsor will notify the staff at the research site, and REC, in writing should the study be prematurely discontinued, and such notification will include the reasons for termination.

In case of an early discontinuation of the study, a final analysis and report will be performed in which all evaluable participants who were recruited during the time of the study will be analysed.

6.4 STUDY SITES

This study shall be conducted at a single mental health NHS Trust within the UK, consisting of one clinical site. In the event that a single site is insufficient to meet recruitment targets, the Sponsor shall seek authorisation to add sites to the study via a protocol amendment.

6.5 ESTIMATED STUDY DURATION

It is estimated that 18 months will be required to randomise 183 participants, with the aim of 122 participants completing the study. This assumes a constant accrual rate of 10 participants per month. A 50% attrition rate at 3- and 6- months follow up has been allowed, to account for extraneous factors that may preclude participant completion.

60 evaluable participants - 30 per treatment arm - shall be required to have completed the study in order to trigger an interim analysis, and it is therefore expected that interim analysis shall be conducted after 16 months (6 months of recruitment at a rate of 10 participants per month, plus 10 months of study participation per participant), at which point the sample size may be recalculated by the Sponsor.

The number of participants required to complete the study for final analysis to take place is 122; 61 per treatment arm. Assuming 122 evaluable participants are randomised within 18 months, final analysis is estimated to take place approximately 28 months after the first subject is randomised.

The true intervals required to meet these milestones may be longer or shorter due to divergence from assumptions, including non-constant accrual rate.

It is estimated that each subject shall participate in the study for an average of 10 months, from time of consent to final psychometric assessment at 6-months post-treatment.

6.6 STUDY TREATMENT BLINDING

This is an open-label trial, and as such, no blinding is required.

6.7 STUDY FLOWCHART AND TREATMENT SCHEDULE

Table 2: Study Flowchart and Treatment Schedule

	Pre-treatment: Screening and randomisation period	**8-week treatment period**								**Follow-up 1: 3 months post-treatment completion (± 7 days)**	**Follow-up 2: 6 months post-treatment completion (± 7 days)**
Week	**-4 to 0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**20**	**32**
Informed consent	√										
Demographic information	√ [a]										
Substance use information	√ [a]	√[c]							√[d]	√	√
Medical history	√ [a]										
Inclusion and exclusion criteria check	√ [a]										
Randomisation	√ [a, b]										
Standardised psychometric assessments *(SDS, PHQ-4, WHOQoL-BREF, RPM)*		√[c]							√[d]	√	√
Breaking Free Online Use (*intervention arm only*)		√	√	√	√	√	√	√	√		
Standard Treatment		√	√	√	√	√	√	√	√		
'Recovery check-in' phone calls *(intervention arm only)*			√		√		√		√		
Adverse and Serious Adverse Events [e]	√ [a]	√	√	√	√	√	√	√	√	√	√

[a:] To occur only after participant has signed the Informed Consent Document (unless routinely reviewed as standard of care). [b:] Randomisation is to only be performed after the inclusion and exclusion criteria check has occurred. [c:] Within 4 days prior to treatment commencement. [d:] Within 3 days after treatment completion. [e:] Please refer to Section 8 of the protocol.

7. TREATMENTS

7.1 BREAKING FREE ONLINE

A full description of the clinical content of the BFO programme can be found in Section 3.2 of this protocol. Participants in the Intervention group will be encouraged to spend one-hour per week working on the content of the BFO programme for the 8-week treatment period. These participants will also receive bi-weekly 15 to 20-minute long 'recovery check-in' telephone calls from the investigator or designee – a total of four telephone calls during the treatment period.

The BFO programme is designed to empower an individual to recover from their drug or alcohol dependence, and overcome their mental health difficulties, by helping them to understand the areas of their life that may be contributing to their difficulties and work through evidence based BCTs to address each of these areas of difficulty. BFO allows individuals to track their personal progress, and promotes long-term recovery because there are multiple resources in the programme that can be printed, emailed or downloaded to a computer, mobile phone or MP3 player, which build into a comprehensive and personalised recovery toolkit that is available after the treatment has finished.
The programme has been designed to be used directly by individuals as either a stand-alone or adjunct treatment programme as self-help or with support from a practitioner. BFO can be used in any clinical or non-clinical setting and has been designed to be suitable for every stage of the treatment and recovery journey**,** from engaging and motivating service users at the first point of contact with services, right through to supporting their ongoing recovery and rehabilitation as part of any aftercare provision.

7.1.1 RECOVERY CHECK-IN PHONE CALLS

'Recovery check-in' phone calls shall be conducted bi-weekly alongside BFO to augment the telehealth model of delivery. The primary purpose of these telehealth check-in phone calls is not to collect study data, but rather to provide support to the individual using Breaking Free in a manner that mirrors the support they would receive during face-to-face intervention delivery, when this method of delivery is not feasible nor safe.

The content of the recovery check-in calls has its basis existing Breaking Free manuals, in particular the *'Guidance for Supporters: Delivering Breaking Free as a One-to-One Intervention'* manual, in order to ensure homogeneity across the Sponsor's portfolio of delivery models. Recovery check-in calls will focus primarily on the information and action strategies contained within the Breaking Free programme and will include questions relating to the participant's understanding and perception of the strategies, completion of the action plans they have developed whilst using the programme, experiences of the topics covered throughout the programme, and support needs whilst accessing the programme.

The full recovery check-in content is contained within the supporting protocol document entitled *'Recovery Check-In Phone Call Guidance'*, which shall be used as a template by practitioners when performing calls in order to ensure standardisation across participants. Whilst efforts should be made

to ensure that recovery check-in phone calls are made via telephone, it is permissible to conduct these recovery check-ins via videoconferencing software (e.g., Zoom, Microsoft Teams) if required.

7.2 STANDARD TREATMENT

Both study groups shall receive standard treatment throughout the treatment period of this study, although existing standard treatment utilised by the research site may be variable, especially as it unknown when in-person services are likely to return to normal functioning given the COVID-19 pandemic has caused many to stop operating. It is expected that there will be a degree of heterogeneity within each of the study groups in terms of the standard treatment received. This heterogeneity will be captured in the participant's source data and shall include key details regarding the specific standardly available treatments and interventions each participant has received.

Treatments usually available in outpatient drug and alcohol services include standard *low-intensity interventions*- defined as motivational and engagement tools to reduce substance use. These interventions are delivered by practitioners and include techniques such as Motivational Interviewing (MI) and Contingency Management (CM). For common mental health problems, low-intensity interventions retain an element of self-help, whereby practitioners act as facilitators for the use of a particular psychosocial intervention. More formal psychological therapies are delivered by a specialist psychological therapist through CBT based interventions.

Treatment sessions shall have a duration range of 30-60 min and shall take place once or twice a week for 8-weeks. The number of interventions the participant will work with in each session may vary but should be appropriately documented in the participants' source data.

During treatment, concomitant alcohol and drug(s) use may be permitted, as well as any prescribed medication, including substitute medications as part of medication-assisted treatment.

8. ADVERSE AND SEVERE ADVERSE EVENTS

8.1 ADVERSE EVENTS

Historically, the recording and reporting of adverse events (AEs) has been inconsistent and poorly defined in the context of randomised controlled trials involving psychological and behavioural interventions. Recent meta-analyses of ninety-nine randomised controlled trials involving cognitive behavioural therapy interventions found that only 32.3% of these studies addressed adverse events in some way, while only 7.1% of these studies met all criteria for adequate reporting of adverse events (Condon, Maurer, and Kyle, 2021).

One factor that may contribute to the under-reporting of adverse events in such trials is the assumption that AEs are purely medical in nature and are thus unlikely to be caused by a non-medicinal intervention. Whilst plausible to believe that many medical adverse events have no causal relationship to biopsychosocial interventions, there remains the possibility that behavioural interventions requiring individuals to reflect on their substance use, and the causes underpinning such use, may indeed cause adverse events such as a worsening of mental health symptoms. In addition to

this, the use of computers to deliver such interventions may mean an increased incidence of technology-related medical adverse events, such as headaches and migraines.

When considering unintended consequences of biopsychosocial interventions, non-medical harms, or 'social AEs' (Moody, Addison, Cannings-John, Sanders, Wallace & Robling, 2019), should also be considered. These events may not be of medical importance, but still have the potential to negatively impact the participant's wellbeing and may also feasibly occur as a result of a participant entering a form of psychological treatment which requires significant self-assessment and/or behavioural change. This category includes events such as involvement with law enforcement, safeguarding referrals, perpetration of domestic abuse, and involvement with social services. These alternative harms are often poorly documented in the context of randomised controlled trials (Papaioannou, Cooper, Mooney, Glover, & Coates, 2021), yet may prove vital when assessing the risk-benefit profile of an intervention.

For the purposes of this study, the following medical adverse events shall be expected and recorded within individual participant case report forms:

- Self-reported worsening of depression or anxiety present at baseline
- Self-reported worsening of any other concurrent mental illness(es) present at baseline
- Development of depression or anxiety not initially present at baseline
- Overdose that does not require inpatient hospitalisation (if >24hr hospitalisation is required, this shall be reported following SAE guidelines below)
- Eye strain and associated symptoms, including migraine, headache, double-vision, or eye irritation
- Musculoskeletal pain, particularly in the spine, neck, and shoulders
- Sleep disturbances
- Carpal tunnel syndrome or associated symptoms, including numbness, tingling, pain or weakness in hands or arms.
- Any other adverse event that could reasonably be considered related to, or resultant from, the participant's involvement in this trial, as determined by the Investigator.

The following social adverse events shall be expected and recorded within individual participant case report forms:

- Involvement with law enforcement commencing after randomisation into the study (ongoing cases shall not be documented as social AEs)
- Aggression or violence towards a member of the study team or other healthcare professional involved in the participant's care
- Safeguarding incidents and referrals after randomisation into the study
- Self-reported new incidents of domestic abuse or violence
- Self-reported incidents of new involvement with social services
- Any other adverse social event that could reasonably be considered related to, or resultant from, the participant's involvement in this trial, as determined by the Investigator.

All adverse event data, both medical and social, shall be gathered retrospectively at the time of the participant's trial completion (with the exception of SAEs, which shall be monitored and reported contemporaneously per the below guidelines). Adverse event data shall be obtained via study team review of the participant's medical notes (including any Datix Incident reports and Treatment Outcomes Profile forms included within), and events corresponding to the criteria

above and occurring between randomisation and the 6-month follow-up timepoint shall be recorded.

8.2 SERIOUS ADVERSE EVENTS

A Serious Adverse Event is defined by the ICH Guideline for Clinical Safety Data Management as an untoward medical occurrence that, at any dose:

- Results in death.
- Is immediately life threatening (i.e., in the opinion of the Investigator, the AE places the subject at imminent risk of death; it does not include an event that, had it occurred in a more severe form, might have caused death).
- Requires inpatient hospitalisation of more than 24 hours (unless this hospitalisation is an elective or previously scheduled procedure) or results in prolongation of an existing hospitalisation.
- Results in a significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may not be immediately life-threatening, result in death, or require hospitalisation, but may be considered an SAE when (based upon appropriate medical judgement) it jeopardises the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

If a research participant experiences a significant or serious adverse event (SAE), this will be recorded on the CRF and reported to the Sponsor (Breaking Free Online Limited) within 24 hours of site staff becoming aware of the SAE, regardless of the causal relationship to the study intervention. Immediately following becoming aware of the SAE on-site study staff will take any measures deemed appropriate to minimise negative consequences to the participant of the SAE.

All SAEs that occur after informed consent through to the 6-month follow-up timepoint shall be reported to the Sponsor. If a subject does not meet the eligibility criteria during screening, then SAEs need only be reported from the time of informed consent through to the time the subject has been determined not to be eligible for study participation.

In the event that the Sponsor is notified of an SAE, they shall submit a report on the SAE to the main REC of the study using the appropriate form within 15 days of becoming aware of the event. The event will be reported when, in the opinion of the Sponsor, it is 'related', that is, it resulted from administration of any of the research procedures; **and** 'unexpected', that is, the type of event is not an expected occurrence. Having assessed the severity, causality, seriousness and expectedness of the event, the form will describe the type of event, the circumstances of the event and the assessment of the implications, if any, for the safety of study participants and how these will be addressed. The possibility of breaching the participant's confidentiality will then be assessed on an individual basis by the Sponsor and will only take place when by doing so the participant may benefit from it. Following submission of the SAE to the REC, any potential protocol amendments or training needs will be addressed by the Sponsor.

9. DATA, DATA ANALYSES, AND STATISTICAL METHODS

9.1 SOURCE DATA

The participant informed consent forms, hospital records, and data from completed standardised psychometric assessments will be the principal sources of data.

Informed consent forms shall be retained by the study site. Data retained within patient hospital records regarding eligibility criteria and compliance with standard treatment programmes shall be directly transcribed onto the CRF after collection, however the original records shall be retained by the study site for source data verification purposes.

Primary source data will also consist of all recorded information captured by the BFO backend database, as well as survey responses from the secure psychometric assessments hosted by SurveyMonkey, which will be electronically managed and will be the responsibility of the Sponsor.

9.2 ANALYSIS POPULATION

The *all-randomised population* will consist of all participants randomised into the study that have completed the Screening Visit and randomised into either the intervention group (BFO plus standard treatment) or control group (standard treatment only).

The Breaking Free *all-treated population* will consist of all randomised participants who have completed 8-weeks of BFO plus standard treatment.

The *protocol-compliant population* will consist of all participants randomised into the study who have completed the 8-week treatment period as well as the follow-up assessments at treatment end, and at 3- and 6-months follow-up.

Interim and final analyses will be performed on the basis of an intention to treat (ITT) population with respect to ITT principles. All randomized participants will be included in the ITT-analysis (ITT population).

A per-protocol final analysis will be made including only participants without a protocol violation.

9.3 SAMPLE SIZE

Since the study is a parallel-group comparison, equal numbers of participants will be required for each of the groups. The projected sample size will require 61 evaluable participants in each treatment group to achieve enough observed power (assuming an observed power of 0.80 with $\alpha = .05$) with an allowance of 50% attrition at 3- and 6-months follow-up. Therefore, to obtain a total of 122 evaluable participants, it is estimated that a total of 183 participants will need to be recruited and screened. The

sample size may be recalculated after an interim analysis when data for 30 evaluable participants per treatment group are available.

These estimations have been based on previous alcohol and drug studies size samples (Carroll et al., 2008), some of which have used longitudinal statistical analyses (Koski-Jännes, Cunningham, & Tolonen, 2009; Kypri, Langley, Saunders, Cashell-Smith, & Herbison, 2008). It is envisaged that the estimated evaluable participant population will be sufficiently large to enable meaningful descriptive comparisons to be performed. However, these participation numbers may be subject to alterations depending on the interim analyses which will be performed.

9.4 ASSESSMENT OF EFFICACY

The efficacy parameters will be the statistically significant reduction from baseline in substance use, substance dependence, mental health outcomes, and increased quality of life and biopsychosocial functioning, assessed by self-administered standardised psychometric assessments, conducted at baseline, immediately following the 8-week treatment period, and 3- and 6-months follow-up. Assessments will be delivered digitally. The assessment for the BFO group will be completed within the BFO program at the post-treatment timepoint, and via online survey at the respective follow-up timepoints. The control group will complete the measures via online survey software at all timepoints.

9.5 DATA ANALYSES

Quantitative data will be analysed and reported by the Sponsor using SPSS® Version 26.0 (or later). Quantitative analyses will be performed as per the Statistical Analysis Plan (SAP). The principal data analytical strategy will be a repeated measures analysis of variance in order to make a longitudinal comparison of treatment groups for the primary and secondary outcomes along the follow-up time points. The appropriate 95% - confidence interval will be applied. The main statistical analyses will be conducted by the Chief Investigator Dr Sarah Elison-Davies and co-investigators at the University of Manchester (Dr Andrew Jones).

Main analyses based on published research (Elison, Jones, et al., 2017) indicate that data will likely be non-normally distributed and that therefore, most appropriate analyses will be Kruskall-Wallis Analysis of Variance (ANOVA) and Analyses of Covariance (ANCOVA) at each psychometric assessment time point, in order to compare the study groups. Changes over time in psychometric assessment scores within each group will be conducted using Wilcoxon Signed Ranks Tests, assuming data are non-normally distributed. Effect sizes will also be calculated to examine robustness of between group differences and within group changes over time, in addition to examining clinically significant changes over time by analyses of numbers of participants fulfilling clinical threshold scores for substance dependence, depression and anxiety. In addition, regression analyses will be conducted to control for baseline differences between groups in terms of sample size, severity of substance dependence and mental health sequelae, recovery capital, social functioning and quality of life as measured by the battery of standardised psychometric assessments.

Qualitative data collected via semi-structured interviews with participants and staff who have been involved with delivery of BFO as part of the research, will be analysed using thematic analyses. Interviews will be recorded using videoconferencing software and audio files will be sent to a professional transcription service to be transcribed verbatim. When text transcripts are available data will be analysed by identifying quotes that reflect themes and sub-themes relevant to the research questions posed in the qualitative component of the study.

9.5.1 STATISTICAL ANALYSIS PLAN DEVIATIONS

The SAP will be written and finalised prior to any lock of the study database. The SAP will provide a detailed description of the summaries and analyses that will be performed and will clearly describe when these analyses will take place. Any deviation/s from the original SAP will be described and justified in the final report.

9.6 INTERIM ANALYSIS AND REPORTS

Interim analyses will be performed on the first 30 participants of each group to have completed the 3- and 6-months follow-up assessments after treatment completion. The data will be subjected to ANOVA and ANCOVA. Changes over time in psychometric assessment scores within each group will be conducted using Wilcoxon Signed Ranks Tests, assuming data are non-normally distributed. An interim report will be issued prior to completion of the study and a final report will be issued and submitted to the ethics committee within 6-months of completion of the study.

10. MONITORING, QUALITY CONTROL, AND QUALITY ASSURANCE

10.1 STUDY MONITORING

Authorised personnel from within the Sponsor organisation (Breaking Free Online Limited) may contact and visit the investigator sites and shall be allowed to inspect the various records of the study on request (CRFs and other pertinent data) for the purposes of monitoring, provided that participant confidentiality is maintained, and that the inspection is conducted in accordance with local regulations. It is the monitor's responsibility to inspect the CRFs at regular intervals throughout the study to verify adherence to the protocol, the completeness, accuracy and consistency of the data, and adherence to ethical requirements and good practice guidelines. The site investigator and study site team will agree to co-operate with the monitor to ensure that any problems detected during the course of the monitoring visits are resolved promptly. Monitoring intervals for this study shall be based on a risk-assessment undertaken by the Sponsor prior to first participant recruitment, and shall be appropriately communicated to the study site in advance.

10.2 QUALITY CONTROL AND QUALITY ASSURANCE

The design of the protocol represents a randomized-controlled multi-centre study with a sufficient number of participants to be analysed. Rigorous planning and implementation ensure the results will

be provided at the highest level of evidence. The study design, distribution of treatment groups and data monitoring will ensure a high quality of the collected data. Quality control and quality assurance are also supported by the monitoring and biostatistics procedures supervised by the Sponsor. All necessary data and documents will be made available to the Sponsor's internal inspection team or ethical authority

10.3 DATA QUALITY CONTROL AND PROTECTION

The expertise of the study investigators, and site coordinators if applicable, will be documented before and during the study as well as the level of psychosocial care of the research sites.

All CRFs will be completed in English using a black ballpoint pen, and entries must be legible. Errors should be crossed by a single line with original erroneous entry still legible, the correction inserted, and the change initialled and dated by the Investigator or authorised member of the investigational site team. The Investigator will sign and date at indicated places on the CRF.

The participant's data collected via the BFO backend database will be recorded via a centralised electronic Case Management System (CMS) and automated dashboard. These are the responsibility of the Sponsor and will contain no identifiable information (the data will be anonymous at the point of entry). Demographic data will be recorded; however this information is neither identifiable nor traceable to any individual and relates to age, gender and ethnicity only. Non-identifiable and anonymous information regarding the participants' alcohol and drug use, severity of alcohol and drug dependence, mental health, quality of life and biopsychosocial functioning, will be collected via standardised psychometric assessments online. There will be no links to health records or any other database. All data shall be encrypted and password protected, and the system shall only be used by authorised personnel within the Sponsor organisation for analysis and appropriate storage. All source data will be stored in secure, locked facilities and archived for a period of 20 years according to MRC guidance, after which time hard copy data will be shredded and disposed of and electronically stored data will be deleted using appropriate software.

10.4 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Sponsor will ensure that it is specified in the protocol or other written agreement that the research sites will permit data collection, study-related monitoring, audits and ethical authorities' review inspections if required, providing direct access to source data or documents as appropriate.

10.5 ETHICS

Before the start of the study, the study protocol, the informed consent documents, and any other appropriate documents will be submitted to the independent REC for approval. Before the first participant is enrolled in the study, all ethical and legal requirements will be met. The REC will be informed of all subsequent protocol amendments, which will be assessed to determine whether a formal approval would be required before implementation and whether the informed consent

document should also be revised. The Sponsor will keep a record of all communications with the REC, which shall also be filed in the Investigator Site File (ISF).

10.6 SUBJECT INFORMED CONSENT

An informed consent document including both information on the study (the "Participant Information Sheet") and the Informed Consent Form will be provided to the participant by the investigator or designee prior to recruitment to the study. All material provided to the participant shall be written in plain English with every effort made to ensure it is understandable to the participant. The authorised person who provides information and obtains informed consent will be named on the documents and will assess that the participant is capable of giving written informed consent. This will be after an adequate explanation of the aims, methods, anticipated benefits and potential inconveniences of the study are explained to the participant.

Only after reading the informed consent documents, and sufficient time and opportunity have been provided to inquire about details of the study and to decide whether or not to participate in the study, the participant may sign the written consent form. A copy of the signed consent document will be provided to the participant. The original signed consent document will be retained by the investigator and may be subject to inspection by representatives from ethical authorities.

Please note that as part of the access to BFO the participant will need to agree to a number of data privacy statement around how Breaking Free Online Limited uses data however, the agreement to these will be overruled by the Consent Form status in any case (i.e. the participant's withdrawal from the study).

10.7 PARTICIPANT CONFIDENTIALITY

The site investigator must ensure that the participant's privacy is maintained. On the CRF or other documents submitted to the Sponsor, participants will be identified by a participant identification number only. If required, site investigators shall permit direct access to participant's records and source documentation for the purposes of inspection by representatives from ethical authorities. The responsible Sponsor monitor (or designee) shall be permitted - on request - to inspect the various records of the trial (CRFs, other pertinent data) in addition to subject records needed to verify entries on the CRF, provided that subject confidentiality is maintained in accordance with local regulations and requirements.

The Sponsor must also ensure that the participant's privacy is maintained. There will be no identifiable information recorded or stored by the Sponsor at any point. Non-identifiable and anonymous information regarding the participants' demographic details, alcohol and drug use, severity of alcohol and drug dependence, mental health, quality of life and biopsychosocial functioning will be collected via the battery of standardised psychometric assessments online.

10.8 STUDY DOCUMENTATION AND DATA STORAGE

All members of the research team will observe and work within the confines of data protection regulations. Study data will be entered manually or electronically as appropriate. The participants will be identified by a study specific participant number – a "screening number" prior to randomisation, and a "randomisation number" thereafter.

Consideration should be given to security and environmental risks when storing data. No study document will be destroyed, assigned to another party or moved to another location without prior written agreement between the Sponsor and the investigator. When the study is completed, the Sponsor will take responsibility for the storage of the study documentation.

10.8.1 SOURCE DOCUMENTS AND BACKGROUND DATA

All information collected during the study by the research site must be entered by the Investigator or designee onto the CRF as soon as possible after the information is collected, in accordance with Good Documentation Practices. Explanation should be provided for all missing/incomplete data in the CRF (with initials and date) by the site investigator. The Sponsor will check completeness and validity of the data. The site investigators (or designees) are obliged to clarify or explain any queries from the Sponsor or representatives from ethical authorities.

For enrolled subjects, all and only data for the procedures and assessments specified in this protocol and are required by the CRFs to be submitted on the appropriate CRF (unless source data are transmitted to the Sponsor or designee electronically, e.g. psychometric assessments completed in BFO or on SurveyMonkey). Copies of completed CRFs shall be submitted to the Sponsor at pre-determined intervals throughout the study to enable ongoing review of study data. Original CRFs shall be retained by the study site.

Subjects' clinical source documents to record key efficacy and safety parameters independent of the CRFs include the subject's clinic records; doctor's and nurse's notes; appointment logs; signed ICFs; consultant letters; and subject Screening Logs. These shall be retained by the study site, and made available to the study monitor upon request, and within the confines of the study site, for source data verification purposes.

All qualitative interview data will be recorded onto an encrypted digital Dictaphone, with all data then being securely transported to the Breaking Free Online offices where the interview data will be transferred to a password protected external hard drive which will be stored in a secure, locked facility after transcription. Interviews will be be sent to a professional transcription service to be transcribed verbatim. All interview transcripts will be anonymous with no participant identifiable information, apart from their study identification number. No participant identifiable information will be included in any evaluation findings dissemination materials.

10.8.2 INVESTIGATOR SITE FILES

The ISF will contain, at a minimum, the protocol and protocol amendments, CRFs, query forms, REC, research authority, and governmental approvals with correspondence, sample informed consent documents, staff curriculum vitae and authorisation/training forms, and other appropriate correspondence and documents pertinent to the study.

The site investigators must retain a comprehensive and centralised filing system of all study-related documentation that is suitable for inspection by the Sponsor and representatives of ethical authorities for the duration of the study and must retain essential documents until notified by the Sponsor. Consideration should be given to security and environmental risks. No study document will be destroyed, assigned to another party, or moved to another location without prior written agreement between the Sponsor and the investigator. When the study is completed, the Sponsor will take responsibility for the storage of the study documentation.

10.8.3 SPONSOR RESEARCH DATABASE

The Sponsor's Research Database Policy states that Breaking Free Online Research Databases must be retained by the Sponsor unless specific permission to do otherwise is granted by the Sponsor based on legal, regulatory, and ethical requirements. The appropriate security measures will be applied to control access to the databases when the study is complete (i.e., secure electronic storage, personnel access restrictions, etc) and databases will be stored in a way that permits retrospective audit if necessary. Ethical approval had been granted for the BFO research database, containing service user assessment and programme usage data, to be used for research purposes ('Breaking Free Online Research Database'; National Health Service Health Research Committee London – South East; Reference 12/LO/0278, 22.05.2017).

10.9 DISCLOSURE OF INFORMATION

Information concerning this study, patent applications, processes, scientific data, or other pertinent information is confidential and remains the property of the Sponsor with the exception of any identifiable information which is the responsibility of the research site. The site investigators may use this information for the purposes of the study's progress or completion only.

It is understood by the site investigators that the Sponsor will use the non-identifiable information developed in this study in connection with the use of BFO therefore, may disclose it as required to other investigators (in compliance with Sponsor's Research Database Policy) and ethical authorities under an appropriate understanding of confidentiality with these parties. This does not supersede any existing confidentiality agreements.

In order to allow the use of the information derived from this study, the site investigator understands that he/she has an obligation to provide complete assessments and all required non-identifiable data developed during this study to the Sponsor. Verbal or written discussion of results to third parties

prior to study completion and full reporting will only be undertaken with written consent from the Sponsor.

11. STUDY MANAGEMENT

Responsibility for study coordination and data management will be with the Chief Investigator and Principal Investigators within the Sponsor organisation (Breaking Free Online Limited) and data analyses will be the responsibility of the Chief Investigator (Dr Sarah Elison-Davies) and Co-Investigators (Dr Andrew Jones). A detailed allocation of responsibilities will be completed by the Chief Investigator as a separate document ('Delegation Log'), which will be followed by the investigational site personnel and Sponsor personnel.

12. FINANCIAL AND INSURANCE ARRANGEMENTS

Financial and Insurance agreements with the research sites will be addressed in a separate document, which will only apply where all study procedures have been carried out according to this protocol. Site investigators must hold their own professional indemnity insurance suitable for the activities in relation to the study, and the investigator's insurance must satisfy any local requirements.

13. SPONSOR PUBLICATION POLICY AND DISSEMINATION OF RESULTS

13.1 PUBLICATION POLICY

The design and the final results of this study will be published and the authorship will be assigned by the Sponsor. All participating Investigators who contribute to this study will be acknowledged in the related publications. It is the intention of the Sponsor to publish the results of the study, once all participants have completed the study and the statistical analyses have been performed. The investigator may not publish or divulge the results of their population cohort or any site data gathered from this study without the Sponsor's written permission. The Sponsor will allow 60 days for Investigators to review and comment on the pre-publication manuscript prior to submission for publication. Extreme care will be taken so that the participants will not be able to be identified by a single, or combination of, details provided in the study.

13.2 DISSEMINATION OF RESULTS TO PARTICIPANTS

Lay-language communication of results will be available to participants via newsletters, social media (e.g. Facebook), peer-reviewed publications, conferences and presentations.

14. CONFLICTS OF INTEREST

All study personnel at the research site must disclose any financial and/or personal relationships with other persons and organisations which might impair the independence of their work. The main database containing all data from the study will be held by Breaking Free Online Limited, however all organisations utilising the treatment programme will be able to access and independently verify the anonymous dataset for their service, thereby minimising the conflict of interest. Additionally, independent Co-Investigators (Dr Andrew Jones) from the University of Manchester will work alongside the Chief Investigator Dr Sarah Elison-Davies (Breaking Free Online Limited) to oversee the research is conducted to an adequate scientific standard.

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