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ABSTRACT

Introduction: Specialised early intervention services have demonstrated improved outcomes in first episode psychosis (FEP); however, clinical gains may not be sustained after patients are transferred to regular care. Moreover, many FEP patients remain socially isolated with poor functional outcomes. To address this, our multidisciplinary team has developed a moderated online social media therapy (HORYZONS) designed to enhance social functioning and maintain clinical gains from specialist FEP services. HORYZONS merges: (i) peer-to-peer social networking; (ii) tailored therapeutic interventions; (iii) expert and peer-moderation; and (iv) new models of psychological therapy (strengths and mindfulness-based interventions) targeting social functioning. The aim of this trial is to determine whether, following two years of specialised support, and 18-month online social media-based intervention (HORYZONS) is superior to 18 months of regular care.

Methods and analysis: This study is a single-blind randomised controlled trial. The treatment conditions include HORYZONS plus Treatment as Usual (TAU) or TAU alone. We recruited 170 young people with FEP, aged 16-27 years, in clinical remission and nearing discharge from EPPIC, Melbourne. The study includes four assessment time points, namely, baseline, 6, 12 and 18-month follow-up. The study is due for completion in July 2018 and included a 40-month recruitment period and an 18-month treatment phase. The primary outcome is social functioning at 18 months. Secondary outcome measures include rate of hospital admissions, cost-effectiveness, vocational status, depression, social support, loneliness, self-esteem, self-efficacy, anxiety, psychological wellbeing, satisfaction with life, quality of life, positive and negative psychotic symptoms and substance use. Social functioning will be also assessed in real time through our Smartphone Ecological Momentary Assessment (SEMA) tool.

Ethics and dissemination: Melbourne Health Human Research Ethics Committee (2013.146) provided ethics approval for this study. Findings will be made available through scientific journals and forums, and to the public via social media and the Orygen website.

Trial registration: ANZCTR; ACTRN12614000009617

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first randomised controlled trial to evaluate the effectiveness of an online intervention designed to extend the benefits of specialised early psychosis services
- HORYZONS is the first intervention to harness online social media technology and use strengths and mindfulness-based interventions to improve long-term recovery in early psychosis
- HORYZONS was developed by a multidisciplinary team in partnership with young people, with the purpose of being scalable across, and embedded within, early intervention services
- In line with recent clinical trials evaluating extended models of care for early psychosis services, the control intervention consists of routine care as opposed to a placebo intervention accounting for increased attention and unspecific therapeutic factors
- Due to the nature of psychosocial interventions, participants and clinicians were not blind to treatment allocation

INTRODUCTION

Psychosis can be a devastating mental health disorder. Onset is often in adolescence and early adulthood and in many cases follows a chronic and relapsing course that results in great personal suffering and societal costs[1-2]. Against this daunting picture, early intervention is now seen as the most promising and evidence-based approach to improve the long-term outcomes of psychosis[3]. Specialist First Episode Psychosis (FEP) services originated in the early 1990s with a focus on reducing treatment delays, providing youth friendly, phase-specific support and preventing the development of long-term functional and social disability[3]. Over the past two decades, several randomised controlled trials (RCTs) conducted across countries and mental health systems have demonstrated that these services improve psychotic symptoms, reduce relapse rates, foster patient satisfaction and result in tangible economic benefits[4-8].

There are limits, however, to the impact of early intervention services. First, specialist FEP services typically have treatment resources for 2 years, and recent reports indicate that the benefits of early intervention seen at the end of 2 years may not persist at 3 years post-discharge[9-10]. Second, even after receiving specialize services, functional recovery lags behind symptomatic remission, and many young people with FEP experience significant social functioning deficits and poor quality of life[11]. Indeed, the onset of psychosis has been characterized as a 'social network crisis'[12], which is not improved by early intervention services. Young people with psychosis have smaller social networks, fewer people to turn to in a crisis[13], are between 5 and 9 times less likely to have confidants compared with their peers[14], and report on average 2-3 lonely days per week[15]. Smaller social networks and lower perceived social support are, in turn, predictive of poorer long-term functional outcomes, shorter time in remission, and increased hospital admissions[16-18]. Taken together, these research findings underscore the need for new treatment approaches that extend the benefits of early intervention services and, ultimately, promote long-term social recovery.

While difficulties with social functioning are commonplace following FEP and can lead to poor long-term outcomes, very few studies have assessed interventions targeting social functioning as a primary outcome. The most researched psychological intervention for FEP

has been cognitive behavioural therapy, which is primarily focused on reducing the positive symptoms of psychosis[19]. Recognizing this gap, a recent trial evaluated a social recovery therapy in combination with early intervention services to enhance social recovery in FEP [19]. Study results showed an improvement in structured activity in those receiving the intervention relative to those receiving early intervention services alone. The renewed focus on social recovery is also consistent with recent psychological models, which have proposed self-efficacy[20-21] and positive emotions[22] as important targets to promote social functioning in psychosis. Strengths- and mindfulness-based interventions have been put forward as key interventions to increase self-efficacy and positive emotions[23], respectively, with preliminary studies supporting their potential to improve social functioning in psychosis[24-25].

A complementary approach to improving long-term recovery in FEP is to extend the duration of specialised treatment[26-27]. This view is underpinned by findings that the first 5 years after psychosis onset constitute a critical period, determining longer term outcomes[27-28]. Similarly, promoting sustained social and functional recovery in the early course of psychosis appears to be a key path towards long-term functional recovery[29]. Two recent randomised controlled trials have evaluated the effects of the current model of early intervention (i.e., 2 years of specialised treatment) vs. an extended model of care (i.e., 5 years of specialised treatment)[30-31] with mixed results. In one of these trials, the extended model of care improved length of remission of positive and negative symptoms relative to regular care[31]. Conversely, a second study showed no significant improvements in clinical or social outcomes associated with the extended model of care[30]. An additional clinical trial examined the effects of prolonging the period of specialised care for 12 months (i.e., three years vs. two years of specialised treatment)[32]. This study showed significant improvements in functional outcomes at the end of the 3-year compared with 2-year specialised support. However, treatment benefits were not sustained, with no significant differences across treatment groups at 1 and 2 years post specialised intervention[32].

An alternative to prolonging the duration of specialised intervention is to offer extended, lower intensity maintenance treatment following the first two years of specialised treatment[27]. This is supported by findings that the termination of the specialised intervention and transfer of care brings about feelings of loss for the patients[9] and significantly derails engagement with treatment services[33], a pivotal element of early

intervention programmes. Thus, a lower intensity level of care may bridge the gap between specialised intervention and standard treatment and provide a cost-effective alternative to bring about sustained benefits in FEP. This approach has shown promising results in a single group study, with improvements seen at 2 years (i.e., end of specialised care) being maintained at 5 years (i.e., after 3 years of lower intensity specialised treatment)[27].

Online- and mobile-based interventions can also provide a lower intensity, cost-effective and engaging approach to prolonging the benefits of specialised FEP services. Indeed, the extant research shows that online interventions are feasible, acceptable, and may improve a range of important domains in psychosis treatment including psychotic symptoms, hospital admissions, social connectedness, and depression[34-35]. However, most studies conducted to date have employed uncontrolled designs, were underpowered, included short follow-up periods, targeted people with chronic schizophrenia, did not use online social media, and did not specifically target social functioning[34]. To the best of our knowledge, only one pilot study has evaluated the acceptability and preliminary benefits of an online intervention in young people with FEP[36].

Finally, online social networks provide a particularly promising avenue to foster social functioning in young people with FEP. A recent study revealed that 89% of young people aged 18-29 use social media daily[37], a frequency that is on the rise[38]. Use of online social media has been associated with increased life satisfaction[39], self-esteem[39], and social capital[40], as well as lower loneliness and depression[41], particularly for those who post content to the social network and are active users[42]. Recent surveys indicate that social media habits of young people with psychosis resemble that of their peers: virtually all regularly use social media, on average 10 times and 2 hours per day[43-44]. Particularly relevant to the therapeutic potential of social media in FEP, 78% would like to obtain help from clinicians via social media, 40% increase their use of social media when experiencing symptoms[43] and the majority strongly agree with using social media as a platform from mental health support[45]. Thus, coupled with psychological interventions specifically addressing social recovery such as strengths- and mindfulness-based approaches, social media provides an opportunity deliver acceptable, extended lower intensity support with potential to foster long term social functioning in FEP.

Aims and hypotheses

The objective of this trial was to determine whether extending the treatment period of a specialised FEP service through an 18-month, step-down, novel online social media-based intervention (HORYZONS) produces better outcomes compared with 2 years of specialist FEP treatment followed by treatment as usual (TAU), using a randomised controlled single-blind design. An additional aim of this trial is to determine the cost-effectiveness of HORYZONS.

The primary hypothesis is that, relative to TAU, HORYZONS will lead to improved social functioning at 18 months amongst young people with FEP. The secondary hypotheses are that, relative to TAU, HORYZONS will reduce the rate of hospital admissions due to psychotic symptoms and lead to improvements in depression, vocational outcomes, satisfaction with life, social support, loneliness, self-esteem, self-efficacy, anxiety, stress, positive and negative psychotic symptoms, psychological wellbeing, quality of life, and substance use. Finally, we hypothesise that HORYZONS will be more cost-effective than TAU.

METHODS AND ANALYSIS

Patient and public involvement

Young people with lived experienced were extensively involved in the design of the HORYZONS system, with continuous consultation and co-design activities over the development period. In addition, as noted above, young people played a key role in the delivery of the intervention, with peer supporters actively management of the social network, the group online problem-solving feature ('Talk it out') as well as providing one on one peer support via the online chat system.

Orygen integrates youth reference and consultation groups whose role is to provide advice on all research activities conducted at the centre. Both groups were involved in the design of the study as well as the evaluation of the face validity of the questionnaires. Patients were not involved in the recruitment of participants into the study.

Online moderators regularly consulted with patients to ensure that the intervention did not result in increased perceived burden for the participants. Moderators and participants collaboratively developed a shared formulation with explicit and agreed expectations for frequency of use and support from moderators and peer supporters.

The results of the study will be disseminated via the Orygen website. In addition, participants will be notified via a text message at the point the results become available.

Study design

The study design is an 18-month, parallel groups, single-blind, randomised controlled trial (RCT) in which 170 participants with remitted FEP have been allocated to either the current mainstream model of early intervention for psychosis (i.e., 2 years of specialised treatment followed by discharge to treatment as usual; TAU), or TAU in tandem with a moderated online social media intervention (HORYZONS), for 18 months.

The design includes four assessment time points: baseline, 6 months, 12 months and 18 months. The RCT includes a 40-month recruitment period and an 18-month treatment phase, with the study being completed within 5 years. The protocol development addressed all aspects of Good Clinical Practice[46], CONSORT EHEALTH criteria[47] and SPIRIT guidelines[48].

Setting

Recruitment of the trial participants commenced in October 2013, with the first participant enrolled 29 November 2013, and finalised in January 2017 at Early Psychosis Prevention and Intervention Centre (EPPIC), a subprogram of Orygen Youth Health, Melbourne. EPPIC is a publicly-funded specialist FEP program servicing 250 new referrals for FEP per year. EPPIC provides 18 months to 2 years of specialised care after which patients are discharged and transferred to treatment as usual[49]. Follow-up assessments will be concluded in July 2018.

Participants

Inclusion criteria for participants were: (a) a first episode of a DSM-IV psychotic disorder or mood disorder with psychotic features; (b) aged 16-27 years inclusive; (c) ≤6 months treatment with an antipsychotic medication prior to registration with EPPIC; (d) remission of positive symptoms of psychosis, defined, using the Positive and Negative Syndrome Scale (PANSS)[50], as 4 weeks or more of scores of 3 (mild) or below on items P2 (conceptual disorganization) and G9 (unusual thought content), and scores of 4 (moderate) or below with no functional impairment on items P3 (hallucinatory behaviour) and P1 (delusions). Additional inclusion criteria to ensure low level of risk within HORYZONS included: (f) low

aggressiveness, defined by a score of 3 or below on the poor impulse control item of the PANNS for the month prior to study entry; and (g) moderate or lower suicidal risk defined as a score of 4 or below on the suicidality subscale of the Brief Psychiatric Rating Scale – expanded version (BPRS)[51] for the month preceding study entry. Finally, participants were required to nominate an emergency contact to be eligible for the study.

Exclusion criteria included: (a) intellectual disability; and (b) inability to converse in or read English. Additional exclusion criteria to ensure safety within the online system included (c) a DSM-IV diagnosis of either antisocial personality disorder (ASPD); or (d) borderline personality disorder (BPD) as well as clinical evidence that the BPD features cause interpersonal difficulties in the treatment environment.

The SCID-I/P[52] was used as the standardized measure of DSM-IV diagnosis of mental illness. The BPD (13 items) and Conduct Disorder/ASPD (22 items) screening questions of the SCID-II Personality Questionnaire were used to assess for BPD and ASPD[53].

Withdrawal from the trial occurred if: (a) participation in the study interfered with appropriate clinical management of risk of harm to self or others (as judged by the treating clinicians and/or senior researchers); (b) serious adverse events developed that could be associated with the online intervention; and (c) participants failed to comply with the terms of use of the online intervention. Withdrawal from the study could be at the request of the participant, or at the discretion of the investigator.

Enrolment and randomisation

The recruitment and allocation procedures are depicted in Figure 1. The study coordinator liaised with the Orygen Youth Health Quality and Evaluation Unit to obtain a list of young people with FEP nearing discharge from EPPIC. This list was updated every 3 months during the recruitment phase. The study coordinator assessed the initial eligibility of young people within 3 months of discharge in consultation with EPPIC case managers and treating doctors. Clients deemed potentially eligible were approached by the study coordinator to obtain written informed consent. Next, eligibility was confirmed through a screening assessment. Eligible participants completed the baseline assessment and were subsequently randomised to either HORYZONS plus TAU or TAU alone at a ratio of 1:1. Randomisation was carried out

remotely according to the International Conference on Harmonization E9 Statistical Principles Guidelines[54]. An independent statistician created the randomisation sequence using permutated blocks. The study coordinator randomised the participants via a secure online Research Project Management System (RPMS). The RPMS sent an automated email to the study coordinator and investigators notifying them of the outcome of randomisation. Finally, the study coordinator informed the participant of the allocation.

The study assessors undertaking the follow-up assessments are kept blind to treatment allocation via the following mechanisms: (1) at the commencement of each research interview the assessor reminds participants of the importance of the blind, (2) study assessors are excluded from all clinically related discussions regarding participants, and (3) the assessors were forbidden from accessing participants' medical records. The assessors record their best guess of participants' treatment allocation at 6, 12 and 18 months' follow-up in order to enable an assessment of the success of treatment concealment. In addition, any instances of unblinding were recorded.

Interventions

HORYZONS

HORYZONS has been developed by a multidisciplinary team of researchers, clinical psychologists, programmers, creative writers, graphic artists and experts in human computer-interaction[36, 55]. HORYZONS was designed following participatory design principles with the purpose of addressing social functioning in early psychosis. For example, focus groups with young people with psychosis revealed that they favoured a social media-based platform enabling meaningful peer-to-peer contact as well as clinicians' support[35, 56]. In addition, young people called for online interventions focused on promoting personal strengths and self-efficacy as opposed to merely ameliorating symptoms and deficits. Finally, young people indicated that the system should provide self-guided, interactive, tailored interventions, relevant to their changing needs[35, 56].

Informed by young people's continual feedback as well as relevant research in the mental health and human computer interaction fields[55], the design of HORYZONS merged (1) interactive online therapy ('Pathways and Steps'), (2) peer-to-peer online social networking ('the café'), and (3) peer and (4) expert moderation. All components of HORYZONS were

designed to reinforce each other, creating a flow for the young person between the social and therapy elements. For example, young people are encouraged to post comments and interact with others while engaging with therapy content, and are, at the same time, prompted by moderators to practice their strengths or use skills they have learned while engaging with the social network. Young people can log on to Horyzons at any time via an Internet-enabled desktop or mobile device.

Interactive online therapy modules ('pathways and steps')

HORYZONS integrates a number of online 'pathways' organized into distinct themes including: understanding psychosis, identifying and exercising personal strengths, promoting positive connections with others, fostering positive emotions, early warning signs and prevention of relapse, managing stress and anxiety, dealing with depression, and vocational skills. With the aim of increasing the usability and take-up of therapeutic content, pathways consist of thematically related interactive therapy 'Steps'. The online 'Steps' are discrete, interactive, evidence-based therapy modules primarily targeting social functioning in young people with psychosis; for example, through fostering self-efficacy (e.g., identifying personal strengths via an interactive card-sort game based on the strengths-based framework [36]), positive emotions and subjective wellbeing (e.g., practicing mindfulness and self-compassion), or positive connections with others (e.g., illustrating how to respond empathically to others). The content of the Steps was informed by previous studies linking use of personal strengths, increased self-efficacy and positive emotions with improved social functioning in psychosis[21-22, 25, 57]. Online Steps further address comorbid symptoms such as anxiety and depression as well as vocational support (informed by our previous work[58]). Finally, the design of HORYZONS and therapeutic content was strongly influenced by self-determination theory, an empirically supported theory of motivation which focuses on the processes and social environments that facilitate or hamper social functioning[59].

The Steps incorporate prompts for participants to share their thoughts and reactions to the therapeutic material with other users through embedded 'Talking Points'. To ensure that therapeutic content is translated into behavioural change, the Steps entail behavioural prompts entitled 'Do its'. For example, following a Step about fostering positive connections, the participant will find specific behavioural suggestions (or 'do its') to exercise a therapeutic skill (e.g., empathy) in specific contexts (e.g., school). 'Do its' are also related

to the participant's specific strengths (e.g., using kindness in social interactions). A 'Playlist' stores and schedules any 'Do it' the participant wants to complete in the future. Moreover, participants can rate, like, comment on, and share any Step or 'Do it' with others via the social networking newsfeed. Participants can also keep track of 'trending' Steps, which users have completed specific steps, 'Do its' or pathways, or identify other young people who share their personal strengths. Finally, young people support each other's efforts to take on specific behavioral changes via the 'Team up' function (e.g., by supporting or joining others in their efforts to take on specific challenges).

Social network features

Participants are encouraged to communicate with one another and with peer and expert moderators through the online social network or 'Café' to foster social support. Expert Moderators (clinicians) are identifiable as a separate user class within the network. Each participant creates their own profile with images, and can visit the wall of fellow users, where their posts and general activity are displayed. Posts can include 'icebreakers' (to encourage social interactions, e.g. What's the worst gift that someone gave you?), user-generated threads, 'reactions' (designed to facilitate social support, e.g., 'I get you', 'thinking of you') as well as content related to mental health (e.g., recent steps taken by others) or general interest.

A final feature of HORYZONS is Talk it out (TiO), an online group function informed by the evidence-based problem-solving framework[60]. A TiO enables users to nominate issues (e.g., 'how to break through shyness and make new friends?'), which are discussed in moderated groups through structured phases (e.g., brainstorming, pros and cons, wrap-up). Previous problems and group solutions are stored in the system providing an easily accessible 'solution wiki' for future young people.

Expert and peer moderation

HORYZONS integrates online personal therapist support (by clinicians with experience treating young people with psychosis). Their role is to customize evidence-based interventions, monitor participant's clinical status and ensure the safety of the social network. Each therapist is assigned a caseload (i.e., a 20% full time equivalent online moderator can comfortably manage 20-25 participants), which they follow for the duration of the trial. Following the baseline assessment and initial face-to-face orientation to the system, the

therapist makes contact with the participant for a brief phone meeting reviewing their personal needs and preferences[61]. Expert moderators then develop brief case formulations which are presented during weekly supervision meetings with senior clinical psychologists from the team. Guided by the individual formulation, moderators send each client tailored content suggestions weekly (e.g., a Step or 'Do it') with a focus on improving social functioning. Suggestions appear on the user's home page and they receive a system notification, which is also delivered via SMS as determined by the participants settings. Young people can rate the helpfulness of the suggestions, which moderators use to tailor subsequent recommendations. Expert moderation was informed by the supportive accountability model[61] a theory-driven framework operationalising how human support increases user engagement, the self-determination theory[59] and strengths-based models[62] as a means of enhancing users' engagement and self-efficacy.

In addition to clinical moderation, HORYZONS incorporates online vocational support. Drawing on our previous work[58], the vocational moderator provides individualised online vocational support, which can include: assessing young people's preferences and training, identifying suitable competitive job openings, supporting young people in specific job seeking activities (e.g., writing a CV), or preparing for a job interview.

The 'cafe' is led by trained young people with lived experience of mental illness ('Super-Users'). Super-Users are peer moderators who facilitate social learning using HORYZONS in desired ways (e.g., self-disclosing, using therapy content to deal with difficulties). Super-Users also seed discussion threads and 'icebreakers' to enable relevant, enjoyable conversations and facilitate meaningful relationships. Finally, peer moderation serves to normalise experiences, counteract stigma and promote engagement. Peer moderation was informed by the social learning theory which posits that those who observe others (i.e., superusers) being rewarded for a particular behaviour (e.g., completing a step or commenting on the social network) are more likely to modify their beliefs and subsequent behaviour[63].

Control intervention

Participants randomised to regular care receive Treatment as Usual (TAU) following discharge from the EPPIC program. TAU consists of a range of treatment options delivered by generic medical or mental health services typically available to young people in the

absence of enrolment in the study. These can include follow-up by a general practitioner, private psychiatrist, primary care youth mental health services, or adult mental health services which deliver multidisciplinary psychiatric care (including medical follow-up, case management and acute psychiatric care as appropriate). Prior to discharge from specialised FEP support the EPPIC team, in collaboration with the young person, recommends the best treatment option based on the complexity of the young person's needs. Those with complex needs are referred to adult mental health services, while young people who attained a good level of recovery and remained stable are recommended primary care services. Additionally, TAU participants are provided with a printed leaflet containing relevant information on existing e-mental health resources for young people (i.e., Moodgym, e-headspace, Reach-out, and OYH Client's hub).

Safety protocol

The safety protocol is comprised of 3 levels of security including: (1) system and privacy protection; (2) online safety; and (3) clinical safety[64].

HORYZONS is hosted on a University of Melbourne web server. The University has industry standard measures in place to prevent unauthorized access to the server. The online system also integrates measures to secure the application and database against unauthorized access. These measures conform to industry best practice as defined by the Open Web Application Security Project (OWASP). Privacy and online safety are managed in accordance with the Australian Communications and Media Authority (ACMA).

The study coordinator carries out an initial face-to-face orientation with HORYZONS participants, including details of the terms of use. Participants were required to accept and comply with the guidelines for safe use of HORYZONS. When needed, participants are offered guidance on appropriate usage of the system. All users are asked to nominate an emergency contact person, such as a close family member. HORYZONS includes a 'report function' which enables young people to report a concern about any material posted by a user. The moderator assesses the basis of the report and responds accordingly, which may include the removal of the material and, in some cases, deactivating or restricting the young person's account. Participants are also able to hide their profile and activity should they become concerned about their privacy.

Clinical risk is managed through manual and automated procedures. First, moderators monitor the system twice daily on weekdays and once daily on weekends for evidence of clinical risk or deterioration. Any detected increased risk activates the HORYZONS crisis protocol which includes one or more of the following: a risk assessment with the young person, inform the research team, alert the emergency contact nominated by the participant, and liaise with suitable emergency services where necessary. In addition, the system incorporates visible emergency guidelines and contact information. Finally, HORYZONS includes an automated keyword detection function, which activates each time a participant posts a contribution indicative of clinical risk or that contains potentially offensive words. The function blocks posts with notifications sent to the young person and the moderator, who can 'unblock' the post should they determine it to be unproblematic.

Temporary withdrawal criteria

In the event of a clinically significant deterioration of psychotic symptoms, increased risk or a hospital admission the clinical moderators perform an assessment to determine the risks and benefits of a temporary withdrawal from HORYZONS. Based on this assessment, and in consultation with the young person, the moderator team determines whether the account is temporarily suspended, or level of access restricted. Following suspensions or restrictions to a user's account, the moderator will contact the young person at monthly intervals to ascertain whether the account is to be reactivated.

Outcome measures

Primary and secondary outcomes are measured at baseline (prior to randomisation), and at 6, 12 and 18 months follow-up (Table 1). Moreover, social functioning is tracked in real time for a period of 7 days after each assessment using ecological momentary assessment using a purpose-built smartphone application, *SEMA*.

Table 1. Schedule of outcome measures

	Baseline	6mo	12mo	18mo
Primary outcome				
Personal and Social Performance Scale (PSP)				
Secondary outcomes				
First Episode Social Functioning Scale (FESFS)				
Hospital admissions[a]				
Calgary Depression Scale for Schizophrenia (CDSS)				
Medical Outcomes Study: Social Support Survey (MOS-SSS)				
UCLA Loneliness Scale				

Self-Esteem Rating Scale-Short Form (SERS-SF)				
Depression Anxiety and Stress Scale (DASS)				
Scales of Psychological Wellbeing (SPWB)				
Satisfaction with Life Scale (SWLS)				
AQoL 8D questionnaire				
The Positive and Negative Syndrome Scale (PANSS)				
Alcohol, Smoking, Substance Involvement Screening Test (ASSIST)				
Smartphone Ecological Momentary Assessment (SEMA)[b]				
Subsidiary measures				
Resource Use Questionnaire				
Exploratory outcomes				
Social Interaction Anxiety Scale (SIAS)				
Social Comparison Scale (SCS)				
2-Way Social Support Scale (2-Way SSS)				
Savoring Beliefs Inventory (SBI)				
Mindful Attention Awareness Scale (MAAS)				
Strengths Use Scale (SUS)				
Self-Compassion Scale Short Form (SCS-SF)				
Physical Activity Questionnaire (IPAQ)				
Waist circumference				
Potential covariates				
Duration of Untreated Psychosis (DUP)				
Scale to Assess Unawareness of Mental Disorder (SUMD)				
Motivational Trait Questionnaire (MTQ)				
Medication Adherence Rating Scale (MARS)				
Bell Lysaker Emotion Recognition Task (BLERT)				
The Hinting Task				
Social Probabilistic Inference Task (SPIT)				
Digit Symbol Substitution Test (DSST)				
Wechsler Test of Adult Reading (WTAR)				
Horyzons specific measures				
Horyzons Perceived Competence Scale (H-PCS)				
Horyzons Self-regulation Questionnaire (HSRQ)				
Horyzons Health Care Climate Questionnaire (HCCQ)				

[a]Continuous from state government databases
[b]Smartphone Ecological Momentary Assessment surveys

Primary outcome

The primary outcome measure is social functioning as measured by the Personal and Social Performance Scale (PSP) at 18 months follow-up. The PSP is a 100-point single-item rating scale derived from Social and Occupational Functioning Assessment Scale (SOFAS) developed specifically to assess social functioning in schizophrenia. The PSP has shown strong psychometric properties[65-66] and has been recommended as one of the best existing tools to assess social functioning in psychosis[67].

Additionally, with the purpose of capturing the full construct of social functioning, the First Episode Social Functioning Scale (FESFS) will be administered at each assessment time point.

The FESFS has been developed to measure social functioning in young people with FEP[68]. Based on their psychometric properties and specific focus on social functioning, the following FESFS subscales were selected: friends and activities (α=0.80); independent living skills (α=0.81); interacting with people (α=0.80); and intimacy (α=0.75). These subscales have shown to correlate with other measures of social functioning, to be independent of psychotic symptoms, and to be sensitive to treatment effects[68].

Secondary outcomes

After the study was initiated, some feasibility issues were identified that led to modifications to the study secondary outcome measures. In the original protocol, we intended to measure psychotic relapse using the PANSS scale via phone or Skype-based assessments conducted every two months throughout the 18-month intervention period. Ongoing measurement of psychotic symptoms at regular intervals is a requirement for the reliable and prospective identification of psychotic relapse[69]. However, despite our best efforts, contacting participants via phone calls at regular intervals raised important feasibility issues, with many participants not answering phone calls or regularly changing phone numbers, leading to significant missing data. Thus, 12 months after study commencement, it was decided to discontinue the regular phone calls and prospective assessment of psychotic relapse. Given the feasibility issues measuring relapse of psychotic symptoms at regular intervals, the following secondary outcomes were added:

1. Hospital admissions due to psychotic symptoms and mental health issues were added as a secondary outcome variable. We have access to reliable and objective hospital admission data from research assessments, clinical files as well as state databases (i.e., Centre for Victorian Data Linkage) spanning the 18-month assessment period. Data on hospital admission from the state databases will be provided by an independent person blind to study design and purpose.

2. Positive and negative psychotic symptoms as measured by the PANNS scale at each assessment time-point.

3. *Physical health* was also initially included as secondary outcome variable because we originally intended to incorporate online modules targeting this domain. However, we

decided not to include therapy content addressing physical health and therefore this variable will be analysed as an exploratory outcome.

Secondary outcome measures include:

(1) *accumulated hospital admissions* due to psychotic symptoms and mental health issues over 18 months;

(2) *vocational status* as measured by employment and/or education status;

(3) *depression* as measured by the Calgary Depression Scale for Schizophrenia (CDSS[70]);

(4) *social support and loneliness* as assessed by Medical Outcomes Study: Social Support Survey (MOS-SSS[71]) and the UCLA Loneliness Scale (Version 3[72]);

(5) *self-esteem* and *self-efficacy* as measured by the Self-Esteem Rating Scale-Short Form (SERS-SF[73]) and Mental Health Confidence Scale (MHCS[74]), respectively;

(6) *anxiety and stress* as determined by the Depression Anxiety and Stress Scale (DASS[75]);

(7) *psychological wellbeing* as measured by Scales of Psychological Wellbeing (SPWB[76]);

(8) *satisfaction with life* as measured by Satisfaction with Life Scale (SWLS[77]);

(9) *quality of life* as measured by the AQoL 8D[78]. This questionnaire can also be used to determine quality-adjusted life years (QALYs), which are useful in economic evaluation studies;

(10) *positive and negative psychotic symptoms* assessed by means of The Positive and Negative Syndrome Scale (PANSS[50]);

11) *substance use* as measured by the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST version 3.1) over 18 months follow-up;

(12) *Cost-effective analysis*: A Resource Use Questionnaire (RUQ) is used to determine the broader resource use of participants (e.g. community mental health services, accommodation, work impacts etc). Additionally, for consenting participants, information regarding utilisation of health care services available via the Medicare Benefits Schedule (MBS - medical, allied health, diagnostic and pathology services) and the Pharmaceutical Benefits Schedule (PBS - medications) will be accessed from the Australian Department of Human Services;

To obtain more dynamic and ecologically valid data on young people's social functioning, participants utilise a custom-built smartphone app, SEMA, which is readily downloadable at no charge to participants owning a smartphone (running Android or iOS operating systems). SEMA delivers surveys (administered for 7 days following each assessment time point) approximately eight times per day for 7 consecutive days. Young people are prompted to complete SEMA surveys at random times every 90 min (±30 min) over a 12-h period (e.g. 10 a.m. to 10 p.m.). SEMA tracks participants' responses in (near) real time, ensuring minimal data loss by uploading responses to a secure server or storing responses on the young person's smartphone when an Internet connection is temporarily unavailable. Each SEMA survey begins with four items assessing momentary positive affect ('At the moment, how happy do you feel?', negative affect ('At the moment, how sad do you feel?'; 'At the moment, how stressed do you feel?') and momentary social isolation (e.g. 'At the moment, how lonely do you feel?') rated on visual slider scales anchored at 0 (not at all) and 100 (very). The order of these four items is randomised at each survey.

Following the momentary affect items, the SEMA survey includes items pertaining to social interactions of the young person (e.g. 'How much time have you spent interacting with others, since last survey?'), perceived social efficacy (e.g., 'How well do you think you handled your social interactions, since last survey?'), perceived social support (e.g., 'have you received support or encouragement from others, since last survey?'), critical comments (e.g., 'Have you felt that others criticized or judged you, since last survey'), and social rank (e.g., How competent have you felt in relation to others, since last survey?'), with all responses being made on visual sliding scales ranging from 0 to 100. The order of these items is also randomised at each survey.

Exploratory outcomes and potential covariates

Additional exploratory outcomes included: *social anxiety* measured through the Social Interaction Anxiety Scale (SIAS)[79]; *social comparison and group fit* as assessed through the Social Comparison Scale (SCS)[80]; *the provision of emotional support* measured via the 2-Way Social Support Scale (2-Way SSS[81]); *anticipatory pleasure* assessed through the Savoring Beliefs Inventory (SBI[82]); *mindfulness skills* as assessed using the dispositional Mindful Attention Awareness Scale (MAAS[83]); *strengths use* as assessed by means of the Strengths Use Scale (SUS[84]); *self-Compassion* as assessed by the Self-Compassion Scale

Short Form (SCS-SF[85]); *physical health* as measured by waist circumference over 18 months follow-up; and, *physical activity* as measured by the International Physical Activity Questionnaire (IPAQ[86]) and by measuring sitting time across different domains[87] (e.g., TV, video, computer, working, etc.).

Finally, potential covariates included: *Duration of Untreated Psychosis (DUP)* defined as the time interval between onset of definite positive psychotic symptoms and first engagement and treatment in an Early Intervention (EI) service; *clinical insight* as assessed by means of the Scale to Assess Unawareness of Mental Disorder (SUMD[88]); *intrinsic motivation* measured through the short form of Motivational Trait Questionnaire (MTQ[89]); *medication adherence* measured by the Medication Adherence Rating Scale (MARS[90]); *emotion processing* assessed by means of the Bell Lysaker Emotion Recognition Task (BLERT[91]); *theory of mind* measured using The Hinting Task[92]; *Jumping to conclusions (JTC)* measured through the Social Probabilistic Inference Task (SPIT); *premorbid intelligence* as assessed via Wechsler Test of Adult Reading (WTAR[93]); and *general cognitive deficits* will be measured through the Digit Symbol Substitution Test (DSST[94]).

HORYZONS specific measures

Usage of HORYZONS is continuously monitored across the study intervention period (i.e., frequency, duration, and patterns of use). In addition, users complete self-report measures informed by the self-determination theory including: their perceived competence using the system, motivations for using it; and their perception of moderation by HORYZONS.

Statistical analysis and sample size

Primary analyses will be undertaken on an intention-to-treat basis. Mixed-model repeated measures (MMRM) analyses will be used to compare change in social functioning between the two treatment groups over the 18-month follow-up. MMRM is the analysis of choice because assumptions of traditional data analysis methods (e.g., ANOVA, logistic regression) may be violated, such as the assumption of homogeneity of regression across time points[95]. Time (baseline, 6, 12 and 18 months) will be the within-subjects factor and group (HORYZONS plus TAU vs. TAU) the between-subjects factor. MMRM will also be used to analyse change in the continuous secondary outcomes over 18 months. Experiencing

sampling data will be analysed using a multilevel structural equation modelling (MSEM) framework[96]. Differential rate of hospital admissions will be analyzed using multilevel logistic regression. Time to hospital admissions will be assessed by survival analysis (using either proportional hazard or accelerated life-time models). Additional comparisons between treatment groups based on completers-only analyses will be conducted. Analyses will be undertaken in accordance with ICH 9 guidelines including a full analysis as well as per protocol set. The per protocol sample will be defined based on receiving a pre-specified minimal exposure to the online intervention (i.e., at least 8 logins over 2 months during the 18-month intervention period).

Economic evaluation will comprise a cost-consequences analysis whereby incremental costs of the intervention will be compared to the full spectrum of study outcomes. A cost utility analysis will also be undertaken whereby the AQoL 8D will be used to QALYs. The evaluation will measure and value any change to the use of health care resources over the period of the study (using the data from the RUQ, MBS/PBS and hospitalisation administrative data) between the two treatment arms; and then compare any additional costs to the additional outcomes achieved. Australian sourced unit costs will be attached to the RUQ (from Australian sources such as the Commonwealth Department of Health, Mental Health Branch). Standardised economic evaluation techniques including incremental analysis of mean differences (using statistical techniques such as generalised linear models) and bootstrapping to determine confidence intervals around incremental cost-effectiveness ratios will be used. If, as expected, the intervention is found to be effective, lifetime and population cost-effectiveness of the interventions will be determined using economic modelling techniques. We will determine the likelihood that the intervention is cost-effective at commonly used value-for-money thresholds such as $20,000/QALY and $50,000/QALY.

The primary outcome is change in social functioning at 18 months follow-up. A recent RCT investigating the effects of extending FEP specialist treatment for 12 months (i.e., a total of 3 years of specialist treatment) reported an effect size of 0.53 (Cohen's d) for functional outcomes for the extended model of care at 12-months (i.e., end of the specialised treatment) compared with TAU (i.e., 2 years of specialist treatment)[32]. If we assume that alpha is set at 0.05 and power (1-β) at 0.90, then a sample size of 70 is required for each of the two groups (Total n = 140) to detect medium effect sizes (0.5; Cohen's d). For the second outcome measure of hospital admissions at 18 months follow-up, there will be 80% power to

detect an improvement in the rate of hospital admissions of at least 43% in the TAU+Horyzons, assuming a hospital admission rate in the TAU of 30% over the 18-month follow-up[2]. We recruited 170 participants, accommodating for an 18% attrition rate, which is consistent with a similar study in terms of design and population[32].

Data management

A custom-built online Research Project Management System (RPMS) is used to manage the electronic data from this study. The RPMS includes an electronic Case Report Form (eCRF) and randomisation functionality. The study assessors record participant-level data on a paper-based Case Report Form (CRF). These data are subsequently entered into the eCRF section of the RPMS. The randomisation functionality of the RPMS is operated by the study coordinator. The RPMS is accessed using a secure website and is stored on a secure server. It is designed to maintain the privacy and confidentiality of participant information and to ensure the integrity of the data. Access to RPMS is restricted to study personnel and the level of access is dependent on the person's role. The study assessors and investigators do not have access to the randomisation section to ensure that they remain blind. Data are stored on three separate secure computer servers, including data collected from the SEMA tool, the RPMS and data accumulated from participant activity within the HORYZONS online system. These various data are aggregated into a single electronic secure databank.

Data verification at all assessment time points is being conducted on 20 randomly selected cases. The selected cases are re-entered by the study coordinator. The a priori acceptable error rate has been set at 0.5%.

Ethics and dissemination

Ethics approval for the trial was provided by The Melbourne Health Research and Ethics Committee (No. 2013.146). All trial participants provided written informed consent prior to enrolment in the trial. For all eligible participants under 18 years of age, parental or guardian consent was also obtained.

The main results of this clinical trial will be published in a peer-reviewed scientific journal. Manuscripts will also be prepared for significant findings regarding the secondary and exploratory aims. These results will be submitted and presented at scientific forums

including national and international conferences in schizophrenia, early psychosis and youth mental health.

DISCUSSION

The onset of psychosis often strikes young people at the prime of their lives, triggering a myriad of adverse psychosocial consequences that can result in entrenched social isolation, unemployment and chronicity[3]. Against this, early intervention is now seen as a key strategy to improve long-term recovery and reduce treatment costs[3]. However, while specialist early psychosis services have been demonstrated that they improve outcomes in FEP, follow-up studies have questioned the maintenance of treatment effects beyond the intervention period[9- 10]. Moreover, social recovery, a priority for young people, continues to be resistant to current intervention approaches[19]. This is the first randomised controlled trial to evaluate a novel online social media intervention designed to address both these challenges.

HORYZONS is the first intervention to exploit online social media technology and apply strengths and mindfulness approaches to improve long-term social recovery in FEP. In addition, the design of the intervention builds on our extensive experience developing and evaluating effective relapse prevention[97-99] and vocational recovery interventions[58] in early psychosis. Thus, HORYZONS weaves together two novel intervention approaches for FEP with established evidence-based protocols, while drawing on a strong theoretical base for social recovery in early psychosis (i.e., self-determination theory[59], broaden and build theory[22]).

Building on a previous successful pilot study[36], HORYZONS was co-developed with end-users and service providers. The online system was designed to be scalable, embedded within clinical practice and delivered across early intervention services. Specifically, HORYZONS is moderated by EPPIC clinicians as part of their routine clinical role (i.e., clinicians would allocate a proportion of their clinical time, typically 20 to 30%, to online moderation). Moderation and training procedures have been manualised and require minimum specialised training (2 days). Therapist efficiency using HORYZONS is estimated to be 5 times higher than that of specialised FEP services (100 vs. 20 young people of a typical caseload in an early psychosis clinic). Thus, if successful, HORYZONS will provide a

scalable, cost-effective intervention approach to extend the benefits of early intervention and improve social functioning in FEP patients.

A limitation of the current study is that the control intervention consists of routine care, as opposed to a sham intervention accounting for increased attention and unspecific therapeutic factors. That said, this decision was made to enhance the external validity of the findings by replicating the current mainstream follow-up options available to FEP young people beyond their involvement in early intervention services. As such, this study is expected to provide evidence of cost-effectiveness of a step-down model of care instead of generating controlled evidence on the specific treatment components driving improved outcomes. Of note, the design of this study parallels that of recently published randomised controlled trials examining extended interventions for FEP services, with TAU being the control intervention across all three studies[30-32].

Sustained and meaningful recovery is the ultimate goal of early intervention services as well as the most valued outcome by young people and their families[100]. This is the first randomised controlled trial to evaluate an online-based intervention as a means to extend the benefits of specialised early intervention services and foster long-term social functioning in FEP. Thus, if successful, HORYZONS has the potential to augment the benefits and long-term impact of the current model of early intervention for psychosis.

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AUTHORS' CONTRIBUTIONS

M.A.-J., and J.F.G. led the overall design and conduct of the study. S.B. and S.R. contributed to the supervision of the moderation of the online intervention. S.D., is the technical lead of the HORYZONS project and HORYZONS data analyst. C.M., is the lead front-end designer of the HORYZONS platform. P.R., is the creative content lead of the project. R.L., G.W., O.S., T.G., and R.C., contributed to the design of the intervention. M.A.-J wrote the first draft of the manuscript. D.C., L.V., C.M., H.H., C.G-B., R.D-G., S.M.C., and P.D.M contributed to the design and conduct of the study. All authors critically revised and approved the final manuscript.

COMPETING INTERESTS STATEMENT

The authors report no relevant conflict of interest.

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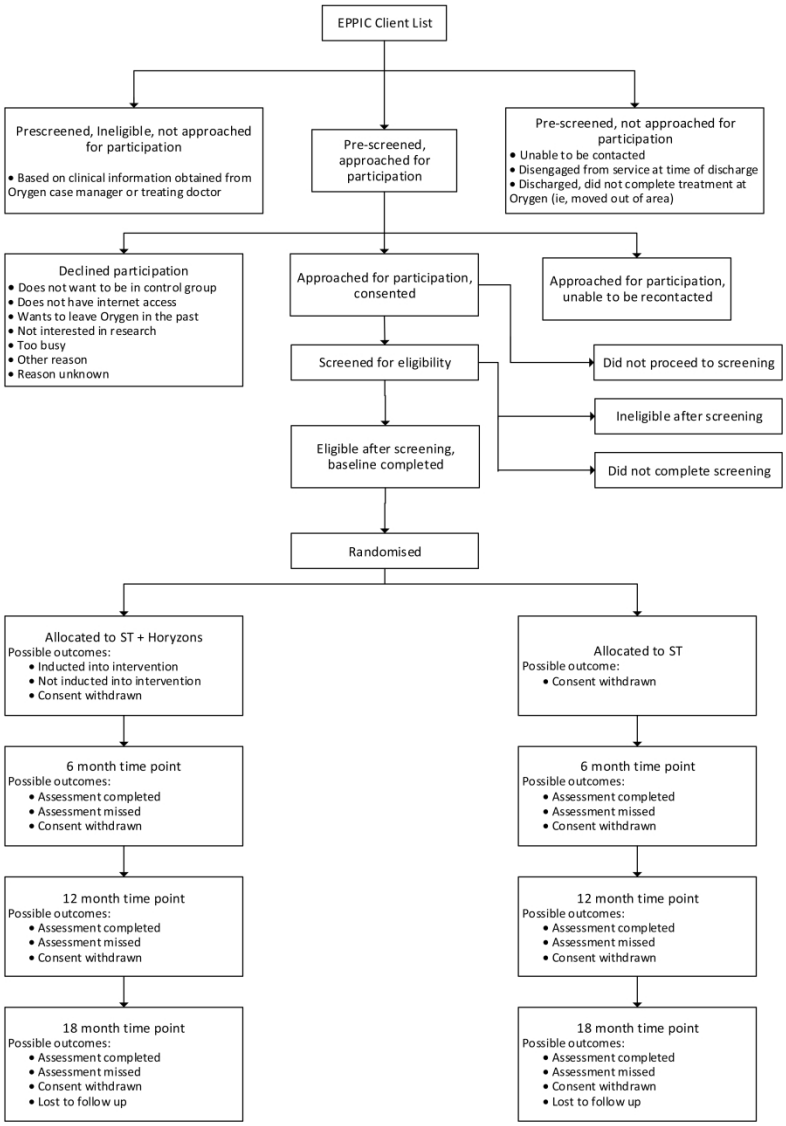
Figure 1. Study flow diagram for HORYZONS.



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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Page 1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Page 2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Pages 3-6
	2b	Specific objectives or hypotheses	Pages 6-7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Pages 7, 9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	Page 8
	4b	Settings and locations where the data were collected	Page 7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Pages 9-13
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Pages 15-18
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Pages 16-17
Sample size	7a	How sample size was determined	Page 20
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Page 9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Page 9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Page 9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Page 9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Page 9, 21

	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Pages 19-21
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Pages 19-21
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	NA
	13b	For each group, losses and exclusions after randomisation, together with reasons	NA
Recruitment	14a	Dates defining the periods of recruitment and follow-up	NA
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	NA
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	NA
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	NA
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Pages 3, 23
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	NA
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	NA
Other information			
Registration	23	Registration number and name of trial registry	Page 2
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Page 23

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

The Horyzons trial: Protocol for a Randomised Controlled Trial of a Moderated Online Social Therapy to Maintain Treatment Effects from First Episode Psychosis Services

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The Horyzons trial: Protocol for a Randomised Controlled Trial of a Moderated Online Social Therapy to Maintain Treatment Effects from First Episode Psychosis Services

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ABSTRACT

Introduction: Specialised early intervention services have demonstrated improved outcomes in first episode psychosis (FEP); however, clinical gains may not be sustained after patients are transferred to regular care. Moreover, many FEP patients remain socially isolated with poor functional outcomes. To address this, our multidisciplinary team has developed a moderated online social media therapy (HORYZONS) designed to enhance social functioning and maintain clinical gains from specialist FEP services. HORYZONS merges: (i) peer-to-peer social networking; (ii) tailored therapeutic interventions; (iii) expert and peer-moderation; and (iv) new models of psychological therapy (strengths and mindfulness-based interventions) targeting social functioning. The aim of this trial is to determine whether, following two years of specialised support, and 18-month online social media-based intervention (HORYZONS) is superior to 18 months of regular care.

Methods and analysis: This study is a single-blind randomised controlled trial. The treatment conditions include HORYZONS plus Treatment as Usual (TAU) or TAU alone. We recruited 170 young people with FEP, aged 16-27 years, in clinical remission and nearing discharge from EPPIC, Melbourne. The study includes four assessment time points, namely, baseline, 6, 12 and 18-month follow-up. The study is due for completion in July 2018 and included a 40-month recruitment period and an 18-month treatment phase. The primary outcome is social functioning at 18 months. Secondary outcome measures include rate of hospital admissions, cost-effectiveness, vocational status, depression, social support, loneliness, self-esteem, self-efficacy, anxiety, psychological wellbeing, satisfaction with life, quality of life, positive and negative psychotic symptoms and substance use. Social functioning will be also assessed in real time through our Smartphone Ecological Momentary Assessment (SEMA) tool.

Ethics and dissemination: Melbourne Health Human Research Ethics Committee (2013.146) provided ethics approval for this study. Findings will be made available through scientific journals and forums, and to the public via social media and the Orygen website.

Trial registration: ANZCTR; ACTRN12614000009617

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first randomised controlled trial to evaluate the effectiveness of an online intervention designed to extend the benefits of specialised early psychosis services
- HORYZONS is the first intervention to harness online social media technology and use strengths and mindfulness-based interventions to improve long-term recovery in early psychosis
- HORYZONS was developed by a multidisciplinary team in partnership with young people, with the purpose of being scalable across, and embedded within, early intervention services
- In line with recent clinical trials evaluating extended models of care for early psychosis services, the control intervention consists of routine care as opposed to a placebo intervention accounting for increased attention and unspecific therapeutic factors
- Due to the nature of psychosocial interventions, participants and clinicians were not blind to treatment allocation

INTRODUCTION

Psychosis can be a devastating mental health disorder. Onset is often in adolescence and early adulthood and in many cases follows a chronic and relapsing course that results in great personal suffering and societal costs [1, 2]. Against this daunting picture, early intervention is now seen as the most promising and evidence-based approach to improve the long-term outcomes of psychosis [3]. Specialist First Episode Psychosis (FEP) services originated in the early 1990s with a focus on reducing treatment delays, providing youth friendly, phase-specific support and preventing the development of long-term functional and social disability [3]. Over the past two decades, several randomised controlled trials (RCTs) conducted across countries and mental health systems have demonstrated that these services improve psychotic symptoms, reduce relapse rates, foster patient satisfaction and result in tangible economic benefits [4-8].

There are limits, however, to the impact of early intervention services. First, specialist FEP services typically have treatment resources for 2 years, and recent reports indicate that the benefits of early intervention seen at the end of 2 years may not persist at 3 years post-discharge [9, 10]. Second, even after receiving specialised services, functional recovery lags behind symptomatic remission, and many young people with FEP experience significant social functioning deficits and poor quality of life [11]. Indeed, the onset of psychosis has been characterized as a 'social network crisis' [12], which is not improved by early intervention services. Young people with psychosis have smaller social networks, fewer people to turn to in a crisis [13], are between 5 and 9 times less likely to have confidants compared with their peers [14], and report on average 2-3 lonely days per week [15]. Smaller social networks and lower perceived social support are, in turn, predictive of poorer long-term functional outcomes, shorter time in remission, and increased hospital admissions [16-18]. Taken together, these research findings underscore the need for new treatment approaches that extend the benefits of early intervention services and, ultimately, promote long-term social recovery.

While difficulties with social functioning are commonplace following FEP and can lead to poor long-term outcomes, very few studies have assessed interventions targeting social functioning as a primary outcome. The most researched psychological intervention for FEP

has been cognitive behavioural therapy, which is primarily focused on reducing the positive symptoms of psychosis [19]. Recognizing this gap, a recent trial evaluated a social recovery therapy in combination with early intervention services to enhance social recovery in FEP [19]. Study results showed an improvement in structured activity in those receiving the intervention relative to those receiving early intervention services alone. The renewed focus on social recovery is also consistent with recent psychological models, which have proposed self-efficacy [20, 21] and positive emotions [22] as important targets to promote social functioning in psychosis. Strengths- and mindfulness-based interventions have been put forward as key interventions to increase self-efficacy and positive emotions [23], respectively, with preliminary studies supporting their potential to improve social functioning in psychosis [24, 25].

A complementary approach to improving long-term recovery in FEP is to extend the duration of specialised treatment [26, 27]. This view is underpinned by findings that the first 5 years after psychosis onset constitute a critical period, determining longer term outcomes [27, 28]. Similarly, promoting sustained social and functional recovery in the early course of psychosis appears to be a key path towards long-term functional recovery [29]. Two recent randomised controlled trials have evaluated the effects of the current model of early intervention (i.e., 2 years of specialised treatment) vs. an extended model of care (i.e., 5 years of specialised treatment) [30, 31] with mixed results. In one of these trials, the extended model of care improved length of remission of positive and negative symptoms relative to regular care [31]. Conversely, a second study showed no significant improvements in clinical or social outcomes associated with the extended model of care [30]. An additional clinical trial examined the effects of prolonging the period of specialised care for 12 months (i.e., three years vs. two years of specialised treatment) [32]. This study showed significant improvements in functional outcomes at the end of the 3-year compared with 2-year specialised support. However, treatment benefits were not sustained, with no significant differences across treatment groups at 1 and 2 years post specialised intervention [32].

An alternative to prolonging the duration of specialised intervention is to offer extended, lower intensity maintenance treatment following the first two years of specialised treatment [27]. This is supported by findings that the termination of the specialised intervention and transfer of care brings about feelings of loss for the patients [9] and significantly derails engagement with treatment services [33], a pivotal element of early intervention programmes.

Thus, a lower intensity level of care may bridge the gap between specialised intervention and standard treatment and provide a cost-effective alternative to bring about sustained benefits in FEP. This approach has shown promising results in a single group study, with improvements seen at 2 years (i.e., end of specialised care) being maintained at 5 years (i.e., after 3 years of lower intensity specialised treatment) [27].

Online- and mobile-based interventions can also provide a lower intensity, cost-effective and engaging approach to prolonging the benefits of specialised FEP services. Indeed, the extant research shows that online interventions are feasible, acceptable, and may improve a range of important domains in psychosis treatment including psychotic symptoms, hospital admissions, social connectedness, and depression [34, 35]. However, most studies conducted to date have employed uncontrolled designs, were underpowered, included short follow-up periods, targeted people with chronic schizophrenia, did not use online social media, and did not specifically target social functioning [34]. To the best of our knowledge, only one pilot study has evaluated the acceptability and preliminary benefits of an online intervention in young people with FEP [36].

Finally, online social networks provide a particularly promising avenue to foster social functioning in young people with FEP. A recent study revealed that 89% of young people aged 18-29 use social media daily [37], a frequency that is on the rise [38]. Use of online social media has been associated with increased life satisfaction [39], self-esteem [39], and social capital [40], as well as lower loneliness and depression [41], particularly for those who post content to the social network and are active users [42]. Recent surveys indicate that social media habits of young people with psychosis resemble that of their peers: virtually all regularly use social media, on average 10 times and 2 hours per day [43, 44]. Particularly relevant to the therapeutic potential of social media in FEP, 78% would like to obtain help from clinicians via social media, 40% increase their use of social media when experiencing symptoms [43] and the majority strongly agree with using social media as a platform from mental health support [45]. Thus, coupled with psychological interventions specifically addressing social recovery such as strengths- and mindfulness-based approaches, social media provides an opportunity deliver acceptable, extended lower intensity support with potential to foster long term social functioning in FEP.

Aims and hypotheses

The objective of this trial was to determine whether extending the treatment period of a specialised FEP service through an 18-month, step-down, novel online social media-based intervention (HORYZONS) produces better outcomes compared with 2 years of specialist FEP treatment followed by treatment as usual (TAU), using a randomised controlled single-blind design. An additional aim of this trial is to determine the cost-effectiveness of HORYZONS.

The primary hypothesis is that, relative to TAU, HORYZONS will lead to improved social functioning at 18 months amongst young people with FEP. The secondary hypotheses are that, relative to TAU, HORYZONS will reduce the rate of hospital admissions due to psychotic symptoms and lead to improvements in depression, vocational outcomes, satisfaction with life, social support, loneliness, self-esteem, self-efficacy, anxiety, stress, positive and negative psychotic symptoms, psychological wellbeing, quality of life, and substance use. Finally, we hypothesise that HORYZONS will be more cost-effective than TAU.

METHODS AND ANALYSIS

Study design

The study design is an 18-month, parallel groups, single-blind, randomised controlled trial (RCT) in which 170 participants with remitted FEP have been allocated to either the current mainstream model of early intervention for psychosis (i.e., 2 years of specialised treatment followed by discharge to treatment as usual; TAU), or TAU in tandem with a moderated online social media intervention (HORYZONS), for 18 months.

The design includes four assessment time points: baseline, 6 months, 12 months and 18 months. The RCT includes a 40-month recruitment period and an 18-month treatment phase, with the study being completed within 5 years. The protocol development addressed all aspects of Good Clinical Practice [46], CONSORT EHEALTH criteria [47] and SPIRIT guidelines [48].

Setting

Recruitment of the trial participants commenced in October 2013 and finalised in January 2017 at Early Psychosis Prevention and Intervention Centre (EPPIC), a subprogram of

Orygen Youth Health, Melbourne. EPPIC is a publicly-funded specialist FEP program servicing 250 new referrals for FEP per year. EPPIC provides 18 months to 2 years of specialised care after which patients are discharged and transferred to treatment as usual [49]. Follow-up assessments will be concluded in July 2018.

Participants

Inclusion criteria for participants were: (a) a first episode of a DSM-IV psychotic disorder or mood disorder with psychotic features; (b) aged 16-27 years inclusive; (c) ≤6 months treatment with an antipsychotic medication prior to registration with EPPIC; (d) remission of positive symptoms of psychosis, defined, using the Positive and Negative Syndrome Scale (PANSS) [50], as 4 weeks or more of scores of 3 (mild) or below on items P2 (conceptual disorganization) and G9 (unusual thought content), and scores of 4 (moderate) or below with no functional impairment on items P3 (hallucinatory behaviour) and P1 (delusions). Additional inclusion criteria to ensure low level of risk within HORYZONS included: (f) low aggressiveness, defined by a score of 3 or below on the poor impulse control item of the PANNS for the month prior to study entry; and (g) moderate or lower suicidal risk defined as a score of 4 or below on the suicidality subscale of the Brief Psychiatric Rating Scale – expanded version (BPRS) [51] for the month preceding study entry. Finally, participants were required to nominate an emergency contact to be eligible for the study.

Exclusion criteria included: (a) intellectual disability; and (b) inability to converse in or read English. Additional exclusion criteria to ensure safety within the online system included (c) a DSM-IV diagnosis of either antisocial personality disorder (ASPD); or (d) borderline personality disorder (BPD) as well as clinical evidence that the BPD features cause interpersonal difficulties in the treatment environment.

The SCID-I/P [52] was used as the standardized measure of DSM-IV diagnosis of mental illness. The BPD (13 items) and Conduct Disorder/ASPD (22 items) screening questions of the SCID-II Personality Questionnaire were used to assess for BPD and ASPD [53].

Withdrawal from the trial occurred if: (a) participation in the study interfered with appropriate clinical management of risk of harm to self or others (as judged by the treating clinicians and/or senior researchers); (b) serious adverse events developed that could be

associated with the online intervention; and (c) participants failed to comply with the terms of use of the online intervention. Withdrawal from the study could be at the request of the participant, or at the discretion of the investigator.

Enrolment and randomisation

The recruitment and allocation procedures are depicted in Figure 1. The study coordinator liaised with the Orygen Youth Health Quality and Evaluation Unit to obtain a list of young people with FEP nearing discharge from EPPIC. This list was updated every 3 months during the recruitment phase. The study coordinator assessed the initial eligibility of young people within 3 months of discharge in consultation with EPPIC case managers and treating doctors. Clients deemed potentially eligible were approached by the study coordinator to obtain written informed consent. Next, eligibility was confirmed through a screening assessment. Eligible participants completed the baseline assessment and were subsequently randomised to either HORYZONS plus TAU or TAU alone at a ratio of 1:1. Randomisation was carried out remotely according to the International Conference on Harmonization E9 Statistical Principles Guidelines [54]. An independent statistician created the randomisation sequence using permutated blocks. The study coordinator randomised the participants via a secure online Research Project Management System (RPMS). The RPMS sent an automated email to the study coordinator and investigators notifying them of the outcome of randomisation. Finally, the study coordinator informed the participant of the allocation.

The study assessors undertaking the follow-up assessments are kept blind to treatment allocation via the following mechanisms: (1) at the commencement of each research interview the assessor reminds participants of the importance of the blind, (2) study assessors are excluded from all clinically related discussions regarding participants, and (3) the assessors were forbidden from accessing participants' medical records. The assessors record their best guess of participants' treatment allocation at 6, 12 and 18 months' follow-up in order to enable an assessment of the success of treatment concealment. Any instances of unblinding were recorded.

Interventions

HORYZONS

HORYZONS has been developed by a large multidisciplinary team of researchers, clinical psychologists, programmers, creative writers, graphic artists and experts in human computer-interaction [36, 55]. HORYZONS was designed following participatory design principles with the purpose of addressing social functioning in early psychosis. For example, focus groups with young people with psychosis revealed that they favoured a social media-based platform enabling meaningful peer-to-peer contact as well as clinicians' support [35, 56]. In addition, young people called for online interventions focused on promoting personal strengths and self-efficacy as opposed to merely ameliorating symptoms and deficits. Finally, young people indicated that the system should provide self-guided, interactive, tailored interventions, relevant to their changing needs [35, 56].

Informed by young people's continual feedback as well as relevant research in the mental health and human computer interaction fields [55], the design of HORYZONS merged (1) interactive online therapy ('Pathways and Steps'), (2) peer-to-peer online social networking ('the café'), and (3) peer and (4) expert moderation. All components of HORYZONS were designed to reinforce each other, creating a flow for the young person between the social and therapy elements. For example, young people are encouraged to post comments and interact with others while engaging with therapy content, and are, at the same time, prompted by moderators to practice their strengths or use skills they have learned while engaging with the social network. Young people can log on to Horyzons at any time via an Internet-enabled desktop or mobile device.

Interactive online therapy modules ('pathways and steps')

HORYZONS integrates a number of online 'pathways' organized into distinct themes including: understanding psychosis, identifying and exercising personal strengths, promoting positive connections with others, fostering positive emotions, early warning signs and prevention of relapse, managing stress and anxiety, dealing with depression, and vocational skills. With the aim of increasing the usability and take-up of therapeutic content, pathways consist of thematically related interactive therapy 'Steps'. The online 'Steps' are discrete, interactive, evidence-based therapy modules primarily targeting social functioning in young people with psychosis; for example, through fostering self-efficacy (e.g., identifying personal strengths via an interactive card-sort game based on the strengths-based framework [36]), positive emotions and subjective wellbeing (e.g., practicing mindfulness and self-compassion), or positive connections with others (e.g., illustrating how to respond

empathically to others). The content of the Steps was informed by previous studies linking use of personal strengths, increased self-efficacy and positive emotions with improved social functioning in psychosis [21, 22, 25, 57]. Online Steps further address comorbid symptoms such as anxiety and depression as well as vocational support (informed by our previous work [58]). Finally, the design of HORYZONS and therapeutic content was strongly influenced by self-determination theory, an empirically supported theory of motivation which focuses on the processes and social environments that facilitate or hamper social functioning [59].

The Steps incorporate prompts for participants to share their thoughts and reactions to the therapeutic material with other users through embedded 'Talking Points'. To ensure that therapeutic content is translated into behavioural change, the Steps entail behavioural prompts entitled 'Do its'. For example, following a Step about fostering positive connections, the participant will find specific behavioural suggestions (or 'do its') to exercise a therapeutic skill (e.g., empathy) in specific contexts (e.g., school). 'Do its' are also related to the participant's specific strengths (e.g., using kindness in social interactions). A 'Playlist' stores and schedules any 'Do it' the participant wants to complete in the future. Moreover, participants can rate, like, comment on, and share any Step or 'Do it' with others via the social networking newsfeed. Participants can also keep track of 'trending' Steps, or identify other young people who share their personal strengths. Finally, young people support each other's efforts to take on specific behavioral changes via the 'Team up' function (e.g., by supporting or joining others in their efforts to take on specific challenges).

Social network features

Participants are encouraged to communicate with one another and with peer and expert moderators through the online social network or 'Café' to foster social support. Expert Moderators (clinicians) are identifiable as a separate user class within the network. Each participant creates their own profile with images, and can visit the wall of fellow users, where their posts and general activity are displayed. Posts can include 'icebreakers' (to encourage social interactions, e.g. What's the worst gift that someone gave you?), user-generated threads, 'reactions' (designed to facilitate social support, e.g., 'I get you', 'thinking of you') as well as content related to mental health (e.g., recent steps taken by others) or general interest.

A final feature of HORYZONS is Talk it out (TiO), an online group function informed by the evidence-based problem-solving framework [60]. A TiO enables users to nominate issues (e.g., 'how to break through shyness and make new friends?'), which are discussed in moderated groups through structured phases (e.g., brainstorming, pros and cons, wrap-up). Previous problems and group solutions are stored in the system providing an easily accessible 'solution wiki' for future young people.

Expert and peer moderation

HORYZONS integrates online personal therapist support (by clinicians with experience treating young people with psychosis). Their role is to customize evidence-based interventions, monitor participant's clinical status and ensure the safety of the social network. Each therapist is assigned a caseload (i.e., a 20% full time equivalent online moderator can comfortably manage 20-25 participants), which they follow for the duration of the trial. Following the baseline assessment and initial face-to-face orientation to the system, the therapist makes contact with the participant for a brief phone meeting reviewing their personal needs and preferences [61]. Expert moderators then develop brief case formulations which are presented during weekly supervision meetings with senior clinical psychologists from the team. Guided by the individual formulation, moderators send each client tailored content suggestions weekly (e.g., a Step or 'Do it') with a focus on improving social functioning. Suggestions appear on the user's home page and they receive a system notification, which is also delivered via SMS as determined by the participants settings. Young people can rate the helpfulness of the suggestions, which moderators use to tailor subsequent recommendations. Expert moderation was informed by the supportive accountability model [61] a theory-driven framework operationalising how human support increases user engagement, the self-determination theory [59] and strengths-based models [62] as a means of enhancing users' engagement and self-efficacy.

In addition to clinical moderation, HORYZONS incorporates online vocational support. Drawing on our previous work [58], the vocational moderator provides individualised online vocational support, which can include: assessing young people's preferences and training, identifying suitable competitive job openings, supporting young people in specific job seeking activities (e.g., writing a CV), or preparing for a job interview.

The 'cafe' is led by trained young people with lived experience of mental illness ('Peer-workers'). Peer-workers are peer moderators who facilitate social learning using HORYZONS in desired ways (e.g., self-disclosing, using therapy content to deal with difficulties). Peer-workers also seed discussion threads and 'icebreakers' to enable relevant, enjoyable conversations and facilitate meaningful relationships. Finally, peer moderation serves to normalise experiences, counteract stigma and promote engagement. Peer moderation was informed by the social learning theory which posits that those who observe others (i.e., superusers) being rewarded for a particular behaviour (e.g., completing a step or commenting on the social network) are more likely to modify their beliefs and subsequent behaviour [63].

Control intervention

Participants randomised to regular care receive Treatment as Usual (TAU) following discharge from the EPPIC program. TAU consists of a range of treatment options delivered by generic medical or mental health services typically available to young people in the absence of enrolment in the study. These can include follow-up by a general practitioner, private psychiatrist, primary care youth mental health services, or adult mental health services which deliver multidisciplinary psychiatric care (including medical follow-up, case management and acute psychiatric care as appropriate). Prior to discharge from specialised FEP support the EPPIC team, in collaboration with the young person, recommends the best treatment option based on the complexity of the young person's needs. Those with complex needs are referred to adult mental health services, while young people who attained a good level of recovery and remained stable are recommended primary care services. Additionally, TAU participants are provided with a printed leaflet containing relevant information on existing e-mental health resources for young people (i.e., Moodgym, e-headspace, Reach-out, and OYH Client's hub).

Safety protocol

The safety protocol is comprised of 3 levels of security including: (1) system and privacy protection; (2) online safety; and (3) clinical safety [64].

HORYZONS is hosted on a University of Melbourne web server. The University has industry standard measures in place to prevent unauthorized access to the server. The online

system also integrates measures to secure the application and database against unauthorized access. These measures conform to industry best practice as defined by the Open Web Application Security Project (OWASP). Privacy and online safety are managed in accordance with the Australian Communications and Media Authority (ACMA).

The study coordinator carries out an initial face-to-face orientation with HORYZONS participants, including details of the terms of use. Participants were required to accept and comply with the guidelines for safe use of HORYZONS. When needed, participants are offered guidance on appropriate usage of the system. All users are asked to nominate an emergency contact person, such as a close family member. HORYZONS includes a 'report function' which enables young people to report a concern about any material posted by a user. The moderator assesses the basis of the report and responds accordingly, which may include the removal of the material and, in some cases, deactivating or restricting the young person's account. Participants are also able to hide their profile and activity should they become concerned about their privacy.

Clinical risk is managed through manual and automated procedures. First, moderators monitor the system twice daily on weekdays and once daily on weekends for evidence of clinical risk or deterioration. Any detected increased risk activates the HORYZONS crisis protocol which includes one or more of the following: a risk assessment with the young person, inform the research team, alert the emergency contact nominated by the participant, and liaise with suitable emergency services where necessary. In addition, the system incorporates visible emergency guidelines and contact information. Finally, HORYZONS includes an automated keyword detection function, which activates each time a participant posts a contribution indicative of clinical risk or that contains potentially offensive words. The function blocks posts with notifications sent to the young person and the moderator, who can 'unblock' the post should they determine it to be unproblematic.

Temporary withdrawal criteria

In the event of a clinically significant deterioration of psychotic symptoms, increased risk or a hospital admission the clinical moderators perform an assessment to determine the risks and benefits of a temporary withdrawal from HORYZONS. Based on this assessment, and in consultation with the young person, the moderator team determines whether the account is temporarily suspended, or level of access restricted. Following suspensions or restrictions to a

user's account, the moderator will contact the young person at monthly intervals to ascertain whether the account is to be reactivated.

Outcome measures

Primary and secondary outcomes are measured at baseline (prior to randomisation), and at 6, 12 and 18 months follow-up (Table 1). Moreover, social functioning is tracked in real time for a period of 7 days after each assessment using ecological momentary assessment using a purpose-built smartphone application, SEMA (Smartphone Ecological Momentary Assessment).

Table 1. Schedule of outcome measures

	Baseline	6mo	12mo	18mo
Primary outcome				
Personal and Social Performance Scale (PSP)	■	■	■	■
First Episode Social Functioning Scale (FESFS)	■	■	■	■
Secondary outcomes				
Hospital admissions[a]	■	■	■	■
Calgary Depression Scale for Schizophrenia (CDSS)	■	■	■	■
Medical Outcomes Study: Social Support Survey (MOS-SSS)	■	■	■	■
UCLA Loneliness Scale	■	■	■	■
Self-Esteem Rating Scale-Short Form (SERS-SF)	■	■	■	■
Depression Anxiety and Stress Scale (DASS)	■	■	■	■
Mental Health Confidence Scale (MHCS)	■	■	■	■
Social Interaction Anxiety Scale (SIAS)	■	■	■	■
Scales of Psychological Wellbeing (SPWB)	■	■	■	■
Satisfaction with Life Scale (SWLS)	■	■	■	■
AQoL 8D questionnaire	■	■	■	■
The Positive and Negative Syndrome Scale (PANSS)	■	■	■	■
Employment and Education Status	■	■	■	■
Alcohol, Smoking, Substance Involvement Screening Test (ASSIST)	■	■	■	■
Smartphone Ecological Momentary Assessment (SEMA)[b]	■	■	■	■
Resource Use Questionnaire	■	■	■	■
Exploratory outcomes				
Social Comparison Scale (SCS)	■	■	■	■
2-Way Social Support Scale (2-Way SSS)	■	■	■	■
Savoring Beliefs Inventory (SBI)	■	■	■	■
Mindful Attention Awareness Scale (MAAS)	■	■	■	■
Strengths Use Scale (SUS)	■	■	■	■
Self-Compassion Scale Short Form (SCS-SF)	■	■	■	■
Physical Activity Questionnaire (IPAQ)	■	■	■	■
Waist circumference	■	■	■	■
Potential covariates				
Duration of Untreated Psychosis (DUP)	■			
Scale to Assess Unawareness of Mental Disorder (SUMD)	■			
Motivational Trait Questionnaire (MTQ)	■			
Medication Adherence Rating Scale (MARS)	■	■	■	■
Bell Lysaker Emotion Recognition Task (BLERT)	■	■	■	■
The Hinting Task	■	■	■	■
Social Probabilistic Inference Task (SPIT)	■	■	■	■
Digit Symbol Substitution Test (DSST)	■			
Wechsler Test of Adult Reading (WTAR)	■			

Horyzons specific measures				
Horyzons Perceived Competence Scale (H-PCS)				
Horyzons Self-regulation Questionnaire (HSRQ)				
Horyzons Health Care Climate Questionnaire (HCCQ)				

[a]Continuous from state government databases
[b]Smartphone Ecological Momentary Assessment surveys

Primary outcome

The primary outcome measure is social functioning as measured by the Personal and Social Performance Scale (PSP) at 18 months follow-up. The PSP is a 100-point single-item rating scale derived from Social and Occupational Functioning Assessment Scale (SOFAS) developed specifically to assess social functioning in schizophrenia. The PSP has shown strong psychometric properties [65, 66] and has been recommended as one of the best existing tools to assess social functioning in psychosis [67].

Additionally, with the purpose of capturing the full construct of social functioning, the First Episode Social Functioning Scale (FESFS) will be administered at each assessment time point.

The FESFS has been developed to measure social functioning in young people with FEP [68]. Based on their psychometric properties and specific focus on social functioning, the following FESFS subscales were selected: friends and activities (α=0.80); independent living skills (α=0.81); interacting with people (α=0.80); and intimacy (α=0.75). These subscales have shown to correlate with other measures of social functioning, to be independent of psychotic symptoms, and to be sensitive to treatment effects [68].

Secondary outcomes

After the study was initiated, some feasibility issues were identified that led to modifications to the study secondary outcome measures. In the original protocol, we intended to measure psychotic relapse using the PANSS scale via phone or Skype-based assessments conducted every two months throughout the 18-month intervention period. Ongoing measurement of psychotic symptoms at regular intervals is a requirement for the reliable and prospective identification of psychotic relapse [69]. However, despite our best efforts, contacting participants via phone calls at regular intervals raised important feasibility issues, with many participants not answering phone calls or regularly changing phone numbers, leading to significant missing data. Thus, 12 months after study commencement, it was decided to discontinue the regular phone calls and prospective assessment of psychotic

relapse. Given the feasibility issues measuring relapse of psychotic symptoms at regular intervals, the following secondary outcomes were added:

1. Hospital admissions due to psychotic symptoms and mental health issues were added as a secondary outcome variable. We have access to reliable and objective hospital admission data from state databases (i.e., Centre for Victorian Data Linkage) spanning the 18-month assessment period. Data on hospital admission from the state databases will be provided by an independent person blind to study design and purpose.

2. Positive and negative psychotic symptoms as measured by the PANNS scale at each assessment time-point.

3. *Physical health* was also initially included as secondary outcome variable because we originally intended to incorporate online modules targeting this domain. However, we decided not to include therapy content addressing physical health and therefore this variable will be analysed as an exploratory outcome.

Secondary outcome measures include:

(1) *accumulated hospital admissions* due to psychotic symptoms and mental health issues over 18 months;

(2) *vocational status* as measured by employment and/or education status;

(3) *depression* as measured by the Calgary Depression Scale for Schizophrenia (CDSS [70]);

(4) *social support and loneliness* as assessed by Medical Outcomes Study: Social Support Survey (MOS-SSS [71]) and the UCLA Loneliness Scale (Version 3 [72]);

(5) *self-esteem* and *self-efficacy* as measured by the Self-Esteem Rating Scale-Short Form (SERS-SF [73]) and Mental Health Confidence Scale (MHCS [74]), respectively;

(6) *anxiety and stress* as determined by the Depression Anxiety and Stress Scale (DASS [75]);

(7) *psychological wellbeing* as measured by Scales of Psychological Wellbeing (SPWB [76]);

(8) *satisfaction with life* as measured by Satisfaction with Life Scale (SWLS [77]);

(9) *quality of life* as measured by the AQoL 8D [78]. This questionnaire can also be used to determine quality-adjusted life years (QALYs), which are useful in economic evaluation studies;

(10) *positive and negative psychotic symptoms* assessed by means of The Positive and Negative Syndrome Scale (PANSS [50]);

11) *substance use* as measured by the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST version 3.1) over 18 months follow-up;

(12) *Cost-effective analysis*: A Resource Use Questionnaire (RUQ) is used to determine the broader resource use of participants (e.g. community mental health services, accommodation, work impacts etc). Additionally, for consenting participants, information regarding utilisation of health care services available via the Medicare Benefits Schedule (MBS - medical, allied health, diagnostic and pathology services) and the Pharmaceutical Benefits Schedule (PBS - medications) will be accessed from the Australian Department of Human Services.

To obtain more dynamic and ecologically valid data on young people's social functioning, participants utilise a custom-built smartphone app, SEMA, which is readily downloadable at no charge to participants owning a smartphone (running Android or iOS operating systems). SEMA delivers surveys (administered for 7 days following each assessment time point) approximately eight times per day for 7 consecutive days. Young people are prompted to complete SEMA surveys at random times every 90 min (±30 min) over a 12-h period (e.g. 10 a.m. to 10 p.m.). SEMA tracks participants' responses in (near) real time, ensuring minimal data loss by uploading responses to a secure server or storing responses on the young person's smartphone when an Internet connection is temporarily unavailable. Each SEMA survey begins with four items assessing momentary positive affect ('At the moment, how happy do you feel?', negative affect ('At the moment, how sad do you feel?'; 'At the moment, how stressed do you feel?') and momentary social isolation (e.g. 'At the moment, how lonely do you feel?') rated on visual slider scales anchored at 0 (not at all) and 100 (very). The order of these four items is randomised at each survey. Following the momentary affect items, the SEMA survey includes items pertaining to social interactions of the young person (e.g. 'How much time have you spent interacting with others, since last survey?'), perceived social efficacy (e.g., 'How well do you think you handled your social interactions, since last survey?'), perceived social support (e.g., 'have you received support or encouragement from others, since last survey?'), critical comments (e.g., 'Have you felt that

others criticized or judged you, since last survey'), and social rank (e.g., How competent have you felt in relation to others, since last survey?'). The order of these items is also randomised at each survey.

Exploratory outcomes and potential covariates

Additional exploratory outcomes included: *social anxiety* measured through the Social Interaction Anxiety Scale (SIAS) [79]; *social comparison and group fit* as assessed through the Social Comparison Scale (SCS) [80]; *the provision of emotional support* measured via the 2-Way Social Support Scale (2-Way SSS [81]); *anticipatory pleasure* assessed through the Savoring Beliefs Inventory (SBI[82]); *mindfulness skills* as assessed using the dispositional Mindful Attention Awareness Scale (MAAS [83]); *strengths use* as assessed by means of the Strengths Use Scale (SUS[84]); *self-Compassion* as assessed by the Self-Compassion Scale Short Form (SCS-SF[85]); *physical health* as measured by waist circumference over 18 months follow-up; and, *physical activity* as measured by the International Physical Activity Questionnaire (IPAQ [86]) and by measuring sitting time across different domains [87] (e.g., TV, video, computer, working, etc.).

Finally, potential covariates included: *Duration of Untreated Psychosis (DUP)* defined as the time interval between onset of definite positive psychotic symptoms and first engagement and treatment in an Early Intervention (EI) service; *clinical insight* as assessed by means of the Scale to Assess Unawareness of Mental Disorder (SUMD [88]); *intrinsic motivation* measured through the short form of Motivational Trait Questionnaire (MTQ [89]); *medication adherence* measured by the Medication Adherence Rating Scale (MARS [90]); *emotion processing* assessed by means of the Bell Lysaker Emotion Recognition Task (BLERT [91]); *theory of mind* measured using The Hinting Task [92]; *Jumping to conclusions (JTC)* measured through the Social Probabilistic Inference Task (SPIT); *premorbid intelligence* as assessed via Wechsler Test of Adult Reading (WTAR [93]); and *general cognitive deficits* will be measured through the Digit Symbol Substitution Test (DSST [94]).

HORYZONS specific measures

Usage of HORYZONS is continuously monitored across the study intervention period (i.e., frequency, duration, and patterns of use). In addition, users complete self-report

measures informed by the self-determination theory including: their perceived competence using the system, motivations for using it; and their perception of moderation by HORYZONS.

Statistical analysis and sample size

Primary analyses will be undertaken on an intention-to-treat basis. Mixed-model repeated measures (MMRM) analyses will be used to compare change in social functioning between the two treatment groups over the 18-month follow-up. MMRM is the analysis of choice because assumptions of traditional data analysis methods (e.g., ANOVA, regression) may be violated, such as the assumption of homogeneity of regression across time points [95]. In addition, MMRM uses all available data (including participants with partial data) to estimate treatment effects. Time (baseline, 6, 12 and 18 months) will be the within-person predictor and treatment group (HORYZONS plus TAU vs. TAU) the between-person predictor. MMRM will also be used to analyse change in the continuous secondary outcomes over 18 months. Additional analyses will use multiple imputation to assess the robustness of the findings to the choice of method for handling missing data. Ecological momentary assessment will be analysed using a multilevel structural equation modelling (MSEM) framework [96]. Differential rate of hospital admissions will be analyzed using multilevel logistic regression. Time to hospital admissions will be assessed by survival analysis (using either proportional hazard or accelerated life-time models). Additional comparisons between treatment groups based on completers-only analyses will be conducted. Analyses will be undertaken in accordance with ICH 9 guidelines including a full analysis as well as per protocol set. The per protocol sample will be defined based on receiving a pre-specified minimal exposure to the online intervention (i.e., more than 16 logins over the 18-month intervention period).

Economic evaluation will comprise a cost-consequences analysis whereby incremental costs of the intervention will be compared to the full spectrum of study outcomes. A cost utility analysis will also be undertaken whereby the AQoL 8D will be used to QALYs. The evaluation will measure and value any change to the use of health care resources over the period of the study (using the data from the RUQ, MBS/PBS and hospitalisation administrative data) between the two treatment arms; and then compare any additional costs to the additional outcomes achieved. Australian sourced unit costs will be attached to the

RUQ (from Australian sources such as the Commonwealth Department of Health, Mental Health Branch). Standardised economic evaluation techniques including incremental analysis of mean differences (using statistical techniques such as generalised linear models) and bootstrapping to determine confidence intervals around incremental cost-effectiveness ratios will be used. If, as expected, the intervention is found to be effective, lifetime and population cost-effectiveness of the interventions will be determined using economic modelling techniques. We will determine the likelihood that the intervention is cost-effective at commonly used value-for-money thresholds such as $20,000/QALY and $50,000/QALY.

The primary outcome is change in social functioning at 18 months follow-up. A recent RCT investigating the effects of extending FEP specialist treatment for 12 months (i.e., a total of 3 years of specialist treatment) reported an effect size of 0.53 (Cohen's d) for functional outcomes for the extended model of care at 12-months (i.e., end of the specialised treatment) compared with TAU (i.e., 2 years of specialist treatment) [32]. If we assume that alpha is set at 0.05 and power (1-β) at 0.90, then a sample size of 70 is required for each of the two groups (Total n = 140) to detect medium effect sizes (0.5; Cohen's d). For the second outcome measure of hospital admissions at 18 months follow-up, there will be 80% power to detect an improvement in the rate of hospital admissions of at least 43% in the TAU+Horyzons, assuming a hospital admission rate in the TAU of 30% over the 18-month follow-up [2]. We recruited 170 participants, accommodating for an 18% attrition rate, which is consistent with a similar study in terms of design and population [32].

Data management

A custom-built online Research Project Management System (RPMS) is used to manage the electronic data from this study. The RPMS includes an electronic Case Report Form (eCRF) and randomisation functionality. The study assessors record participant-level data on a paper-based Case Report Form (CRF). These data are subsequently entered into the eCRF section of the RPMS. The randomisation functionality of the RPMS is operated by the study coordinator. The RPMS is accessed using a secure website and is stored on a secure server. It is designed to maintain the privacy and confidentiality of participant information and to ensure the integrity of the data. Access to RPMS is restricted to study personnel and the level of access is dependent on the person's role. The study assessors and investigators do not have access to the randomisation section to ensure that they remain blind. Data are stored on three separate secure computer servers, including data collected from the SEMA tool, the RPMS

and data accumulated from participant activity within the HORYZONS online system. These various data are aggregated into a single electronic secure databank.

Data verification at all assessment time points is being conducted on 20 randomly selected cases. The selected cases are re-entered by the study coordinator. The a priori acceptable error rate has been set at 0.5%.

Ethics and dissemination

Ethics approval for the trial was provided by the Melbourne Health Research and Ethics Committee (No. 2013.146). All trial participants provided written informed consent prior to enrolment in the trial. For all eligible participants under 18 years of age, parental or guardian consent was also obtained.

Any adverse events (e.g., hospital admissions) including an independent assessment of whether the adverse event was related to the online intervention (i.e., made by a psychiatrist) were reported to the Melbourne Health Research and Ethics Committee. The study was considered to be low risk by the study sponsor and a trial management group was established in place of a data monitoring committee.

The main results of this clinical trial will be published in a peer-reviewed scientific journal. Manuscripts will also be prepared for significant findings regarding the secondary and exploratory aims. These results will be submitted and presented at scientific forums including national and international conferences in schizophrenia, early psychosis and youth mental health.

Patient and Public Statement

Patients were included in the development of the research questions and outcome measures in a number of ways. First, Orygen includes a youth reference group which provides consultation on the design, conduct and ethics of all studies carried out within the organisation. This group provided input into the main research question, design and outcome measures of the RCT. In addition, Orygen's internal Research and Review Committee integrates two youth representatives which also provided feedback on the key methodological aspects of the study from the consumers perspective.

Secondly, the design, development and therapeutic content of the intervention was also designed in partnership with young people. We conducted a series of focus groups with young people with lived experience to inform the development of HORYZONS. Young people participating in these focus groups consistently stated that HORYZONS should focus on promoting social connectedness and personal strengths [35-36]. This is consistent with previous qualitative research with young people [97]. The outcome measures were selected based on the combination of this research and this feedback. However, we did not seek specific assessment from young people on the burden of assessments or the intervention. Given that participants can select the frequency with which they use the system and receive contact from the moderator team, this seemed less salient with respect to the intervention.

Patients were not involved in the recruitment into the study. However, peer workers were involved in the conduct of the online intervention. We established a peer workers reference group led by our youth participation coordinator. This group provided online peer support via HORYZONS as well as ongoing consultation on the management of the trial and intervention updates. In addition, a number of focus groups with participants from the HORYZONS trial were conducted to obtain feedback on the management (moderation) and content of the online system.

We have created an email list to inform all participants of the results of the study and provided a contact email for participants to contact the research team should they require any additional information or wish to participate in online peer support.

DISCUSSION

The onset of psychosis often strikes young people at the prime of their lives, triggering a myriad of adverse psychosocial consequences that can result in entrenched social isolation, unemployment and chronicity [3]. Against this, early intervention is now seen as a key strategy to improve long-term recovery and reduce treatment costs [3]. However, while specialist early psychosis services have been demonstrated that they improve outcomes in FEP, follow-up studies have questioned the maintenance of treatment effects beyond the intervention period [9, 10]. Moreover, social recovery, a priority for young people, continues to be resistant to current intervention approaches [19]. This is the first randomised controlled trial to evaluate a novel online social media intervention designed to address both these challenges.

HORYZONS is the first intervention to exploit online social media technology and apply strengths and mindfulness approaches to improve long-term social recovery in FEP. In addition, the design of the intervention builds on our extensive experience developing and evaluating effective relapse prevention [98-100] and vocational recovery interventions [58] in early psychosis. Thus, HORYZONS weaves together two novel intervention approaches for FEP with established evidence-based protocols, while drawing on a strong theoretical base for social recovery in early psychosis (i.e., self-determination theory [59], broaden and build theory [22]).

Building on a previous successful pilot study [36], HORYZONS was co-developed with end-users and service providers. The online system was designed to be scalable, embedded within clinical practice and delivered across early intervention services. Specifically, HORYZONS is moderated by EPPIC clinicians as part of their routine clinical role (i.e., clinicians would allocate a proportion of their clinical time, typically 20 to 30%, to online moderation). Moderation and training procedures have been manualised and require minimum specialised training (2 days). Therapist efficiency using HORYZONS is estimated to be 5 times higher than that of specialised FEP services (100 vs. 20 young people of a typical caseload in an early psychosis clinic). Thus, if successful, HORYZONS will provide a scalable, cost-effective intervention approach to extend the benefits of early intervention and improve social functioning in FEP patients.

A limitation of the current study is that the control intervention consists of routine care, as opposed to a sham intervention accounting for increased attention and unspecific therapeutic factors. That said, this decision was made to enhance the external validity of the findings by replicating the current mainstream follow-up options available to FEP young people beyond their involvement in early intervention services. As such, this study is expected to provide evidence of cost-effectiveness of a step-down model of care instead of generating controlled evidence on the specific treatment components driving improved outcomes. Of note, the design of this study parallels that of recently published randomised controlled trials examining extended interventions for FEP services, with TAU being the control intervention across all three studies [30-32].

Sustained and meaningful recovery is the ultimate goal of early intervention services as well as the most valued outcome by young people and their families [101]. This is the first

randomised controlled trial to evaluate an online-based intervention as a means to extend the benefits of specialised early intervention services and foster long-term social functioning in FEP. Thus, if successful, HORYZONS has the potential to augment the benefits and long-term impact of the current model of early intervention for psychosis.

Figure 1. Horyzons recruitment and allocation procedure.

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AUTHORS' CONTRIBUTIONS

M.A.-J., and J.F.G. led the overall design and conduct of the study. S.B. and S.R. contributed to the supervision of the moderation of the online intervention. P.K., is the lead statistics and ecologically momentary expert in the study. J.P., was the peer workers supervisor during the study. S.D., is the lead engineer of the HORYZONS project. C.Miles, is the lead front-end designer of the HORYZONS platform. P.R., is the creative content lead of the project. R.L., G.W., O.S., T.G., and C.L. contributed to the design of the intervention. R.C. developed the mindfulness and self-compassion components of HORYZONS. M.A.-J wrote the first draft of the manuscript. D.C., L.V., C.Mihalopoulos, H.H., C.G-B., R.D-G., E.K., S.M.C., S.L., and P.D.M contributed to the design and conduct of the study. All authors critically revised and approved the final manuscript.

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COMPETING INTERESTS STATEMENT

The authors report no relevant conflict of interest.

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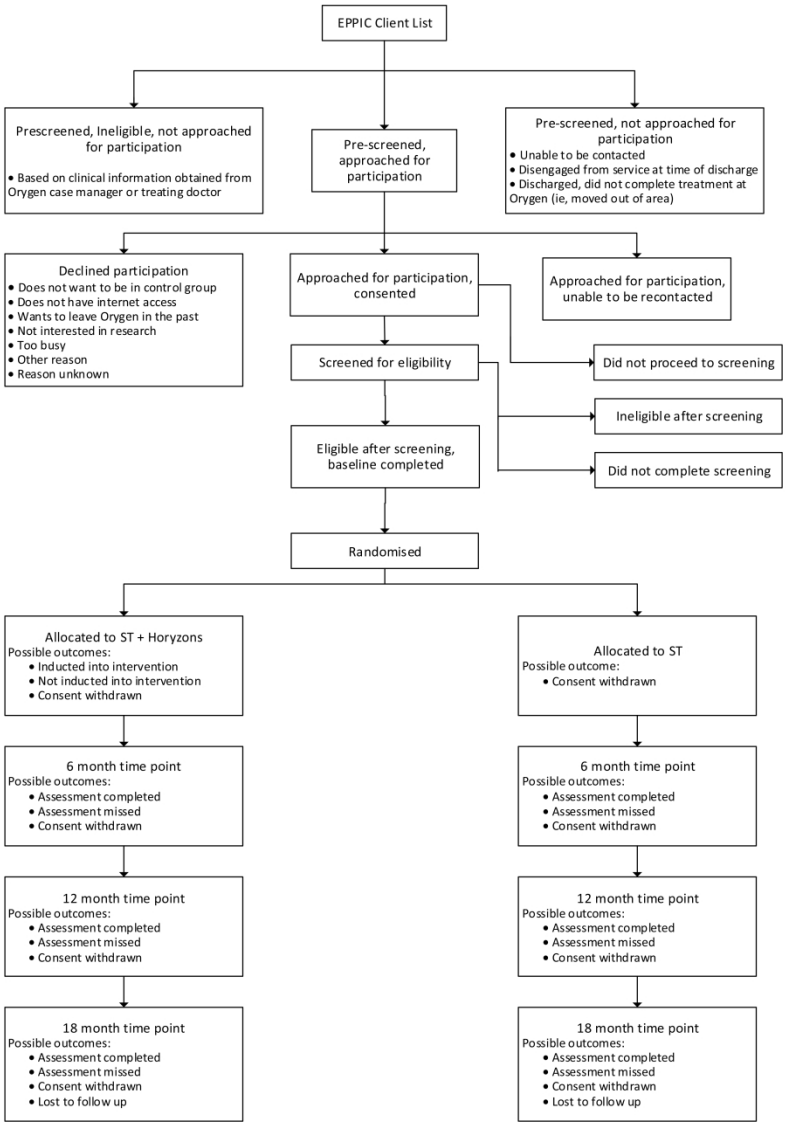
Figure 1. Study flow diagram for HORYZONS.



Horyzons recruitment and allocation procedure

318x473mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	22
	5b	Name and contact information for the trial sponsor	23
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-9
	6b	Explanation for choice of comparators	9
Objectives	7	Specific objectives or hypotheses	9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14-6
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	N/A

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	20
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	21
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	22
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	16
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	N/A
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Page 1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Page 2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Pages 3-6
	2b	Specific objectives or hypotheses	Pages 6-7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Pages 7, 9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	Page 8
	4b	Settings and locations where the data were collected	Page 7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Pages 9-13
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Pages 15-18
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Pages 16-17
Sample size	7a	How sample size was determined	Page 20
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Page 9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Page 9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Page 9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Page 9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Page 9, 21

	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Pages 19-21
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Pages 19-21
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	NA
	13b	For each group, losses and exclusions after randomisation, together with reasons	NA
Recruitment	14a	Dates defining the periods of recruitment and follow-up	NA
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	NA
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	NA
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	NA
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Pages 3, 23
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	NA
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	NA
Other information			
Registration	23	Registration number and name of trial registry	Page 2
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Page 23

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.