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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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024104
Article Type:	Protocol
Date Submitted by the Author:	20-Jun-2018
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<p>Keywords:</p>	<p>Schizophrenia & psychotic disorders < PSYCHIATRY, PSYCHIATRY, MENTAL HEALTH</p>



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3 The Horyzons trial: Protocol for a Randomised Controlled Trial of a Moderated
4 Online Social Therapy to Maintain Treatment Effects from First Episode
5 Psychosis Services
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44 **Word Count**

45 7593
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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 specialized 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

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3 has been cognitive behavioural therapy, which is primarily focused on reducing the positive
4 symptoms of psychosis[19]. Recognizing this gap, a recent trial evaluated a social recovery
5 therapy in combination with early intervention services to enhance social recovery in FEP
6 [19]. Study results showed an improvement in structured activity in those receiving the
7 intervention relative to those receiving early intervention services alone. The renewed focus
8 on social recovery is also consistent with recent psychological models, which have proposed
9 self-efficacy[20-21] and positive emotions[22] as important targets to promote social
10 functioning in psychosis. Strengths- and mindfulness-based interventions have been put
11 forward as key interventions to increase self-efficacy and positive emotions[23], respectively,
12 with preliminary studies supporting their potential to improve social functioning in
13 psychosis[24-25].

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22 A complementary approach to improving long-term recovery in FEP is to extend the
23 duration of specialised treatment[26-27]. This view is underpinned by findings that the first 5
24 years after psychosis onset constitute a critical period, determining longer term outcomes[27-
25 28]. Similarly, promoting sustained social and functional recovery in the early course of
26 psychosis appears to be a key path towards long-term functional recovery[29]. Two recent
27 randomised controlled trials have evaluated the effects of the current model of early
28 intervention (i.e., 2 years of specialised treatment) vs. an extended model of care (i.e., 5 years
29 of specialised treatment)[30-31] with mixed results. In one of these trials, the extended model
30 of care improved length of remission of positive and negative symptoms relative to regular
31 care[31]. Conversely, a second study showed no significant improvements in clinical or
32 social outcomes associated with the extended model of care[30]. An additional clinical trial
33 examined the effects of prolonging the period of specialised care for 12 months (i.e., three
34 years vs. two years of specialised treatment)[32]. This study showed significant
35 improvements in functional outcomes at the end of the 3-year compared with 2-year
36 specialised support. However, treatment benefits were not sustained, with no significant
37 differences across treatment groups at 1 and 2 years post specialised intervention[32].

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50 An alternative to prolonging the duration of specialised intervention is to offer extended,
51 lower intensity maintenance treatment following the first two years of specialised
52 treatment[27]. This is supported by findings that the termination of the specialised
53 intervention and transfer of care brings about feelings of loss for the patients[9] and
54 significantly derails engagement with treatment services[33], a pivotal element of early
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3 intervention programmes. Thus, a lower intensity level of care may bridge the gap between
4 specialised intervention and standard treatment and provide a cost-effective alternative to
5 bring about sustained benefits in FEP. This approach has shown promising results in a single
6 group study, with improvements seen at 2 years (i.e., end of specialised care) being
7 maintained at 5 years (i.e., after 3 years of lower intensity specialised treatment)[27].
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12 Online- and mobile-based interventions can also provide a lower intensity, cost-effective
13 and engaging approach to prolonging the benefits of specialised FEP services. Indeed, the
14 extant research shows that online interventions are feasible, acceptable, and may improve a
15 range of important domains in psychosis treatment including psychotic symptoms, hospital
16 admissions, social connectedness, and depression[34-35]. However, most studies conducted
17 to date have employed uncontrolled designs, were underpowered, included short follow-up
18 periods, targeted people with chronic schizophrenia, did not use online social media, and did
19 not specifically target social functioning[34]. To the best of our knowledge, only one pilot
20 study has evaluated the acceptability and preliminary benefits of an online intervention in
21 young people with FEP[36].
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31 Finally, online social networks provide a particularly promising avenue to foster social
32 functioning in young people with FEP. A recent study revealed that 89% of young people
33 aged 18-29 use social media daily[37], a frequency that is on the rise[38]. Use of online
34 social media has been associated with increased life satisfaction[39], self-esteem[39], and
35 social capital[40], as well as lower loneliness and depression[41], particularly for those who
36 post content to the social network and are active users[42]. Recent surveys indicate that social
37 media habits of young people with psychosis resemble that of their peers: virtually all
38 regularly use social media, on average 10 times and 2 hours per day[43-44]. Particularly
39 relevant to the therapeutic potential of social media in FEP, 78% would like to obtain help
40 from clinicians via social media, 40% increase their use of social media when experiencing
41 symptoms[43] and the majority strongly agree with using social media as a platform from
42 mental health support[45]. Thus, coupled with psychological interventions specifically
43 addressing social recovery such as strengths- and mindfulness-based approaches, social
44 media provides an opportunity deliver acceptable, extended lower intensity support with
45 potential to foster long term social functioning in FEP.
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56 **Aims and hypotheses**

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3 The objective of this trial was to determine whether extending the treatment period of a
4 specialised FEP service through an 18-month, step-down, novel online social media-based
5 intervention (HORYZONS) produces better outcomes compared with 2 years of specialist
6 FEP treatment followed by treatment as usual (TAU), using a randomised controlled single-
7 blind design. An additional aim of this trial is to determine the cost-effectiveness of
8 HORYZONS.
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14 The primary hypothesis is that, relative to TAU, HORYZONS will lead to improved social
15 functioning at 18 months amongst young people with FEP. The secondary hypotheses are
16 that, relative to TAU, HORYZONS will reduce the rate of hospital admissions due to
17 psychotic symptoms and lead to improvements in depression, vocational outcomes,
18 satisfaction with life, social support, loneliness, self-esteem, self-efficacy, anxiety, stress,
19 positive and negative psychotic symptoms, psychological wellbeing, quality of life, and
20 substance use. Finally, we hypothesise that HORYZONS will be more cost-effective than
21 TAU.
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29 **METHODS AND ANALYSIS**

30 **Patient and public involvement**

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33 Young people with lived experience were extensively involved in the design of the
34 HORYZONS system, with continuous consultation and co-design activities over the
35 development period. In addition, as noted above, young people played a key role in the
36 delivery of the intervention, with peer supporters actively managing the social network,
37 the group online problem-solving feature ('Talk it out') as well as providing one on one peer
38 support via the online chat system.
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44 Orygen integrates youth reference and consultation groups whose role is to provide advice
45 on all research activities conducted at the centre. Both groups were involved in the design of
46 the study as well as the evaluation of the face validity of the questionnaires. Patients were not
47 involved in the recruitment of participants into the study.
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51 Online moderators regularly consulted with patients to ensure that the intervention did not
52 result in increased perceived burden for the participants. Moderators and participants
53 collaboratively developed a shared formulation with explicit and agreed expectations for
54 frequency of use and support from moderators and peer supporters.
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3 The results of the study will be disseminated via the Orygen website. In addition,
4 participants will be notified via a text message at the point the results become available.
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8 9 **Study design**

10 The study design is an 18-month, parallel groups, single-blind, randomised controlled trial
11 (RCT) in which 170 participants with remitted FEP have been allocated to either the current
12 mainstream model of early intervention for psychosis (i.e., 2 years of specialised treatment
13 followed by discharge to treatment as usual; TAU), or TAU in tandem with a moderated
14 online social media intervention (HORYZONS), for 18 months.
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20 The design includes four assessment time points: baseline, 6 months, 12 months and 18
21 months. The RCT includes a 40-month recruitment period and an 18-month treatment phase,
22 with the study being completed within 5 years. The protocol development addressed all
23 aspects of Good Clinical Practice[46], CONSORT EHEALTH criteria[47] and SPIRIT
24 guidelines[48].
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29 30 **Setting**

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32 Recruitment of the trial participants commenced in October 2013, with the first participant
33 enrolled 29 November 2013, and finalised in January 2017 at Early Psychosis Prevention and
34 Intervention Centre (EPPIC), a subprogram of Orygen Youth Health, Melbourne. EPPIC is a
35 publicly-funded specialist FEP program servicing 250 new referrals for FEP per year. EPPIC
36 provides 18 months to 2 years of specialised care after which patients are discharged and
37 transferred to treatment as usual[49]. Follow-up assessments will be concluded in July 2018.
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43 44 **Participants**

45 Inclusion criteria for participants were: (a) a first episode of a DSM-IV psychotic disorder
46 or mood disorder with psychotic features; (b) aged 16-27 years inclusive; (c) ≤ 6 months
47 treatment with an antipsychotic medication prior to registration with EPPIC; (d) remission of
48 positive symptoms of psychosis, defined, using the Positive and Negative Syndrome Scale
49 (PANSS)[50], as 4 weeks or more of scores of 3 (mild) or below on items P2 (conceptual
50 disorganization) and G9 (unusual thought content), and scores of 4 (moderate) or below with
51 no functional impairment on items P3 (hallucinatory behaviour) and P1 (delusions).
52 Additional inclusion criteria to ensure low level of risk within HORYZONS included: (f) low
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3 aggressiveness, defined by a score of 3 or below on the poor impulse control item of the
4 PANNS for the month prior to study entry; and (g) moderate or lower suicidal risk defined as
5 a score of 4 or below on the suicidality subscale of the Brief Psychiatric Rating Scale –
6 expanded version (BPRS)[51] for the month preceding study entry. Finally, participants were
7 required to nominate an emergency contact to be eligible for the study.
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12 Exclusion criteria included: (a) intellectual disability; and (b) inability to converse in or
13 read English. Additional exclusion criteria to ensure safety within the online system included
14 (c) a DSM-IV diagnosis of either antisocial personality disorder (ASPD); or (d) borderline
15 personality disorder (BPD) as well as clinical evidence that the BPD features cause
16 interpersonal difficulties in the treatment environment.
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22 The SCID-I/P[52] was used as the standardized measure of DSM-IV diagnosis of mental
23 illness. The BPD (13 items) and Conduct Disorder/ASPD (22 items) screening questions of
24 the SCID-II Personality Questionnaire were used to assess for BPD and ASPD[53].
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29 Withdrawal from the trial occurred if: (a) participation in the study interfered with
30 appropriate clinical management of risk of harm to self or others (as judged by the treating
31 clinicians and/or senior researchers); (b) serious adverse events developed that could be
32 associated with the online intervention; and (c) participants failed to comply with the terms of
33 use of the online intervention. Withdrawal from the study could be at the request of the
34 participant, or at the discretion of the investigator.
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40 **Enrolment and randomisation**

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42 The recruitment and allocation procedures are depicted in Figure 1. The study coordinator
43 liaised with the Orygen Youth Health Quality and Evaluation Unit to obtain a list of young
44 people with FEP nearing discharge from EPPIC. This list was updated every 3 months during
45 the recruitment phase. The study coordinator assessed the initial eligibility of young people
46 within 3 months of discharge in consultation with EPPIC case managers and treating doctors.
47 Clients deemed potentially eligible were approached by the study coordinator to obtain
48 written informed consent. Next, eligibility was confirmed through a screening assessment.
49 Eligible participants completed the baseline assessment and were subsequently randomised to
50 either HORYZONS plus TAU or TAU alone at a ratio of 1:1. Randomisation was carried out
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3 remotely according to the International Conference on Harmonization E9 Statistical
4 Principles Guidelines[54]. An independent statistician created the randomisation sequence
5 using permuted blocks. The study coordinator randomised the participants via a secure
6 online Research Project Management System (RPMS). The RPMS sent an automated email
7 to the study coordinator and investigators notifying them of the outcome of randomisation.
8 Finally, the study coordinator informed the participant of the allocation.
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14 The study assessors undertaking the follow-up assessments are kept blind to treatment
15 allocation via the following mechanisms: (1) at the commencement of each research
16 interview the assessor reminds participants of the importance of the blind, (2) study assessors
17 are excluded from all clinically related discussions regarding participants, and (3) the
18 assessors were forbidden from accessing participants' medical records. The assessors record
19 their best guess of participants' treatment allocation at 6, 12 and 18 months' follow-up in
20 order to enable an assessment of the success of treatment concealment. In addition, any
21 instances of unblinding were recorded.
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29 **Interventions**

30 **HORYZONS**

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32 HORYZONS has been developed by a multidisciplinary team of researchers, clinical
33 psychologists, programmers, creative writers, graphic artists and experts in human computer-
34 interaction[36, 55]. HORYZONS was designed following participatory design principles with
35 the purpose of addressing social functioning in early psychosis. For example, focus groups
36 with young people with psychosis revealed that they favoured a social media-based platform
37 enabling meaningful peer-to-peer contact as well as clinicians' support[35, 56]. In addition,
38 young people called for online interventions focused on promoting personal strengths and
39 self-efficacy as opposed to merely ameliorating symptoms and deficits. Finally, young people
40 indicated that the system should provide self-guided, interactive, tailored interventions,
41 relevant to their changing needs[35, 56].
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50 Informed by young people's continual feedback as well as relevant research in the mental
51 health and human computer interaction fields[55], the design of HORYZONS merged (1)
52 interactive online therapy ('Pathways and Steps'), (2) peer-to-peer online social networking
53 ('the café'), and (3) peer and (4) expert moderation. All components of HORYZONS were
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3 designed to reinforce each other, creating a flow for the young person between the social and
4 therapy elements. For example, young people are encouraged to post comments and interact
5 with others while engaging with therapy content, and are, at the same time, prompted by
6 moderators to practice their strengths or use skills they have learned while engaging with the
7 social network. Young people can log on to Horyzons at any time via an Internet-enabled
8 desktop or mobile device.
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13 14 ***Interactive online therapy modules ('pathways and steps')*** 15

16 HORYZONS integrates a number of online 'pathways' organized into distinct themes
17 including: understanding psychosis, identifying and exercising personal strengths, promoting
18 positive connections with others, fostering positive emotions, early warning signs and
19 prevention of relapse, managing stress and anxiety, dealing with depression, and vocational
20 skills. With the aim of increasing the usability and take-up of therapeutic content, pathways
21 consist of thematically related interactive therapy 'Steps'. The online 'Steps' are discrete,
22 interactive, evidence-based therapy modules primarily targeting social functioning in young
23 people with psychosis; for example, through fostering self-efficacy (e.g., identifying personal
24 strengths via an interactive card-sort game based on the strengths-based framework [36]),
25 positive emotions and subjective wellbeing (e.g., practicing mindfulness and self-
26 compassion), or positive connections with others (e.g., illustrating how to respond
27 empathically to others). The content of the Steps was informed by previous studies linking
28 use of personal strengths, increased self-efficacy and positive emotions with improved social
29 functioning in psychosis[21-22, 25, 57]. Online Steps further address comorbid symptoms
30 such as anxiety and depression as well as vocational support (informed by our previous
31 work[58]). Finally, the design of HORYZONS and therapeutic content was strongly
32 influenced by self-determination theory, an empirically supported theory of motivation which
33 focuses on the processes and social environments that facilitate or hamper social
34 functioning[59].
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48 The Steps incorporate prompts for participants to share their thoughts and reactions to the
49 therapeutic material with other users through embedded 'Talking Points'. To ensure that
50 therapeutic content is translated into behavioural change, the Steps entail behavioural
51 prompts entitled 'Do its'. For example, following a Step about fostering positive
52 connections, the participant will find specific behavioural suggestions (or 'do its') to exercise
53 a therapeutic skill (e.g., empathy) in specific contexts (e.g., school). 'Do its' are also related
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3 to the participant's specific strengths (e.g., using kindness in social interactions). A 'Playlist'
4 stores and schedules any 'Do it' the participant wants to complete in the future. Moreover,
5 participants can rate, like, comment on, and share any Step or 'Do it' with others via the
6 social networking newsfeed. Participants can also keep track of 'trending' Steps, which users
7 have completed specific steps, 'Do its' or pathways, or identify other young people who share
8 their personal strengths. Finally, young people support each other's efforts to take on specific
9 behavioral changes via the 'Team up' function (e.g., by supporting or joining others in their
10 efforts to take on specific challenges).
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16 *Social network features*

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19 Participants are encouraged to communicate with one another and with peer and expert
20 moderators through the online social network or 'Café' to foster social support. Expert
21 Moderators (clinicians) are identifiable as a separate user class within the network. Each
22 participant creates their own profile with images, and can visit the wall of fellow users, where
23 their posts and general activity are displayed. Posts can include 'icebreakers' (to encourage
24 social interactions, e.g. What's the worst gift that someone gave you?), user-generated
25 threads, 'reactions' (designed to facilitate social support, e.g., 'I get you', 'thinking of you')
26 as well as content related to mental health (e.g., recent steps taken by others) or general
27 interest.
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35 A final feature of HORYZONS is Talk it out (TiO), an online group function informed by
36 the evidence-based problem-solving framework[60]. A TiO enables users to nominate issues
37 (e.g., 'how to break through shyness and make new friends?'), which are discussed in
38 moderated groups through structured phases (e.g., brainstorming, pros and cons, wrap-up).
39 Previous problems and group solutions are stored in the system providing an easily accessible
40 'solution wiki' for future young people.
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46 **Expert and peer moderation**

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48 HORYZONS integrates online personal therapist support (by clinicians with experience
49 treating young people with psychosis). Their role is to customize evidence-based
50 interventions, monitor participant's clinical status and ensure the safety of the social network.
51 Each therapist is assigned a caseload (i.e., a 20% full time equivalent online moderator can
52 comfortably manage 20-25 participants), which they follow for the duration of the trial.
53 Following the baseline assessment and initial face-to-face orientation to the system, the
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3 therapist makes contact with the participant for a brief phone meeting reviewing their
4 personal needs and preferences[61]. Expert moderators then develop brief case formulations
5 which are presented during weekly supervision meetings with senior clinical psychologists
6 from the team. Guided by the individual formulation, moderators send each client tailored
7 content suggestions weekly (e.g., a Step or 'Do it') with a focus on improving social
8 functioning. Suggestions appear on the user's home page and they receive a system
9 notification, which is also delivered via SMS as determined by the participants settings.
10 Young people can rate the helpfulness of the suggestions, which moderators use to tailor
11 subsequent recommendations. Expert moderation was informed by the supportive
12 accountability model[61] a theory-driven framework operationalising how human support
13 increases user engagement, the self-determination theory[59] and strengths-based models[62]
14 as a means of enhancing users' engagement and self-efficacy.
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24 In addition to clinical moderation, HORYZONS incorporates online vocational support.
25 Drawing on our previous work[58], the vocational moderator provides individualised online
26 vocational support, which can include: assessing young people's preferences and training,
27 identifying suitable competitive job openings, supporting young people in specific job
28 seeking activities (e.g., writing a CV), or preparing for a job interview.
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34 The 'cafe' is led by trained young people with lived experience of mental illness ('Super-
35 Users'). Super-Users are peer moderators who facilitate social learning using HORYZONS in
36 desired ways (e.g., self-disclosing, using therapy content to deal with difficulties). Super-
37 Users also seed discussion threads and 'icebreakers' to enable relevant, enjoyable
38 conversations and facilitate meaningful relationships. Finally, peer moderation serves to
39 normalise experiences, counteract stigma and promote engagement. Peer moderation was
40 informed by the social learning theory which posits that those who observe others (i.e.,
41 superusers) being rewarded for a particular behaviour (e.g., completing a step or commenting
42 on the social network) are more likely to modify their beliefs and subsequent behaviour[63].
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50 **Control intervention**

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

22 **Safety protocol**

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

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

40 The study coordinator carries out an initial face-to-face orientation with HORYZONS
41 participants, including details of the terms of use. Participants were required to accept and
42 comply with the guidelines for safe use of HORYZONS. When needed, participants are
43 offered guidance on appropriate usage of the system. All users are asked to nominate an
44 emergency contact person, such as a close family member. HORYZONS includes a 'report
45 function' which enables young people to report a concern about any material posted by a
46 user. The moderator assesses the basis of the report and responds accordingly, which may
47 include the removal of the material and, in some cases, deactivating or restricting the young
48 person's account. Participants are also able to hide their profile and activity should they
49 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				

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3	Self-Esteem Rating Scale-Short Form (SERS-SF)			
4	Depression Anxiety and Stress Scale (DASS)			
5	Scales of Psychological Wellbeing (SPWB)			
6	Satisfaction with Life Scale (SWLS)			
7	AQoL 8D questionnaire			
8	The Positive and Negative Syndrome Scale (PANSS)			
9	Alcohol, Smoking, Substance Involvement Screening Test (ASSIST)			
10	Smartphone Ecological Momentary Assessment (SEMA) ^b			
11	Subsidiary measures			
12	Resource Use Questionnaire			
13	Exploratory outcomes			
14	Social Interaction Anxiety Scale (SIAS)			
15	Social Comparison Scale (SCS)			
16	2-Way Social Support Scale (2-Way SSS)			
17	Savoring Beliefs Inventory (SBI)			
18	Mindful Attention Awareness Scale (MAAS)			
19	Strengths Use Scale (SUS)			
20	Self-Compassion Scale Short Form (SCS-SF)			
21	Physical Activity Questionnaire (IPAQ)			
22	Waist circumference			
23	Potential covariates			
24	Duration of Untreated Psychosis (DUP)			
25	Scale to Assess Unawareness of Mental Disorder (SUMD)			
26	Motivational Trait Questionnaire (MTQ)			
27	Medication Adherence Rating Scale (MARS)			
28	Bell Lysaker Emotion Recognition Task (BLERT)			
29	The Hinting Task			
30	Social Probabilistic Inference Task (SPIT)			
31	Digit Symbol Substitution Test (DSST)			
32	Wechsler Test of Adult Reading (WTAR)			
33	Horyzons specific measures			
34	Horyzons Perceived Competence Scale (H-PCS)			
35	Horyzons Self-regulation Questionnaire (HSRQ)			
36	Horyzons Health Care Climate Questionnaire (HCCQ)			

^aContinuous from state government databases

^bSmartphone 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.

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

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16 After the study was initiated, some feasibility issues were identified that led to
17 modifications to the study secondary outcome measures. In the original protocol, we intended
18 to measure psychotic relapse using the PANSS scale via phone or Skype-based assessments
19 conducted every two months throughout the 18-month intervention period. Ongoing
20 measurement of psychotic symptoms at regular intervals is a requirement for the reliable and
21 prospective identification of psychotic relapse[69]. However, despite our best efforts,
22 contacting participants via phone calls at regular intervals raised important feasibility issues,
23 with many participants not answering phone calls or regularly changing phone numbers,
24 leading to significant missing data. Thus, 12 months after study commencement, it was
25 decided to discontinue the regular phone calls and prospective assessment of psychotic
26 relapse. Given the feasibility issues measuring relapse of psychotic symptoms at regular
27 intervals, the following secondary outcomes were added:
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37 1. Hospital admissions due to psychotic symptoms and mental health issues were added as
38 a secondary outcome variable. We have access to reliable and objective hospital admission
39 data from research assessments, clinical files as well as state databases (i.e., Centre for
40 Victorian Data Linkage) spanning the 18-month assessment period. Data on hospital
41 admission from the state databases will be provided by an independent person blind to study
42 design and purpose.
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48 2. Positive and negative psychotic symptoms as measured by the PANNS scale at each
49 assessment time-point.
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53 3. *Physical health* was also initially included as secondary outcome variable because we
54 originally intended to incorporate online modules targeting this domain. However, we
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3 decided not to include therapy content addressing physical health and therefore this variable
4 will be analysed as an exploratory outcome.
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8 Secondary outcome measures include:

- 9 (1) *accumulated hospital admissions* due to psychotic symptoms and mental health issues
10 over 18 months;
11 (2) *vocational status* as measured by employment and/or education status;
12 (3) *depression* as measured by the Calgary Depression Scale for Schizophrenia
13 (CDSS[70]);
14 (4) *social support and loneliness* as assessed by Medical Outcomes Study: Social Support
15 Survey (MOS-SSS[71]) and the UCLA Loneliness Scale (Version 3[72]);
16 (5) *self-esteem* and *self-efficacy* as measured by the Self-Esteem Rating Scale-Short Form
17 (SERS-SF[73]) and Mental Health Confidence Scale (MHCS[74]), respectively;
18 (6) *anxiety and stress* as determined by the Depression Anxiety and Stress Scale
19 (DASS[75]);
20 (7) *psychological wellbeing* as measured by Scales of Psychological Wellbeing
21 (SPWB[76]);
22 (8) *satisfaction with life* as measured by Satisfaction with Life Scale (SWLS[77]);
23 (9) *quality of life* as measured by the AQoL 8D[78]. This questionnaire can also be used to
24 determine quality-adjusted life years (QALYs), which are useful in economic evaluation
25 studies;
26 (10) *positive and negative psychotic symptoms* assessed by means of The Positive and
27 Negative Syndrome Scale (PANSS[50]);
28 (11) *substance use* as measured by the Alcohol, Smoking and Substance Involvement
29 Screening Test (ASSIST version 3.1) over 18 months follow-up;
30 (12) *Cost-effective analysis*: A Resource Use Questionnaire (RUQ) is used to determine
31 the broader resource use of participants (e.g. community mental health services,
32 accommodation, work impacts etc). Additionally, for consenting participants, information
33 regarding utilisation of health care services available via the Medicare Benefits Schedule
34 (MBS - medical, allied health, diagnostic and pathology services) and the Pharmaceutical
35 Benefits Schedule (PBS - medications) will be accessed from the Australian Department
36 of Human Services;
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3 To obtain more dynamic and ecologically valid data on young people's social functioning,
4 participants utilise a custom-built smartphone app, SEMA, which is readily downloadable at
5 no charge to participants owning a smartphone (running Android or iOS operating systems).
6 SEMA delivers surveys (administered for 7 days following each assessment time point)
7 approximately eight times per day for 7 consecutive days. Young people are prompted to
8 complete SEMA surveys at random times every 90 min (± 30 min) over a 12-h period (e.g. 10
9 a.m. to 10 p.m.). SEMA tracks participants' responses in (near) real time, ensuring minimal
10 data loss by uploading responses to a secure server or storing responses on the young
11 person's smartphone when an Internet connection is temporarily unavailable. Each SEMA
12 survey begins with four items assessing momentary positive affect ('At the moment, how
13 happy do you feel?'), negative affect ('At the moment, how sad do you feel?'; 'At the
14 moment, how stressed do you feel?') and momentary social isolation (e.g. 'At the moment,
15 how lonely do you feel?') rated on visual slider scales anchored at 0 (not at all) and 100
16 (very). The order of these four items is randomised at each survey.
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27 Following the momentary affect items, the SEMA survey includes items pertaining to
28 social interactions of the young person (e.g. 'How much time have you spent interacting with
29 others, since last survey?'), perceived social efficacy (e.g., 'How well do you think you
30 handled your social interactions, since last survey?'), perceived social support (e.g., 'have
31 you received support or encouragement from others, since last survey?'), critical comments
32 (e.g., 'Have you felt that others criticized or judged you, since last survey?'), and social rank
33 (e.g., 'How competent have you felt in relation to others, since last survey?'), with all
34 responses being made on visual sliding scales ranging from 0 to 100. The order of these items
35 is also randomised at each survey.
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44 ***Exploratory outcomes and potential covariates***

45 Additional exploratory outcomes included: *social anxiety* measured through the Social
46 Interaction Anxiety Scale (SIAS)[79]; *social comparison and group fit* as assessed through
47 the Social Comparison Scale (SCS)[80]; *the provision of emotional support* measured via the
48 2-Way Social Support Scale (2-Way SSS[81]); *anticipatory pleasure* assessed through the
49 Savoring Beliefs Inventory (SBI[82]); *mindfulness skills* as assessed using the dispositional
50 Mindful Attention Awareness Scale (MAAS[83]); *strengths use* as assessed by means of the
51 Strengths Use Scale (SUS[84]); *self-Compassion* as assessed by the Self-Compassion Scale
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3 Short Form (SCS-SF[85]); *physical health* as measured by waist circumference over 18
4 months follow-up; and, *physical activity* as measured by the International Physical Activity
5 Questionnaire (IPAQ[86]) and by measuring sitting time across different domains[87] (e.g.,
6 TV, video, computer, working, etc.).
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11 Finally, potential covariates included: *Duration of Untreated Psychosis (DUP)* defined as
12 the time interval between onset of definite positive psychotic symptoms and first engagement
13 and treatment in an Early Intervention (EI) service; *clinical insight* as assessed by means of
14 the Scale to Assess Unawareness of Mental Disorder (SUMD[88]); *intrinsic motivation*
15 measured through the short form of Motivational Trait Questionnaire (MTQ[89]); *medication*
16 *adherence* measured by the Medication Adherence Rating Scale (MARS[90]); *emotion*
17 *processing* assessed by means of the Bell Lysaker Emotion Recognition Task (BLERT[91]);
18 *theory of mind* measured using The Hinting Task[92]; *Jumping to conclusions (JTC)*
19 measured through the Social Probabilistic Inference Task (SPIT); *premorbid intelligence* as
20 assessed via Wechsler Test of Adult Reading (WTAR[93]); and *general cognitive deficits*
21 will be measured through the Digit Symbol Substitution Test (DSST[94]).
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30 ***HORYZONS specific measures***

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

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44 Primary analyses will be undertaken on an intention-to-treat basis. Mixed-model repeated
45 measures (MMRM) analyses will be used to compare change in social functioning between
46 the two treatment groups over the 18-month follow-up. MMRM is the analysis of choice
47 because assumptions of traditional data analysis methods (e.g., ANOVA, logistic regression)
48 may be violated, such as the assumption of homogeneity of regression across time points[95].
49 Time (baseline, 6, 12 and 18 months) will be the within-subjects factor and group
50 (HORYZONS plus TAU vs. TAU) the between-subjects factor. MMRM will also be used to
51 analyse change in the continuous secondary outcomes over 18 months. Experiencing
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3 sampling data will be analysed using a multilevel structural equation modelling (MSEM)
4 framework[96]. Differential rate of hospital admissions will be analyzed using multilevel
5 logistic regression. Time to hospital admissions will be assessed by survival analysis (using
6 either proportional hazard or accelerated life-time models). Additional comparisons between
7 treatment groups based on completers-only analyses will be conducted. Analyses will be
8 undertaken in accordance with ICH 9 guidelines including a full analysis as well as per
9 protocol set. The per protocol sample will be defined based on receiving a pre-specified
10 minimal exposure to the online intervention (i.e., at least 8 logins over 2 months during the
11 18-month intervention period).
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19 Economic evaluation will comprise a cost-consequences analysis whereby incremental
20 costs of the intervention will be compared to the full spectrum of study outcomes. A cost
21 utility analysis will also be undertaken whereby the AQoL 8D will be used to QALYs. The
22 evaluation will measure and value any change to the use of health care resources over the
23 period of the study (using the data from the RUQ, MBS/PBS and hospitalisation
24 administrative data) between the two treatment arms; and then compare any additional costs
25 to the additional outcomes achieved. Australian sourced unit costs will be attached to the
26 RUQ (from Australian sources such as the Commonwealth Department of Health, Mental
27 Health Branch). Standardised economic evaluation techniques including incremental analysis
28 of mean differences (using statistical techniques such as generalised linear models) and
29 bootstrapping to determine confidence intervals around incremental cost-effectiveness ratios
30 will be used. If, as expected, the intervention is found to be effective, lifetime and population
31 cost-effectiveness of the interventions will be determined using economic modelling
32 techniques. We will determine the likelihood that the intervention is cost-effective at
33 commonly used value-for-money thresholds such as \$20,000/QALY and \$50,000/QALY.
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45 The primary outcome is change in social functioning at 18 months follow-up. A recent
46 RCT investigating the effects of extending FEP specialist treatment for 12 months (i.e., a
47 total of 3 years of specialist treatment) reported an effect size of 0.53 (Cohen's d) for
48 functional outcomes for the extended model of care at 12-months (i.e., end of the specialised
49 treatment) compared with TAU (i.e., 2 years of specialist treatment)[32]. If we assume that
50 alpha is set at 0.05 and power (1- β) at 0.90, then a sample size of 70 is required for each of
51 the two groups (Total n = 140) to detect medium effect sizes (0.5; Cohen's d). For the second
52 outcome measure of hospital admissions at 18 months follow-up, there will be 80% power to
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3 detect an improvement in the rate of hospital admissions of at least 43% in the
4 TAU+Horyzons, assuming a hospital admission rate in the TAU of 30% over the 18-month
5 follow-up[2]. We recruited 170 participants, accommodating for an 18% attrition rate, which
6 is consistent with a similar study in terms of design and population[32].
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10 11 **Data management**

12 A custom-built online Research Project Management System (RPMS) is used to manage
13 the electronic data from this study. The RPMS includes an electronic Case Report Form
14 (eCRF) and randomisation functionality. The study assessors record participant-level data on
15 a paper-based Case Report Form (CRF). These data are subsequently entered into the eCRF
16 section of the RPMS. The randomisation functionality of the RPMS is operated by the study
17 coordinator. The RPMS is accessed using a secure website and is stored on a secure server. It
18 is designed to maintain the privacy and confidentiality of participant information and to
19 ensure the integrity of the data. Access to RPMS is restricted to study personnel and the level
20 of access is dependent on the person's role. The study assessors and investigators do not have
21 access to the randomisation section to ensure that they remain blind. Data are stored on three
22 separate secure computer servers, including data collected from the SEMA tool, the RPMS
23 and data accumulated from participant activity within the HORYZONS online system. These
24 various data are aggregated into a single electronic secure databank.
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35 Data verification at all assessment time points is being conducted on 20 randomly selected
36 cases. The selected cases are re-entered by the study coordinator. The a priori acceptable
37 error rate has been set at 0.5%.
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41 42 **Ethics and dissemination**

43 Ethics approval for the trial was provided by The Melbourne Health Research and Ethics
44 Committee (No. 2013.146). All trial participants provided written informed consent prior to
45 enrolment in the trial. For all eligible participants under 18 years of age, parental or guardian
46 consent was also obtained.
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51 The main results of this clinical trial will be published in a peer-reviewed scientific
52 journal. Manuscripts will also be prepared for significant findings regarding the secondary
53 and exploratory aims. These results will be submitted and presented at scientific forums
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3 including national and international conferences in schizophrenia, early psychosis and youth
4 mental health.
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7 8 **DISCUSSION**

9 The onset of psychosis often strikes young people at the prime of their lives, triggering a
10 myriad of adverse psychosocial consequences that can result in entrenched social isolation,
11 unemployment and chronicity[3]. Against this, early intervention is now seen as a key
12 strategy to improve long-term recovery and reduce treatment costs[3]. However, while
13 specialist early psychosis services have been demonstrated that they improve outcomes in
14 FEP, follow-up studies have questioned the maintenance of treatment effects beyond the
15 intervention period[9- 10]. Moreover, social recovery, a priority for young people, continues
16 to be resistant to current intervention approaches[19]. This is the first randomised controlled
17 trial to evaluate a novel online social media intervention designed to address both these
18 challenges.
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27 HORYZONS is the first intervention to exploit online social media technology and apply
28 strengths and mindfulness approaches to improve long-term social recovery in FEP. In
29 addition, the design of the intervention builds on our extensive experience developing and
30 evaluating effective relapse prevention[97-99] and vocational recovery interventions[58] in
31 early psychosis. Thus, HORYZONS weaves together two novel intervention approaches for
32 FEP with established evidence-based protocols, while drawing on a strong theoretical base
33 for social recovery in early psychosis (i.e., self-determination theory[59], broaden and build
34 theory[22]).
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42 Building on a previous successful pilot study[36], HORYZONS was co-developed with
43 end-users and service providers. The online system was designed to be scalable, embedded
44 within clinical practice and delivered across early intervention services. Specifically,
45 HORYZONS is moderated by EPPIC clinicians as part of their routine clinical role (i.e.,
46 clinicians would allocate a proportion of their clinical time, typically 20 to 30%, to online
47 moderation). Moderation and training procedures have been manualised and require
48 minimum specialised training (2 days). Therapist efficiency using HORYZONS is estimated
49 to be 5 times higher than that of specialised FEP services (100 vs. 20 young people of a
50 typical caseload in an early psychosis clinic). Thus, if successful, HORYZONS will provide a
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3 scalable, cost-effective intervention approach to extend the benefits of early intervention and
4 improve social functioning in FEP patients.
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8 A limitation of the current study is that the control intervention consists of routine care, as
9 opposed to a sham intervention accounting for increased attention and unspecific therapeutic
10 factors. That said, this decision was made to enhance the external validity of the findings by
11 replicating the current mainstream follow-up options available to FEP young people beyond
12 their involvement in early intervention services. As such, this study is expected to provide
13 evidence of cost-effectiveness of a step-down model of care instead of generating controlled
14 evidence on the specific treatment components driving improved outcomes. Of note, the
15 design of this study parallels that of recently published randomised controlled trials
16 examining extended interventions for FEP services, with TAU being the control intervention
17 across all three studies[30-32].
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25 Sustained and meaningful recovery is the ultimate goal of early intervention services as
26 well as the most valued outcome by young people and their families[100]. This is the first
27 randomised controlled trial to evaluate an online-based intervention as a means to extend the
28 benefits of specialised early intervention services and foster long-term social functioning in
29 FEP. Thus, if successful, HORYZONS has the potential to augment the benefits and long-
30 term impact of the current model of early intervention for psychosis.
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39 **FUNDING STATEMENT**

40
41 The HORYZONS trial was supported by the Mental Illness Research Fund (MIRF) from the
42 State Government of Victoria. M.A-J. was supported by a Career Development Fellowship
43 (APP1082934) from the National Health and Medical Research Council (NHMRC). S.M.C.
44 has been supported by a Career Development Fellowship (APP1061998) and Senior Research
45 Fellowship (APP1136344) from NHMRC. CM was supported by a NHMRC Early Career
46 Fellowship (APP1035887) during the conduct of the trial. SL was supported in part by a New
47 Investigator Salary Award from the Canadian Institutes of Health Research and previously in
48 part by a Research Scholar Salary Award from the Fonds de recherche du Québec—Santé
49 (FRQS).
50

51 **ACKNOWLEDGMENTS**

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54 The authors acknowledge the contribution of the Orygen Youth Advisory Group in the
55 development of the Horyzons platform. The authors acknowledge the work of the team of
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3 clinical moderators and peer workers for their dedication to the project. The authors also
4 thank the participants for their contribution to making this project possible.
5

6 **AUTHORS' CONTRIBUTIONS**

7 M.A.-J., and J.F.G. led the overall design and conduct of the study. S.B. and S.R. contributed
8 to the supervision of the moderation of the online intervention. S.D., is the technical lead of
9 the HORYZONS project and HORYZONS data analyst. C.M., is the lead front-end designer
10 of the HORYZONS platform. P.R., is the creative content lead of the project. R.L., G.W.,
11 O.S., T.G., and R.C., contributed to the design of the intervention. M.A.-J wrote the first draft
12 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
13 to the design and conduct of the study. All authors critically revised and approved the final
14 manuscript.
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19 **COMPETING INTERESTS STATEMENT**

20 The authors report no relevant conflict of interest.
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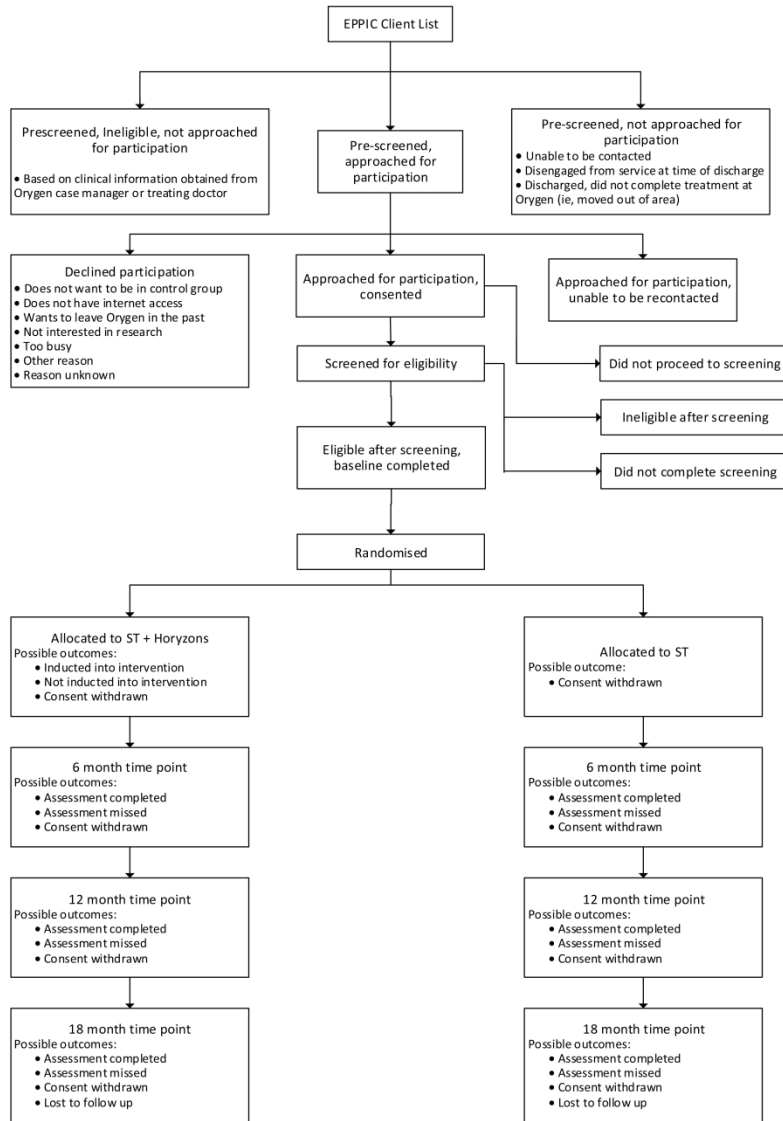
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Figure 1. Study flow diagram for HORYZONS.



318x473mm (300 x 300 DPI)



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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024104.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Oct-2018
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	Schizophrenia & psychotic disorders < PSYCHIATRY, PSYCHIATRY, MENTAL HEALTH

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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

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3 has been cognitive behavioural therapy, which is primarily focused on reducing the positive
4 symptoms of psychosis [19]. Recognizing this gap, a recent trial evaluated a social recovery
5 therapy in combination with early intervention services to enhance social recovery in FEP
6 [19]. Study results showed an improvement in structured activity in those receiving the
7 intervention relative to those receiving early intervention services alone. The renewed focus
8 on social recovery is also consistent with recent psychological models, which have proposed
9 self-efficacy [20, 21] and positive emotions [22] as important targets to promote social
10 functioning in psychosis. Strengths- and mindfulness-based interventions have been put
11 forward as key interventions to increase self-efficacy and positive emotions [23],
12 respectively, with preliminary studies supporting their potential to improve social functioning
13 in psychosis [24, 25].
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22 A complementary approach to improving long-term recovery in FEP is to extend the
23 duration of specialised treatment [26, 27]. This view is underpinned by findings that the first
24 5 years after psychosis onset constitute a critical period, determining longer term outcomes
25 [27, 28]. Similarly, promoting sustained social and functional recovery in the early course of
26 psychosis appears to be a key path towards long-term functional recovery [29]. Two recent
27 randomised controlled trials have evaluated the effects of the current model of early
28 intervention (i.e., 2 years of specialised treatment) vs. an extended model of care (i.e., 5 years
29 of specialised treatment) [30, 31] with mixed results. In one of these trials, the extended
30 model of care improved length of remission of positive and negative symptoms relative to
31 regular care [31]. Conversely, a second study showed no significant improvements in clinical
32 or social outcomes associated with the extended model of care [30]. An additional clinical
33 trial examined the effects of prolonging the period of specialised care for 12 months (i.e.,
34 three years vs. two years of specialised treatment) [32]. This study showed significant
35 improvements in functional outcomes at the end of the 3-year compared with 2-year
36 specialised support. However, treatment benefits were not sustained, with no significant
37 differences across treatment groups at 1 and 2 years post specialised intervention [32].
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50 An alternative to prolonging the duration of specialised intervention is to offer extended,
51 lower intensity maintenance treatment following the first two years of specialised treatment
52 [27]. This is supported by findings that the termination of the specialised intervention and
53 transfer of care brings about feelings of loss for the patients [9] and significantly derails
54 engagement with treatment services [33], a pivotal element of early intervention programmes.
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3 Thus, a lower intensity level of care may bridge the gap between specialised intervention and
4 standard treatment and provide a cost-effective alternative to bring about sustained benefits in
5 FEP. This approach has shown promising results in a single group study, with improvements
6 seen at 2 years (i.e., end of specialised care) being maintained at 5 years (i.e., after 3 years of
7 lower intensity specialised treatment) [27].
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12 Online- and mobile-based interventions can also provide a lower intensity, cost-effective
13 and engaging approach to prolonging the benefits of specialised FEP services. Indeed, the
14 extant research shows that online interventions are feasible, acceptable, and may improve a
15 range of important domains in psychosis treatment including psychotic symptoms, hospital
16 admissions, social connectedness, and depression [34, 35]. However, most studies conducted
17 to date have employed uncontrolled designs, were underpowered, included short follow-up
18 periods, targeted people with chronic schizophrenia, did not use online social media, and did
19 not specifically target social functioning [34]. To the best of our knowledge, only one pilot
20 study has evaluated the acceptability and preliminary benefits of an online intervention in
21 young people with FEP [36].
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31 Finally, online social networks provide a particularly promising avenue to foster social
32 functioning in young people with FEP. A recent study revealed that 89% of young people
33 aged 18-29 use social media daily [37], a frequency that is on the rise [38]. Use of online
34 social media has been associated with increased life satisfaction [39], self-esteem [39], and
35 social capital [40], as well as lower loneliness and depression [41], particularly for those who
36 post content to the social network and are active users [42]. Recent surveys indicate that
37 social media habits of young people with psychosis resemble that of their peers: virtually all
38 regularly use social media, on average 10 times and 2 hours per day [43, 44]. Particularly
39 relevant to the therapeutic potential of social media in FEP, 78% would like to obtain help
40 from clinicians via social media, 40% increase their use of social media when experiencing
41 symptoms [43] and the majority strongly agree with using social media as a platform from
42 mental health support [45]. Thus, coupled with psychological interventions specifically
43 addressing social recovery such as strengths- and mindfulness-based approaches, social
44 media provides an opportunity deliver acceptable, extended lower intensity support with
45 potential to foster long term social functioning in FEP.
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56 **Aims and hypotheses**

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3 The objective of this trial was to determine whether extending the treatment period of a
4 specialised FEP service through an 18-month, step-down, novel online social media-based
5 intervention (HORYZONS) produces better outcomes compared with 2 years of specialist
6 FEP treatment followed by treatment as usual (TAU), using a randomised controlled single-
7 blind design. An additional aim of this trial is to determine the cost-effectiveness of
8 HORYZONS.
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14 The primary hypothesis is that, relative to TAU, HORYZONS will lead to improved social
15 functioning at 18 months amongst young people with FEP. The secondary hypotheses are
16 that, relative to TAU, HORYZONS will reduce the rate of hospital admissions due to
17 psychotic symptoms and lead to improvements in depression, vocational outcomes,
18 satisfaction with life, social support, loneliness, self-esteem, self-efficacy, anxiety, stress,
19 positive and negative psychotic symptoms, psychological wellbeing, quality of life, and
20 substance use. Finally, we hypothesise that HORYZONS will be more cost-effective than
21 TAU.
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29 **METHODS AND ANALYSIS**

30 **Study design**

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32 The study design is an 18-month, parallel groups, single-blind, randomised controlled trial
33 (RCT) in which 170 participants with remitted FEP have been allocated to either the current
34 mainstream model of early intervention for psychosis (i.e., 2 years of specialised treatment
35 followed by discharge to treatment as usual; TAU), or TAU in tandem with a moderated
36 online social media intervention (HORYZONS), for 18 months.
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42 The design includes four assessment time points: baseline, 6 months, 12 months and 18
43 months. The RCT includes a 40-month recruitment period and an 18-month treatment phase,
44 with the study being completed within 5 years. The protocol development addressed all
45 aspects of Good Clinical Practice [46], CONSORT EHEALTH criteria [47] and SPIRIT
46 guidelines [48].
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52 **Setting**

53 Recruitment of the trial participants commenced in October 2013 and finalised in January
54 2017 at Early Psychosis Prevention and Intervention Centre (EPPIC), a subprogram of
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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

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3 associated with the online intervention; and (c) participants failed to comply with the terms of
4 use of the online intervention. Withdrawal from the study could be at the request of the
5 participant, or at the discretion of the investigator.
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8 9 **Enrolment and randomisation**

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11 The recruitment and allocation procedures are depicted in Figure 1. The study coordinator
12 liaised with the Orygen Youth Health Quality and Evaluation Unit to obtain a list of young
13 people with FEP nearing discharge from EPPIC. This list was updated every 3 months during
14 the recruitment phase. The study coordinator assessed the initial eligibility of young people
15 within 3 months of discharge in consultation with EPPIC case managers and treating doctors.
16 Clients deemed potentially eligible were approached by the study coordinator to obtain
17 written informed consent. Next, eligibility was confirmed through a screening assessment.
18 Eligible participants completed the baseline assessment and were subsequently randomised to
19 either HORYZONS plus TAU or TAU alone at a ratio of 1:1. Randomisation was carried out
20 remotely according to the International Conference on Harmonization E9 Statistical
21 Principles Guidelines [54]. An independent statistician created the randomisation sequence
22 using permuted blocks. The study coordinator randomised the participants via a secure
23 online Research Project Management System (RPMS). The RPMS sent an automated email
24 to the study coordinator and investigators notifying them of the outcome of randomisation.
25 Finally, the study coordinator informed the participant of the allocation.
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37 The study assessors undertaking the follow-up assessments are kept blind to treatment
38 allocation via the following mechanisms: (1) at the commencement of each research
39 interview the assessor reminds participants of the importance of the blind, (2) study assessors
40 are excluded from all clinically related discussions regarding participants, and (3) the
41 assessors were forbidden from accessing participants' medical records. The assessors record
42 their best guess of participants' treatment allocation at 6, 12 and 18 months' follow-up in
43 order to enable an assessment of the success of treatment concealment. Any instances of
44 unblinding were recorded.
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51 **Interventions**

52 **HORYZONS**

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3 HORYZONS has been developed by a large multidisciplinary team of researchers, clinical
4 psychologists, programmers, creative writers, graphic artists and experts in human computer-
5 interaction [36, 55]. HORYZONS was designed following participatory design principles
6 with the purpose of addressing social functioning in early psychosis. For example, focus
7 groups with young people with psychosis revealed that they favoured a social media-based
8 platform enabling meaningful peer-to-peer contact as well as clinicians' support [35, 56]. In
9 addition, young people called for online interventions focused on promoting personal
10 strengths and self-efficacy as opposed to merely ameliorating symptoms and deficits. Finally,
11 young people indicated that the system should provide self-guided, interactive, tailored
12 interventions, relevant to their changing needs [35, 56].
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21 Informed by young people's continual feedback as well as relevant research in the mental
22 health and human computer interaction fields [55], the design of HORYZONS merged (1)
23 interactive online therapy ('Pathways and Steps'), (2) peer-to-peer online social networking
24 ('the café'), and (3) peer and (4) expert moderation. All components of HORYZONS were
25 designed to reinforce each other, creating a flow for the young person between the social and
26 therapy elements. For example, young people are encouraged to post comments and interact
27 with others while engaging with therapy content, and are, at the same time, prompted by
28 moderators to practice their strengths or use skills they have learned while engaging with the
29 social network. Young people can log on to Horyzons at any time via an Internet-enabled
30 desktop or mobile device.
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39 ***Interactive online therapy modules ('pathways and steps')***

40 HORYZONS integrates a number of online 'pathways' organized into distinct themes
41 including: understanding psychosis, identifying and exercising personal strengths, promoting
42 positive connections with others, fostering positive emotions, early warning signs and
43 prevention of relapse, managing stress and anxiety, dealing with depression, and vocational
44 skills. With the aim of increasing the usability and take-up of therapeutic content, pathways
45 consist of thematically related interactive therapy 'Steps'. The online 'Steps' are discrete,
46 interactive, evidence-based therapy modules primarily targeting social functioning in young
47 people with psychosis; for example, through fostering self-efficacy (e.g., identifying personal
48 strengths via an interactive card-sort game based on the strengths-based framework [36]),
49 positive emotions and subjective wellbeing (e.g., practicing mindfulness and self-
50 compassion), or positive connections with others (e.g., illustrating how to respond
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3 empathically to others). The content of the Steps was informed by previous studies linking
4 use of personal strengths, increased self-efficacy and positive emotions with improved social
5 functioning in psychosis [21, 22, 25, 57]. Online Steps further address comorbid symptoms
6 such as anxiety and depression as well as vocational support (informed by our previous work
7 [58]). Finally, the design of HORYZONS and therapeutic content was strongly influenced by
8 self-determination theory, an empirically supported theory of motivation which focuses on
9 the processes and social environments that facilitate or hamper social functioning [59].
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16 The Steps incorporate prompts for participants to share their thoughts and reactions to the
17 therapeutic material with other users through embedded 'Talking Points'. To ensure that
18 therapeutic content is translated into behavioural change, the Steps entail behavioural
19 prompts entitled 'Do its'. For example, following a Step about fostering positive
20 connections, the participant will find specific behavioural suggestions (or 'do its') to exercise
21 a therapeutic skill (e.g., empathy) in specific contexts (e.g., school). 'Do its' are also related
22 to the participant's specific strengths (e.g., using kindness in social interactions). A 'Playlist'
23 stores and schedules any 'Do it' the participant wants to complete in the future. Moreover,
24 participants can rate, like, comment on, and share any Step or 'Do it' with others via the
25 social networking newsfeed. Participants can also keep track of 'trending' Steps, or identify
26 other young people who share their personal strengths. Finally, young people support each
27 other's efforts to take on specific behavioral changes via the 'Team up' function (e.g., by
28 supporting or joining others in their efforts to take on specific challenges).
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38 *Social network features*

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40 Participants are encouraged to communicate with one another and with peer and expert
41 moderators through the online social network or 'Café' to foster social support. Expert
42 Moderators (clinicians) are identifiable as a separate user class within the network. Each
43 participant creates their own profile with images, and can visit the wall of fellow users, where
44 their posts and general activity are displayed. Posts can include 'icebreakers' (to encourage
45 social interactions, e.g. What's the worst gift that someone gave you?), user-generated
46 threads, 'reactions' (designed to facilitate social support, e.g., 'I get you', 'thinking of you')
47 as well as content related to mental health (e.g., recent steps taken by others) or general
48 interest.
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3 A final feature of HORYZONS is Talk it out (TiO), an online group function informed by
4 the evidence-based problem-solving framework [60]. A TiO enables users to nominate issues
5 (e.g., ‘how to break through shyness and make new friends?’), which are discussed in
6 moderated groups through structured phases (e.g., brainstorming, pros and cons, wrap-up).
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8 Previous problems and group solutions are stored in the system providing an easily accessible
9 ‘solution wiki’ for future young people.
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14 **Expert and peer moderation**

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16 HORYZONS integrates online personal therapist support (by clinicians with experience
17 treating young people with psychosis). Their role is to customize evidence-based
18 interventions, monitor participant’s clinical status and ensure the safety of the social network.
19 Each therapist is assigned a caseload (i.e., a 20% full time equivalent online moderator can
20 comfortably manage 20-25 participants), which they follow for the duration of the trial.
21 Following the baseline assessment and initial face-to-face orientation to the system, the
22 therapist makes contact with the participant for a brief phone meeting reviewing their
23 personal needs and preferences [61]. Expert moderators then develop brief case formulations
24 which are presented during weekly supervision meetings with senior clinical psychologists
25 from the team. Guided by the individual formulation, moderators send each client tailored
26 content suggestions weekly (e.g., a Step or ‘Do it’) with a focus on improving social
27 functioning. Suggestions appear on the user’s home page and they receive a system
28 notification, which is also delivered via SMS as determined by the participants settings.
29 Young people can rate the helpfulness of the suggestions, which moderators use to tailor
30 subsequent recommendations. Expert moderation was informed by the supportive
31 accountability model [61] a theory-driven framework operationalising how human support
32 increases user engagement, the self-determination theory [59] and strengths-based models
33 [62] as a means of enhancing users’ engagement and self-efficacy.
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46 In addition to clinical moderation, HORYZONS incorporates online vocational support.
47 Drawing on our previous work [58], the vocational moderator provides individualised online
48 vocational support, which can include: assessing young people’s preferences and training,
49 identifying suitable competitive job openings, supporting young people in specific job
50 seeking activities (e.g., writing a CV), or preparing for a job interview.
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3 The 'cafe' is led by trained young people with lived experience of mental illness ('Peer-
4 workers'). Peer-workers are peer moderators who facilitate social learning using
5 HORYZONS in desired ways (e.g., self-disclosing, using therapy content to deal with
6 difficulties). Peer-workers also seed discussion threads and 'icebreakers' to enable relevant,
7 enjoyable conversations and facilitate meaningful relationships. Finally, peer moderation
8 serves to normalise experiences, counteract stigma and promote engagement. Peer
9 moderation was informed by the social learning theory which posits that those who observe
10 others (i.e., superusers) being rewarded for a particular behaviour (e.g., completing a step or
11 commenting on the social network) are more likely to modify their beliefs and subsequent
12 behaviour [63].
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21 **Control intervention**

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

48 The safety protocol is comprised of 3 levels of security including: (1) system and privacy
49 protection; (2) online safety; and (3) clinical safety [64].
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53 HORYZONS is hosted on a University of Melbourne web server. The University has
54 industry standard measures in place to prevent unauthorized access to the server. The online
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3 system also integrates measures to secure the application and database against unauthorized
4 access. These measures conform to industry best practice as defined by the Open Web
5 Application Security Project (OWASP). Privacy and online safety are managed in accordance
6 with the Australian Communications and Media Authority (ACMA).
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11 The study coordinator carries out an initial face-to-face orientation with HORYZONS
12 participants, including details of the terms of use. Participants were required to accept and
13 comply with the guidelines for safe use of HORYZONS. When needed, participants are
14 offered guidance on appropriate usage of the system. All users are asked to nominate an
15 emergency contact person, such as a close family member. HORYZONS includes a 'report
16 function' which enables young people to report a concern about any material posted by a
17 user. The moderator assesses the basis of the report and responds accordingly, which may
18 include the removal of the material and, in some cases, deactivating or restricting the young
19 person's account. Participants are also able to hide their profile and activity should they
20 become concerned about their privacy.
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29 Clinical risk is managed through manual and automated procedures. First, moderators
30 monitor the system twice daily on weekdays and once daily on weekends for evidence of
31 clinical risk or deterioration. Any detected increased risk activates the HORYZONS crisis
32 protocol which includes one or more of the following: a risk assessment with the young
33 person, inform the research team, alert the emergency contact nominated by the participant,
34 and liaise with suitable emergency services where necessary. In addition, the system
35 incorporates visible emergency guidelines and contact information. Finally, HORYZONS
36 includes an automated keyword detection function, which activates each time a participant
37 posts a contribution indicative of clinical risk or that contains potentially offensive words.
38 The function blocks posts with notifications sent to the young person and the moderator, who
39 can 'unblock' the post should they determine it to be unproblematic.
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48 **Temporary withdrawal criteria**

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

^aContinuous from state government databases

^bSmartphone 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 ($\alpha=0.80$); independent living skills ($\alpha=0.81$); interacting with people ($\alpha=0.80$); and intimacy ($\alpha=0.75$). 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

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3 relapse. Given the feasibility issues measuring relapse of psychotic symptoms at regular
4 intervals, the following secondary outcomes were added:
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8 1. Hospital admissions due to psychotic symptoms and mental health issues were added as
9 a secondary outcome variable. We have access to reliable and objective hospital admission
10 data from state databases (i.e., Centre for Victorian Data Linkage) spanning the 18-month
11 assessment period. Data on hospital admission from the state databases will be provided by
12 an independent person blind to study design and purpose.
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17 2. Positive and negative psychotic symptoms as measured by the PANNS scale at each
18 assessment time-point.
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22 3. *Physical health* was also initially included as secondary outcome variable because we
23 originally intended to incorporate online modules targeting this domain. However, we
24 decided not to include therapy content addressing physical health and therefore this variable
25 will be analysed as an exploratory outcome.
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31 Secondary outcome measures include:

32 (1) *accumulated hospital admissions* due to psychotic symptoms and mental health issues
33 over 18 months;
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35 (2) *vocational status* as measured by employment and/or education status;
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37 (3) *depression* as measured by the Calgary Depression Scale for Schizophrenia (CDSS
38 [70]);
39

40 (4) *social support and loneliness* as assessed by Medical Outcomes Study: Social Support
41 Survey (MOS-SSS [71]) and the UCLA Loneliness Scale (Version 3 [72]);
42

43 (5) *self-esteem* and *self-efficacy* as measured by the Self-Esteem Rating Scale-Short Form
44 (SERS-SF [73]) and Mental Health Confidence Scale (MHCS [74]), respectively;
45

46 (6) *anxiety and stress* as determined by the Depression Anxiety and Stress Scale (DASS
47 [75]);
48

49 (7) *psychological wellbeing* as measured by Scales of Psychological Wellbeing (SPWB
50 [76]);
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53 (8) *satisfaction with life* as measured by Satisfaction with Life Scale (SWLS [77]);
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3 (9) *quality of life* as measured by the AQoL 8D [78]. This questionnaire can also be used
4 to determine quality-adjusted life years (QALYs), which are useful in economic
5 evaluation studies;

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

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

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14 (12) *Cost-effective analysis*: A Resource Use Questionnaire (RUQ) is used to determine
15 the broader resource use of participants (e.g. community mental health services,
16 accommodation, work impacts etc). Additionally, for consenting participants, information
17 regarding utilisation of health care services available via the Medicare Benefits Schedule
18 (MBS - medical, allied health, diagnostic and pathology services) and the Pharmaceutical
19 Benefits Schedule (PBS - medications) will be accessed from the Australian Department
20 of Human Services.
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27 To obtain more dynamic and ecologically valid data on young people's social functioning,
28 participants utilise a custom-built smartphone app, SEMA, which is readily downloadable at
29 no charge to participants owning a smartphone (running Android or iOS operating systems).
30 SEMA delivers surveys (administered for 7 days following each assessment time point)
31 approximately eight times per day for 7 consecutive days. Young people are prompted to
32 complete SEMA surveys at random times every 90 min (± 30 min) over a 12-h period (e.g. 10
33 a.m. to 10 p.m.). SEMA tracks participants' responses in (near) real time, ensuring minimal
34 data loss by uploading responses to a secure server or storing responses on the young
35 person's smartphone when an Internet connection is temporarily unavailable. Each SEMA
36 survey begins with four items assessing momentary positive affect ('At the moment, how
37 happy do you feel?', negative affect ('At the moment, how sad do you feel?'; 'At the
38 moment, how stressed do you feel?') and momentary social isolation (e.g. 'At the moment,
39 how lonely do you feel?') rated on visual slider scales anchored at 0 (not at all) and 100
40 (very). The order of these four items is randomised at each survey. Following the momentary
41 affect items, the SEMA survey includes items pertaining to social interactions of the young
42 person (e.g. 'How much time have you spent interacting with others, since last survey?'),
43 perceived social efficacy (e.g., 'How well do you think you handled your social interactions,
44 since last survey?'), perceived social support (e.g., 'have you received support or
45 encouragement from others, since last survey?'), critical comments (e.g., 'Have you felt that
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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

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3 measures informed by the self-determination theory including: their perceived competence
4 using the system, motivations for using it; and their perception of moderation by
5 HORYZONS.
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8 9 **Statistical analysis and sample size**

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11 Primary analyses will be undertaken on an intention-to-treat basis. Mixed-model repeated
12 measures (MMRM) analyses will be used to compare change in social functioning between
13 the two treatment groups over the 18-month follow-up. MMRM is the analysis of choice
14 because assumptions of traditional data analysis methods (e.g., ANOVA, regression) may be
15 violated, such as the assumption of homogeneity of regression across time points [95]. In
16 addition, MMRM uses all available data (including participants with partial data) to estimate
17 treatment effects. Time (baseline, 6, 12 and 18 months) will be the within-person predictor
18 and treatment group (HORYZONS plus TAU vs. TAU) the between-person predictor.
19 MMRM will also be used to analyse change in the continuous secondary outcomes over 18
20 months. Additional analyses will use multiple imputation to assess the robustness of the
21 findings to the choice of method for handling missing data. Ecological momentary
22 assessment will be analysed using a multilevel structural equation modelling (MSEM)
23 framework [96]. Differential rate of hospital admissions will be analyzed using multilevel
24 logistic regression. Time to hospital admissions will be assessed by survival analysis (using
25 either proportional hazard or accelerated life-time models). Additional comparisons between
26 treatment groups based on completers-only analyses will be conducted. Analyses will be
27 undertaken in accordance with ICH 9 guidelines including a full analysis as well as per
28 protocol set. The per protocol sample will be defined based on receiving a pre-specified
29 minimal exposure to the online intervention (i.e., more than 16 logins over the 18-month
30 intervention period).
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45 Economic evaluation will comprise a cost-consequences analysis whereby incremental
46 costs of the intervention will be compared to the full spectrum of study outcomes. A cost
47 utility analysis will also be undertaken whereby the AQoL 8D will be used to QALYs. The
48 evaluation will measure and value any change to the use of health care resources over the
49 period of the study (using the data from the RUQ, MBS/PBS and hospitalisation
50 administrative data) between the two treatment arms; and then compare any additional costs
51 to the additional outcomes achieved. Australian sourced unit costs will be attached to the
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3 RUQ (from Australian sources such as the Commonwealth Department of Health, Mental
4 Health Branch). Standardised economic evaluation techniques including incremental analysis
5 of mean differences (using statistical techniques such as generalised linear models) and
6 bootstrapping to determine confidence intervals around incremental cost-effectiveness ratios
7 will be used. If, as expected, the intervention is found to be effective, lifetime and population
8 cost-effectiveness of the interventions will be determined using economic modelling
9 techniques. We will determine the likelihood that the intervention is cost-effective at
10 commonly used value-for-money thresholds such as \$20,000/QALY and \$50,000/QALY.
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17 The primary outcome is change in social functioning at 18 months follow-up. A recent
18 RCT investigating the effects of extending FEP specialist treatment for 12 months (i.e., a
19 total of 3 years of specialist treatment) reported an effect size of 0.53 (Cohen's d) for
20 functional outcomes for the extended model of care at 12-months (i.e., end of the specialised
21 treatment) compared with TAU (i.e., 2 years of specialist treatment) [32]. If we assume that
22 alpha is set at 0.05 and power (1- β) at 0.90, then a sample size of 70 is required for each of
23 the two groups (Total n = 140) to detect medium effect sizes (0.5; Cohen's d). For the second
24 outcome measure of hospital admissions at 18 months follow-up, there will be 80% power to
25 detect an improvement in the rate of hospital admissions of at least 43% in the
26 TAU+Horyzons, assuming a hospital admission rate in the TAU of 30% over the 18-month
27 follow-up [2]. We recruited 170 participants, accommodating for an 18% attrition rate, which
28 is consistent with a similar study in terms of design and population [32].
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38 **Data management**

39 A custom-built online Research Project Management System (RPMS) is used to manage
40 the electronic data from this study. The RPMS includes an electronic Case Report Form
41 (eCRF) and randomisation functionality. The study assessors record participant-level data on
42 a paper-based Case Report Form (CRF). These data are subsequently entered into the eCRF
43 section of the RPMS. The randomisation functionality of the RPMS is operated by the study
44 coordinator. The RPMS is accessed using a secure website and is stored on a secure server. It
45 is designed to maintain the privacy and confidentiality of participant information and to
46 ensure the integrity of the data. Access to RPMS is restricted to study personnel and the level
47 of access is dependent on the person's role. The study assessors and investigators do not have
48 access to the randomisation section to ensure that they remain blind. Data are stored on three
49 separate secure computer servers, including data collected from the SEMA tool, the RPMS
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3 and data accumulated from participant activity within the HORYZONS online system. These
4 various data are aggregated into a single electronic secure databank.
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8 Data verification at all assessment time points is being conducted on 20 randomly selected
9 cases. The selected cases are re-entered by the study coordinator. The a priori acceptable
10 error rate has been set at 0.5%.
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13 14 **Ethics and dissemination**

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16 Ethics approval for the trial was provided by the Melbourne Health Research and Ethics
17 Committee (No. 2013.146). All trial participants provided written informed consent prior to
18 enrolment in the trial. For all eligible participants under 18 years of age, parental or guardian
19 consent was also obtained.
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23 Any adverse events (e.g., hospital admissions) including an independent assessment of
24 whether the adverse event was related to the online intervention (i.e., made by a psychiatrist)
25 were reported to the Melbourne Health Research and Ethics Committee. The study was
26 considered to be low risk by the study sponsor and a trial management group was established
27 in place of a data monitoring committee.
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31 The main results of this clinical trial will be published in a peer-reviewed scientific
32 journal. Manuscripts will also be prepared for significant findings regarding the secondary
33 and exploratory aims. These results will be submitted and presented at scientific forums
34 including national and international conferences in schizophrenia, early psychosis and youth
35 mental health.
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42 **Patient and Public Statement**

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44 Patients were included in the development of the research questions and outcome
45 measures in a number of ways. First, Orygen includes a youth reference group which
46 provides consultation on the design, conduct and ethics of all studies carried out within the
47 organisation. This group provided input into the main research question, design and outcome
48 measures of the RCT. In addition, Orygen's internal Research and Review Committee
49 integrates two youth representatives which also provided feedback on the key methodological
50 aspects of the study from the consumers perspective.
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3 Secondly, the design, development and therapeutic content of the intervention was also
4 designed in partnership with young people. We conducted a series of focus groups with
5 young people with lived experience to inform the development of HORYZONS. Young
6 people participating in these focus groups consistently stated that HORYZONS should focus
7 on promoting social connectedness and personal strengths [35-36]. This is consistent with
8 previous qualitative research with young people [97]. The outcome measures were selected
9 based on the combination of this research and this feedback. However, we did not seek
10 specific assessment from young people on the burden of assessments or the intervention.
11 Given that participants can select the frequency with which they use the system and receive
12 contact from the moderator team, this seemed less salient with respect to the intervention.
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16 Patients were not involved in the recruitment into the study. However, peer workers were
17 involved in the conduct of the online intervention. We established a peer workers reference
18 group led by our youth participation coordinator. This group provided online peer support via
19 HORYZONS as well as ongoing consultation on the management of the trial and intervention
20 updates. In addition, a number of focus groups with participants from the HORYZONS trial
21 were conducted to obtain feedback on the management (moderation) and content of the
22 online system.
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26 We have created an email list to inform all participants of the results of the study and
27 provided a contact email for participants to contact the research team should they require any
28 additional information or wish to participate in online peer support.
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31 32 33 34 35 36 37 **DISCUSSION**

38
39 The onset of psychosis often strikes young people at the prime of their lives, triggering a
40 myriad of adverse psychosocial consequences that can result in entrenched social isolation,
41 unemployment and chronicity [3]. Against this, early intervention is now seen as a key
42 strategy to improve long-term recovery and reduce treatment costs [3]. However, while
43 specialist early psychosis services have been demonstrated that they improve outcomes in
44 FEP, follow-up studies have questioned the maintenance of treatment effects beyond the
45 intervention period [9, 10]. Moreover, social recovery, a priority for young people, continues
46 to be resistant to current intervention approaches [19]. This is the first randomised controlled
47 trial to evaluate a novel online social media intervention designed to address both these
48 challenges.
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3 HORIZONS is the first intervention to exploit online social media technology and apply
4 strengths and mindfulness approaches to improve long-term social recovery in FEP. In
5 addition, the design of the intervention builds on our extensive experience developing and
6 evaluating effective relapse prevention [98-100] and vocational recovery interventions [58] in
7 early psychosis. Thus, HORIZONS weaves together two novel intervention approaches for
8 FEP with established evidence-based protocols, while drawing on a strong theoretical base
9 for social recovery in early psychosis (i.e., self-determination theory [59], broaden and build
10 theory [22]).
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17 Building on a previous successful pilot study [36], HORIZONS was co-developed with
18 end-users and service providers. The online system was designed to be scalable, embedded
19 within clinical practice and delivered across early intervention services. Specifically,
20 HORIZONS is moderated by EPPIC clinicians as part of their routine clinical role (i.e.,
21 clinicians would allocate a proportion of their clinical time, typically 20 to 30%, to online
22 moderation). Moderation and training procedures have been manualised and require
23 minimum specialised training (2 days). Therapist efficiency using HORIZONS is estimated
24 to be 5 times higher than that of specialised FEP services (100 vs. 20 young people of a
25 typical caseload in an early psychosis clinic). Thus, if successful, HORIZONS will provide a
26 scalable, cost-effective intervention approach to extend the benefits of early intervention and
27 improve social functioning in FEP patients.
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37 A limitation of the current study is that the control intervention consists of routine care, as
38 opposed to a sham intervention accounting for increased attention and unspecific therapeutic
39 factors. That said, this decision was made to enhance the external validity of the findings by
40 replicating the current mainstream follow-up options available to FEP young people beyond
41 their involvement in early intervention services. As such, this study is expected to provide
42 evidence of cost-effectiveness of a step-down model of care instead of generating controlled
43 evidence on the specific treatment components driving improved outcomes. Of note, the
44 design of this study parallels that of recently published randomised controlled trials
45 examining extended interventions for FEP services, with TAU being the control intervention
46 across all three studies [30-32].
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54 Sustained and meaningful recovery is the ultimate goal of early intervention services as
55 well as the most valued outcome by young people and their families [101]. This is the first
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3 randomised controlled trial to evaluate an online-based intervention as a means to extend the
4 benefits of specialised early intervention services and foster long-term social functioning in
5 FEP. Thus, if successful, HORYZONS has the potential to augment the benefits and long-
6 term impact of the current model of early intervention for psychosis.
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13 Figure 1. Horyzons recruitment and allocation procedure.
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16 **FUNDING STATEMENT**

17
18 The HORYZONS trial was supported by the Mental Illness Research Fund (MIRF) from the
19 State Government of Victoria. M.A.-J. was supported by a Career Development Fellowship
20 (APP1082934) from the National Health and Medical Research Council (NHMRC). S.M.C.
21 has been supported by a Career Development Fellowship (APP1061998) and Senior Research
22 Fellowship (APP1136344) from NHMRC. CMihalopoulos was supported by a NHMRC
23 Early Career Fellowship (APP1035887) during the conduct of the trial. SL was supported in
24 part by a New Investigator Salary Award from the Canadian Institutes of Health Research
25 and previously in part by a Research Scholar Salary Award from the Fonds de recherche du
26 Québec—Santé (FRQS).
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38 **AUTHORS' CONTRIBUTIONS**

39
40 M.A.-J., and J.F.G. led the overall design and conduct of the study. S.B. and S.R. contributed
41 to the supervision of the moderation of the online intervention. P.K., is the lead statistics and
42 ecologically momentary expert in the study. J.P., was the peer workers supervisor during the
43 study. S.D., is the lead engineer of the HORYZONS project. C.Miles, is the lead front-end
44 designer of the HORYZONS platform. P.R., is the creative content lead of the project. R.L.,
45 G.W., O.S., T.G., and C.L. contributed to the design of the intervention. R.C. developed the
46 mindfulness and self-compassion components of HORYZONS. M.A.-J wrote the first draft of
47 the manuscript. D.C., L.V., C.Mihalopoulos, H.H., C.G-B., R.D-G., E.K., S.M.C., S.L., and
48 P.D.M contributed to the design and conduct of the study. All authors critically revised and
49 approved the final manuscript.
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54 **ACKNOWLEDGMENTS**

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3 The authors wish to thank the Orygen Youth Advisory Council and Orygen Youth Research
4 Council for their input into the development of Horyzons. The authors thank the peer workers
5 (Damian, Mabigail, Samantha, Kay, Stuart, Amal, Margie, Megan, Gene, Matt, Booma,
6 Nicole, Rebecca, Elise, Emily, Sarah, Ally, Matt, Joanne, Imesha and Tricia) and online
7 moderators (Catherine Spillane, Jasmin Watson, Lisa Rumney, Sandra Seif, Jacqui
8 Mackinnon, Edwina Ford, Gina Chinnery, Dylan Alexander, Rebecca Davenport, Nerida
9 Barclay, Jennifer Butler, Melanie Cooke and Matthew Stuckey) for their valuable
10 contributions to the study. The authors also wish to thank the inspiring and generous young
11 people who took part in the study.
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17 **COMPETING INTERESTS STATEMENT**

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19 The authors report no relevant conflict of interest.
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21

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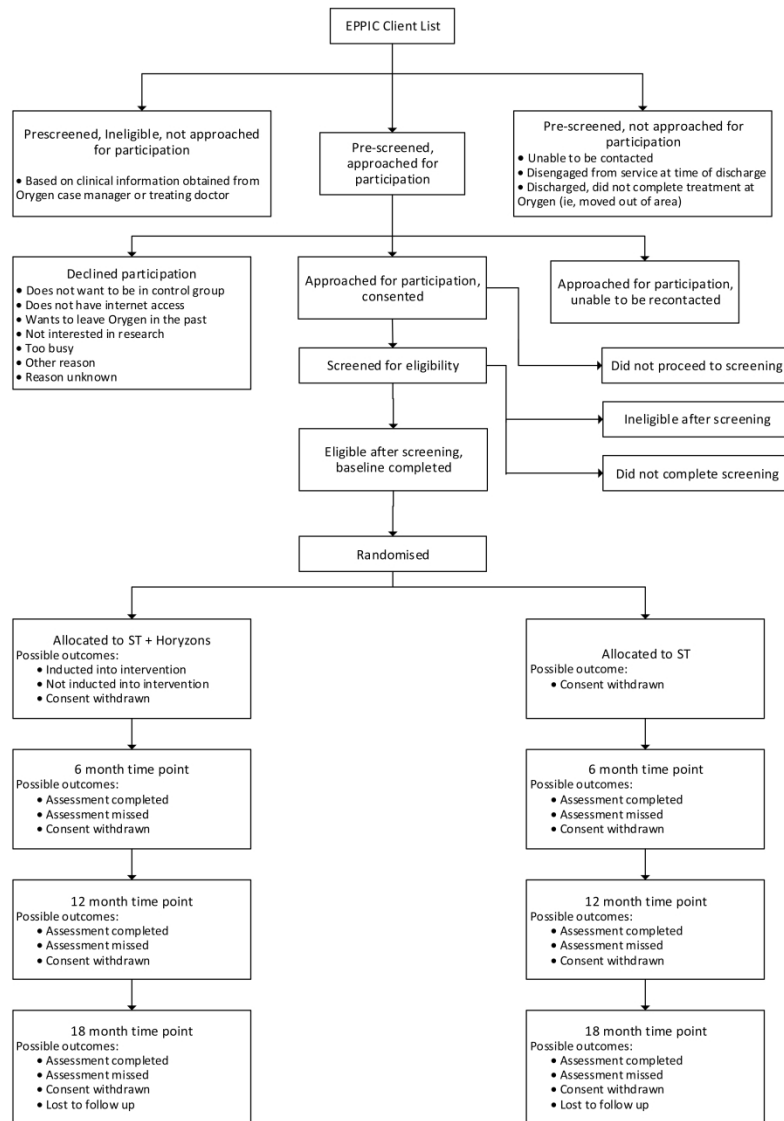
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Figure 1. Study flow diagram for HORYZONS.



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__

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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

1
2
3 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including _____20_____
4 clinical and statistical assumptions supporting any sample size calculations

5
6 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size _____11_____
7

8 **Methods: Assignment of interventions (for controlled trials)**
9

10 Allocation:

11
12 Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any _____11_____
13 factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
14 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
15 or assign interventions
16

17 Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, _____11_____
18 opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
19
20

21 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to _____11_____
22 interventions
23

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome _____11_____
25 assessors, data analysts), and how
26

27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's _____N/A_____
28 allocated intervention during the trial
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31 **Methods: Data collection, management, and analysis**
32

33 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related _____15_____
34 processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
36 Reference to where data collection forms can be found, if not in the protocol
37

38 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be _____N/A_____
39 collected for participants who discontinue or deviate from intervention protocols
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3 Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality _____ 21 _____
4 (eg, double data entry; range checks for data values). Reference to where details of data management
5 procedures can be found, if not in the protocol
6
7 Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the _____ 19 _____
8 statistical analysis plan can be found, if not in the protocol
9
10 20b Methods for any additional analyses (eg, subgroup and adjusted analyses) _____ N/A _____
11
12 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any
13 statistical methods to handle missing data (eg, multiple imputation) _____ 19 _____
14

15 **Methods: Monitoring**

16
17 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of _____ 22 _____
18 whether it is independent from the sponsor and competing interests; and reference to where further details
19 about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not
20 needed
21
22 21b Description of any interim analyses and stopping guidelines, including who will have access to these interim _____ N/A _____
23 results and make the final decision to terminate the trial
24
25 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse _____ N/A _____
26 events and other unintended effects of trial interventions or trial conduct
27
28 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent _____ N/A _____
29 from investigators and the sponsor
30
31

32 **Ethics and dissemination**

33
34 Research ethics 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval _____ 22 _____
35 approval
36
37 Protocol 25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, _____ N/A _____
38 amendments analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals,
39 regulators)
40
41
42
43
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1				
2				
3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____11_____
4				
5				
6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____16_____
7				
8	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_____
9				
10				
11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____23_____
12				
13				
14	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_____
15				
16				
17	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_____
18				
19				
20	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_____
21				
22				
23				
24				
25		31b	Authorship eligibility guidelines and any intended use of professional writers	_____N/A_____
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____N/A_____
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____N/A_____
32				
33				
34	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_____
35				
36				

37 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.
 40



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.