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Randomised controlled trial to assess feasibility and acceptability of web-based enhanced relapse prevention for bipolar disorder (ERPonline)

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Abstract

Background: Interventions that teach people with Bipolar Disorder (BD) to recognise and respond to early warning signs of relapse are NICE recommended but implementation in clinical practice is poor.

Objective: This study tests the feasibility and acceptability of a randomised controlled trial to evaluate an online enhanced relapse prevention intervention (ERPonline), and reports preliminary evidence of effectiveness.

Methods: Single blind, parallel primarily online randomised controlled trial (n=96) over 48 weeks comparing ERPonline plus usual treatment to waitlist (WL) control plus usual treatment for people with BD recruited through National Health Services, voluntary organisations, and media. Randomisation was independent, minimised on number of previous episodes (<8,8-20,21+). Primary outcomes were feasibility and acceptability assessed by rates of study recruitment and retention, levels of intervention use, adverse events and participant feedback. Process and clinical outcomes were assessed by telephone and online and compared using linear models with intention-to-treat analysis.

Results: Two hundred and eighty people registered interest online, from which ninety-six met inclusion criteria, consented and were randomised (49 to WL, 47 to ERPonline) over seventeen months, with 80% retention in telephone and online follow up, except week 48 online (76%). Acceptability was high for both ERPonline and trial methods. ERPonline cost approximately £19,340 to create, and £2176 per year to host and maintain the site. Qualitative data highlighted the importance of the relationship users have with online interventions and how this is created as an extension of the relationship with the humans perceived as offering and supporting its use. Differences between the group means suggested that access to ERPonline was associated with: a more positive model of bipolar disorder at 24 (10.70 (0.90-20.5 95%CIs)) and 48 weeks (13.1 (2.44-23.93 95%CIs)); increased monitoring of early warning signs of depression at 48 weeks (-1.39 (-2.61, -.163 95%CIs)) and of (hypo)mania at 24 (-1.72 (-2.98, -0.47 95%CIs)) and 48 weeks (-1.61 (-2.92, -0.30 95%CIs)), compared to WL. There was no evidence of impact of ERPonline on clinical outcomes or medication adherence, but relapse rates across both arms were very low (15%) and the sample remained high functioning throughout. One person died by suicide prior to randomisation. Five people in ERPonline and six in WL control reported ideas of suicide or self-harm during the study. None were deemed study related by an independent Trial Steering Committee.

Conclusions: ERPonline offers a cheap accessible option for people seeking ongoing support following successful treatment. However, given high functioning and low relapse rates in this study, testing clinical effectiveness for this population would require very large sample sizes. Building in human support to use ERPonline should be considered.

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Declaration of interest: The ERPonline intervention was developed by the authors and therefore this is not an independent evaluation

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Key words – online, randomised controlled trial, feasibility, acceptability, Bipolar Disorder

Introduction

Bipolar Disorder (BD) is a lifelong mental health condition characterised by extreme fluctuating mood including recurrent episodes of depression and mania, that generally starts in adolescence and effects approximately 1-1.5% of adults worldwide [1]. The impact of BD on employment and relationships can be devastating, and the condition has high financial costs, estimated at £5.2 billion annually in England alone [2]. Preventing relapse is a key goal of most interventions for Bipolar Disorder (BD). Interventions that teach people to recognise and respond to early warning signs are recommended by clinical guidelines worldwide [3-5] but implementation in routine clinical practice is poor [6]. Enhanced Relapse Prevention (ERP), a structured manualised intervention for frontline care staff, has shown significant benefit and is well received by patients and staff [7]. However, delivered face-to-face it will only ever be available to a small percentage of people with BD due to low rates of psychological intervention provision even among those who remain in secondary care services. Here we test the feasibility and acceptability of an online version of ERP: ERPonline. Online interventions in mental health offer the potential to: broaden access, reduce waiting times, delivery costs and stigma; and improve quality through standardised delivery [8, 9]. There is growing evidence for short term benefits of internet-delivered psychological treatments for depression and anxiety disorders compared to wait-list controls [10], though understanding their implementation into real-world services is still in its infancy [11]. In BD, the evidence, whilst promising, is at an earlier stage, comprising small-scale feasibility studies [12-18]. These studies, along with results from an international multisite survey [19], suggest that people with BD can use, and are interested in further using, online mental health support. However, detailed evidence is lacking on what kinds of psychosocial support can be offered online, the best ways to deliver these, who accesses online interventions, what processes and outcomes are impacted on, and how to best design rigorous trials to evaluate them online. This information is essential to inform definitive clinical and cost-effectiveness trials. Here we address these issues in a novel randomised controlled trial (RCT) to assess feasibility and acceptability of ERPonline with all recruitment and assessments of outcome performed remotely.

Aims were to:

1. Assess the feasibility of: (i) creating a web-based version of Enhanced Relapse Prevention for BD (ERPonline) and (ii) an RCT design using web-based and telephone data collection to evaluate effectiveness.
2. Determine the acceptability of ERPonline for people with BD via (i) ERPonline website usage, (ii) number and type of adverse events associated with site use , and (iii) detailed feedback from participants about their experiences of ERPonline to inform future developments.
3. Determine the feasibility and acceptability of data collection via the internet and telephone measured by recruitment & retention rates, data completion, and direct feedback from participants.
4. Test the impact of the intervention on hypothesised mechanisms of change to understand processes underlying any impact.
5. Estimate the likely effect size of the intervention on a range of outcomes, particularly noting any negative impacts.

Method

Design

A single blind randomised controlled trial (RCT) with nested qualitative study comparing ERPonline plus usual treatment to a "waitlist control" arm with delayed access to ERP online plus usual treatment. Primary outcomes were feasibility and acceptability. Process and clinical outcomes were assessed to identify measures sensitive to change collected remotely and to explore potential positive and negative impacts of the intervention. Remote data collection and online recruitment increased the external validity of the trial by encouraging participation from those unable or unwilling to engage in face to face clinical trials, who are also more likely to be those people unable or unwilling to engage in face to face clinical support for whatever reason. The study was not powered to test statistically significant impact. The trial was preregistered and full protocol published [16]. Ethics approval was given by UK National Research Ethics Service (NRES) Committee North West (Ref 12/NW/0594). Statistical protocol is published at https://figshare.com/articles/Statistical_analysis_protocol_-_ERPonline_docx/3978567.

Participants

We aimed to recruit 125 participants, anticipating a dropout rate of up to 35% (based on retention rates from previous trials of web-based interventions for BD [12-18]) providing 40 people per arm, sufficient to meet the aims of our study to assess feasibility and acceptability. Participants were aged >=18, resident in the UK, with a confirmed diagnosis of BD (I or 2), at risk of relapse (>= 3 previous episodes, >= 1 in the preceding 2 years) and with access to the internet. We excluded people in

current episode (within previous 4 weeks), currently under Mental Health Act section and therefore likely to be in current episode or at high risk of harm to self or others, or unable to understand English sufficiently to engage with the study.

Recruitment strategy

The study was presented to clinical teams in eight NHS Mental Health Trusts in England, and staff were reminded in monthly team meetings to direct service users to the online registration site. An advert was placed in a UK charity newsletter (Bipolar UK), and on a charity website (Bipolar Scotland). A link to ERPonline was put in NHS Choices, and BBC health online presented a short article that linked to the website. The research team regularly tweeted about the study, and our service user lead was interviewed on local radio about the study. The number of people coming into the study via each route is shown in Figure 1.

People were invited to visit the site which explained the study, allowed them to check eligibility, and to register an interest in participating. Participants read an online participant information sheet and completed an online consent form. Consent and capacity were reassessed prior to the SCID interview and at each subsequent telephone assessment.

Intervention

ERPonline was developed with extensive input from a reference group of eight adults with BD to adapt the original ERP manual to an online format. Input (online and face to face) occurred throughout the study but was more extensive during the initial development of the ERPonline site and included feedback on content of draft modules, user testing of the ERPonline website, and providing video and case material of lived experience which are integral parts of the intervention site. The aim of the intervention is to help people develop a coherent working model of their mood changes, recognise and manage triggers and early warning signs, and develop coping strategies to manage these effectively. Key modules are summarised in Table 1 with more detail in the protocol paper [20].

Table 1. Key Intervention Modules in ERPonline

Section	Module title	Module description	ERPonline (n = 47) average number of module views per person	ERPonline (n = 47) average time spent per module per person (minutes)

			Mean (SD) **Median (min-max)**	**Mean (SD)** **Median (min-max)**
Getting Started	How to use the site	Ways to navigate the site to get the best from the available modules	7.43 (5.77) 7 (0-25)	8.61 (8.70) 7.5 (0-46.5)
	Introduction	Explains what ERPonline is, rationale for this approach, why it might be useful, and how to involve a relative/ friend if desired	4.28 (5.46) 3 (0-30)	5.88 (8.99) 2 (0-40)
	What is Bipolar?	Background information about what Bipolar Disorder is, theories about causes, common consequences, and an overview of available treatments	8.00 (7.34) 7 (0-30)	11.95 (13.51) 7 (0-52.5)
Key Modules	Mood Charting	How to use an online tool to monitor mood on a daily basis to help recognise normal mood fluctuation and pick up early signs of a mood episode	138.38(445.54) 13 (0-2519)	122.89 (386.43) 14.5 (0-2150.5)
	Life Charting	Complete a chart of past mood episodes, identifying potential triggers and coping strategies for future mood changes	49.09 (147.55) 11 (0-990)	47.34 (114.45) 8.00 (0-744)
	Identifying Triggers	Detailed analysis of triggers of previous mood episodes, followed by a personalised plan of how to manage triggers	11.34 (25.57) 1 (0-148)	15.07 (30.09) 0.5 (0-140.5)
Specific Moods	Early Warning Signs (EWS)- high mood	Detailed analysis of EWS of high mood to develop a relapse signature for (hypo) mania	14.47 (26.72) 0 (0-90)	17.36 (32.31) 0 (0-114)
	Coping Strategies – high mood	Review of current strategies to manage high mood and introduction to new strategies that may be helpful	5.68 (10.62) 0 (0-44)	10.0 (19.78) 0 (0-71.5)
	Early Warning Signs (EWS)- low mood	Detailed analysis of EWS of low mood to develop a relapse signature for depression	9.26 (22.47) 0 (0-94)	9.38 (21.87) 0 (0-84.5)
	Coping Strategies – low mood	Review of current strategies to manage low mood and introduction to new strategies that may be helpful	3.83 (11.26) 0 (0-59)	3.95 (11.23) 0 (0-52.5)

Wrapping Things Up	Staying Well Strategies	Identifying and managing stress levels Understanding the importance of social rhythms and how to regulate these to manage mood How relationships with other people impact on mood	4.06 (6.11) 0 (0-25)	4.39 (8.30) 0 (0-37)
	Your Staying Well Plan	An individualised summary of staying well strategies, early warning signs to look out for, and coping strategies to regulate mood	3.09 (5.94) 0 (0-30)	2.35 (4.60) 0 (0-18.5)

Note: where the median value 0 then at least half the sample did not visit this module

Each module included information, suggested strategies, and case examples. Users interacted with the site to input personal information relevant to their own triggers, early warning signs and coping strategies. These informed an individualised staying well plan. The site also provided signposting to additional formal and informal support. Participants were free to choose the order they visited modules (although they were listed in logical order), and were invited to involve a supporter of their choosing. Each module included recommendations of how the supporter could be involved in relapse prevention. All participants continued to receive any other treatment as usual throughout the study. The home page is shown in Figure 1 for illustration.


Home
Give feedback on this page
Contact us
The ERP team
My account
Logout
Enhanced Relapse Prevention
Introduction
What is ERP?
Who is ERP for?
Why use ERP?
How to use ERP
Involving someone in ERP
The study process
Modules
How to use this site
What is bipolar disorder?
Mood charting
Life charting
Identifying triggers
Early warning signs (highs)
Coping strategies for highs
Early warning signs (lows)
Coping strategies for lows
Staying well strategies
Your staying well plan
Questions and help
Forums
FAQs
Support services
Technical support
Welcome
Getting started
How to use this site
Why: Gives you an overview of the site
What: How to navigate and find help
Time: 20 minutes
What is bipolar?
Why: To learn more about bipolar disorder
What: Reading about causes and effects
Time: 20-40 minutes
Key modules
Mood charting
Why: Helps with monitoring mood
What: Plotting mood over a short period of time
Time: 20-40 minutes
Life charting
Why: Gives you an overview of past episodes
What: Drawing a life chart
Time: 20-40 minutes
Identifying triggers
Why: To highlight possible triggers of relapse
What: Reading about common triggers
Time: 20-40 minutes
Specific moods
Early warning signs (highs)
Why: Help to recognise the early signs of relapse
What: looking at high mood
Time: 20-40 minutes
Coping strategies for highs
Why: Help you to manage high moods
What: planning coping strategies
Time: 20-40 minutes
Early warning signs (lows)
Why: Help to recognise the early signs of relapse
What: looking at low mood
Time: 20-40 minutes
Coping strategies for lows
Why: Help you to manage feelings of low mood
What: planning coping strategies
Time: 20-40 minutes

Figure 1. ERPonline homepage

Procedure- randomisation and masking

Diagnostic eligibility was confirmed using SCID Clinical Interview for DSM-IV [21] administered by telephone by trained research assistants. Training consisted of scoring training videos, conducting clinical sensitive interviews on the telephone, and recording an interview with someone with Bipolar Disorder who provided experiential feedback and which was then rated by a supervising clinical academic. Training continued until ratings were reliable and clinical style was of high quality. Monthly supervision to ensure reliability in scoring of telephone interviews continued throughout the study. Following baseline assessments (by telephone and online) participants were randomly allocated by an independent clinical trials unit (CTU) using 1:1 ratio, minimised on number of previous episodes (<8,8-20, 21+) and including a random element to minimise predictability of allocation. Those in the ERPonline arm received an email containing a web-link and instructions of how to log onto the site using a unique username and password. Control participants received an email or telephone call informing them of the allocation and emphasising the importance of continued participation throughout the trial. All communication with CTU and participants regarding randomisation was conducted by the trial manager (unblinded). All communication with participants reiterated the importance of not telling the researcher carrying out the follow-up interviews which group they were in, and why this was important. All assessments were conducted by blind researchers. Blindness was further maintained using restricted file access to any data showing randomisation, and prefacing each follow-up interview with a reminder about why it was important not to say anything about which arm they were in.

During the trial, participants were sent an additional email inviting them to provide qualitative feedback. The ERPonline group were asked to complete an online survey about their views of the ERPonline site and any improvements they would recommend. They were also given the option (between 2-12 months following randomisation) to take part in a telephone interview about their experiences of using ERPonline. Given the relatively novel primarily online trial design, the WL control group were sent a survey prior to accessing the site about their reasons for engaging in the trial, and their experience of taking part in the trial.

A reflective log detailed our experiences throughout the trial.

Measures

Proposed mechanisms of change, were assessed online at baseline, 24 and 48 weeks including: frequency of early warning signs monitoring (Early Warning Signs checklist for relapse in depression and mania [22] Likert scale 1 = never to 4 = very regularly); adapted Brief Illness Perception Questionnaire (BIPQ score 0-110: higher score = more negative beliefs) [23]; and the Medication Adherence Rating Scale (MARS 0-10: higher score = higher compliance) [24]. These measures were either designed for use with people with Bipolar Disorder (EWS checklists and BIPQ), and / or have been successfully used with this population (MARS). They are all self-report, have high face validity, and have been shown to be valid and reliable measures, making them highly applicable to online use.

Interviewer – rated outcome measures were administered by telephone by two trained research assistants, at baseline, 12, 24, 36 and 48 week follow-up. These included: SCID- LIFE [25] providing a retrospective weekly rating of depression (1-6) and mania (1-6), (scores of 5/6 indicate major mood episode); Hamilton Depression Rating Scale (HAM-D scores above 7 indicate mild depression, above 13 moderate, and above 18 severe) [26], and Mania Rating Scale (MRS scores of 11 and above indicate hypomania) [27]; the Personal and Social Performance Scale (PSP scores 70-80 indicate mild difficulties, above 80 is good functioning) [28]; and the Multidimensional Scale of Independent Functioning (MSIF Likert scale 1 = normal functioning, to 7 = total disability) [29]. Self-report outcome measures were collected online at baseline, 24 and 48 weeks and included: the Work and Social Adjustment Scale (WSAS less than 10 = subclinical; 10-20 some functional impairment; above 20 moderate psychopathology) [30]; Quality of Life in BD (QoLBD range 48-240 with high score = higher quality of life) [31]; and the Bipolar Recovery Questionnaire (BRQ score 0-3600 high score = higher recovery) [32]. Online versions of the EQ5D5L [33]and the Client Service Receipt Inventory (CSRI) [34] were piloted to assess the feasibility of collecting this data online and to test the sensitivity to change in this population as neither have been previously used in online self-report format. A checklist to record current treatment was developed for the study to define usual treatment.

The only change to the published protocol was to record only the frequency of monitoring of EWS for (hypo)mania and depression, as early feedback from participants indicated the full checklist was too long. All serious adverse events were recorded and reported to the Trial Steering Committee. All participants were given a £10 shopping voucher on completion of measures at each assessment point.

Analysis

Descriptive statistics report the characteristics of the sample recruited; use of the website; rates of recruitment, retention, and data completion in each arm of the trial. The impact on repeated process and outcome measures was tested using linear models with correlated errors, which allow for correlation between repeated measures from the same participant. For ordinal data, we used generalised linear mixed models. We report both unadjusted analyses, and those adjusting for any differences in baseline demographic (age, gender, ethnicity, employment, education) and clinical variables (number of previous episodes, and whether or not prescribed a mood stabiliser).

Incomplete records from participants were retained, and analyses used maximum likelihood estimation for all model parameters. Statistical comparison of outcomes was made between the two trial arms at 24 and 48 weeks follow-up.

Weekly ratings of depression and mania from the SCID-LIFE were used to analyse time to first relapse (any and separately for depression (requiring 2 consecutive weeks), or mania (1 week)) and the proportion of time spent in episode (defined as SCID-LIFE rating of 5/6), or in sub-syndromal state (SCID-LIFE rating of 3/4) or euthymic (SCID-LIFE rating of 1/2). To analyse the impact of the intervention on time to first relapse we used a Cox's proportional hazards regression model. Beta regression was used to compare the proportion of time spent in episode / sub-syndromal / euthymic in each arm.

The study is not powered to test for statistically significant impact and therefore we do not specify a primary outcome, or set a level of statistical significance for interpreting analyses. All analyses were run from R open-source computing environment (version 3.3.1).

Content analysis of qualitative survey data highlighted the individual points made and these were grouped into key themes. Interview transcripts were analysed in depth using indexing and charting methods inspired by Framework Analysis [35]. All transcripts were independently coded by the interviewer (MG) and a second member of the research team. Codes were compiled into a tentative coding frame with thematic headings. Narrative summaries were created from each of the conceptual themes across all cases. This data will be reported in full elsewhere but here we present key data relevant to the feasibility and acceptability aims of the trial.

Results

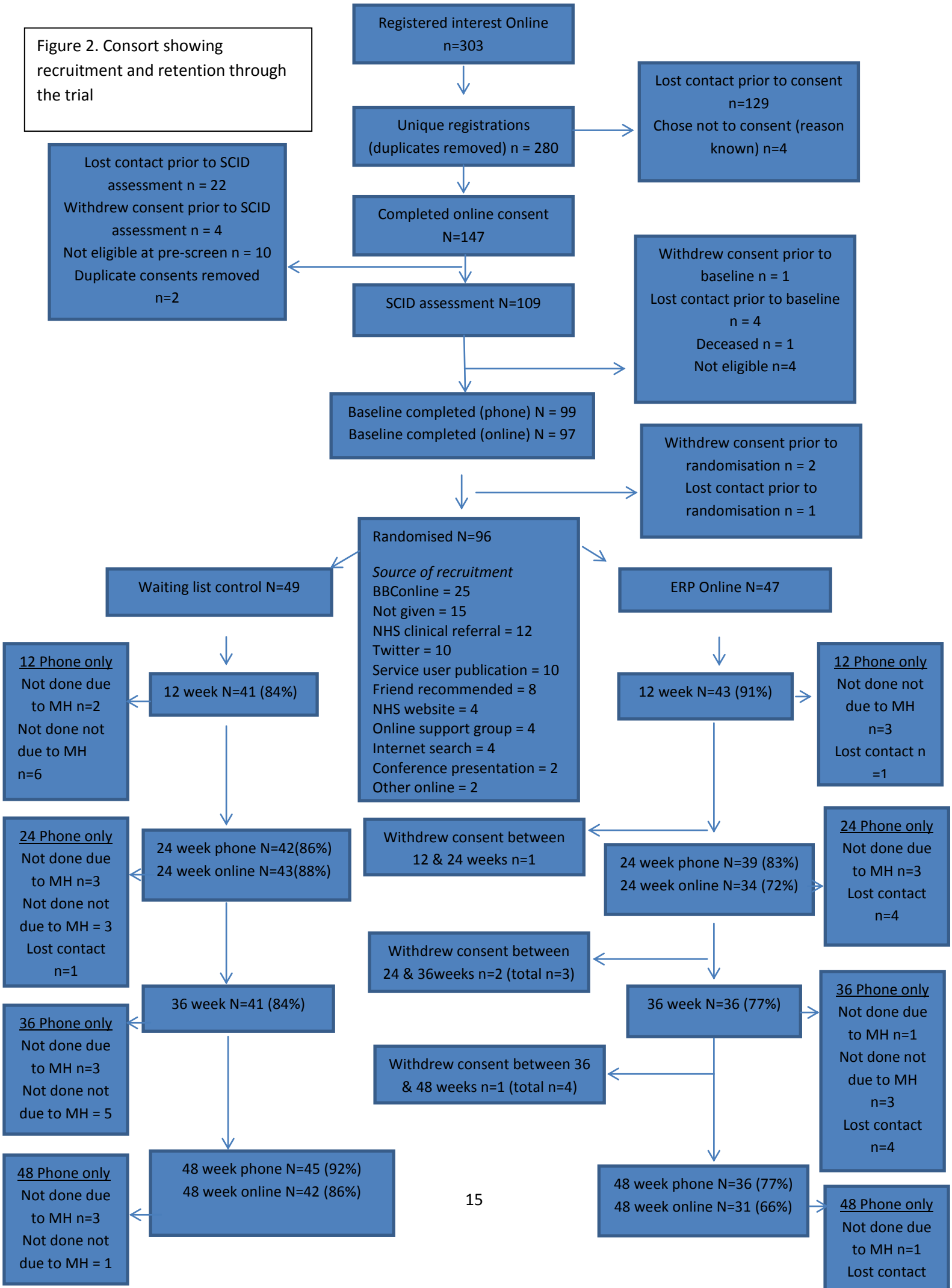
Quality assurance

Only two unblindings occurred. In both instances, the participant inadvertently indicated their group during a telephone assessment (one waitlist control, one ERPonline). Subsequent assessments were completed by a blind RA. At each follow up, 10% of the SCID-LIFE interviews were rated by both researchers and kappa statistic calculated to assess interrater reliability. These ranged from acceptable (κ = .54 (95% CI, .39 to .69) at 36 weeks based on 142 weekly ratings for 6 participants) to high (κ = .90 (95% CI .82 to .98) at 12 weeks based on 192 weekly ratings for 8 people).

Feasibility and acceptability of trial design

Participant flow is detailed in Figure 2, including recruitment, over half of which came via online sources. Ninety-six were randomised, 49 to WL, 47 to ERPonline over a 17 month period, with 80% retention in telephone and online follow up at all time points, except week 48 online (76%). Attrition was 11% lower in WL arm.

Figure 2. Consort showing recruitment and retention through the trial



Participants were predominantly diagnosed with BD1 (90%) and had a chronic relapsing course (67% had over 21 relapses; see Table 2). Despite this, the group were currently high functioning and had a positive attitude to recovery. The vast majority were taking and adherent to medication to manage their mood and over half had previously received psychological treatment for BD (where specified, this was most commonly described as Cognitive Behaviour Therapy (CBT)).

Table 2 – Key characteristics of participant sample at baseline

	Wait List (n = 49)	**ERPonline (n = 47)**
Baseline demographic and clinical variables		
Age (mean, SD)	43.8 (11.45)	42 (12.23)
Gender – female N (%)	32 (65.3)	27 (57.4)
Ethnicity N (%)		
White British	44 (89.8)	38 (80.9)
Any other white	2 (4.1)	5 (10.6)
Black British	-	1 (2.1)
Caribbean	1 (2)	-
Asian British	1 (2)	-
Indian	-	1 (2.1)
Any other mixed	-	1 (2.1)
Missing	1 (2)	1 (2.1)
Occupational status N (%)		
Full-time paid or self	16 (32.7)	21 (44.7)
Part-time paid or self	13 (26.5)	6 (12.8)
Voluntary	3 (6.1)	4 (8.5)
Not employed	10 (20.4)	6 (12.8)
Student	3 (6.1)	2 (4.3)
Housewife/house husband	-	3 (6.4)
Retired	4 (8.2)	5 (10.6)
Education N (%)		
No formal qualifications	1 (2)	-
CSE/O Level/ GCSE	5 (10.2)	4 (8.5)
A Level	7 (14.3)	7 (14.9)
Degree	17 (34.7)	16 (34)
PG Diploma/qualification	13 (26.5)	13 (27.7)
Doctorate/PhD	3 (6.1)	7 (14.9)
Total number of past episodes (baseline) N (%)		
<7	6 (12.2)	2 (4.3)
8-20	12 (24.5)	12 (25.5)
21+	31 (63.3)	33 (70.2)
Taking mood stabiliser (baseline) N (%)		
Not on any medication (so item rated not applicable)	3 (6.1)	2 (4.3)

No mood stabiliser	15 (30.6)	11 (23.4)
Lithium	12 (24.5)	11 (23.4)
Sodium valproate	5 (10.2)	14 (29.8)
Carbamazepine	3 (6.1)	1 (2.1)
Lamotrigine	11 (22.4)	8 (17)
Treatment History (Baseline) N (%)		
Ever used mental health services	46 (93.9)	42 (89.4)
Clinical diagnosis of BD1 (vs BD2)	44 (89.8)	44 (93.6)
Ever seen a psychiatrist	46 (93.9)	43 (91.5)
Ever prescribed medication for BD	49 (100)	46 (97.9)
Currently taking medication for Bipolar Disorder	40 (81.6)	40 (85.1)
Ever received therapy/psychosocial intervention for Bipolar Disorder	26 (53.1)	27 (57.4)
Currently receiving therapy for Bipolar Disorder	8 (16.3)	10 (21.3)
Process Measures		
Early Warning Signs monitoring frequency - depression N (%)	never 3(6) occasionally 18(37) fairly regularly 8(37) very regularly 10(20)	never 3(6) occasionally 11(23) fairly regularly 20(43) very regularly 13(28)
Early Warning Signs monitoring frequency - (hypo)mania N (%)	never 6 (12) occasionally 21(43) fairly regularly 16(33) very regularly 6 (12)	never 5(11) occasionally 14(30) fairly regularly 18(38) very regularly 10(21)
Brief Illness Perception Questionnaire- total (high score = more negative model) mean (SD)	60.6 (10.5)	60.7 (9.9)
Medication Adherence Rating Scale mean,(SD)	6.9 (2.2)	7.0 (2.1)
Outcome measures		
Hamilton Depression Rating Scale mean (SD)	4.5 (5.3)	3.5 (4.2)
Mania Rating Scale mean (SD)	1.3 (2.4)	1.0 (1.7)
Personal and Social Performance Scale mean (SD)	79.7 (11.2)	79.1 (13.1)
Multidimensional Scale of Independent Functioning N (%)	1 25 (51) 2 14 (29) 3 8 (16) 4 2 (4) 5 0 (0) 6 0 (0)	1 21 (45) 2 16 (34) 3 6 (13) 4 2 (4) 5 2 (4) 6 0 (0)
Work and Social Adjustment Scale mean (SD)	11.4 (9.4)	12.8 (8.7)
Quality of Life in Bipolar Disorder mean (SD)	162.7 (33.5)	162.5 (22.8)
Bipolar Recovery Questionnaire mean (SD)	2332 (394)	2342 (383)

N = number of participants: % = percentage of people in the group: SD = standard deviation

Feasibility and acceptability of data collection

Telephone and online data collection procedures were generally acceptable to participants based on information from 41 participants (WL survey n = 22; ERPonline interviews n = 19 reported separately). Survey data indicated factors that encouraged people to take part including: opportunity to improve their own resilience and self-management; wanting to help others; and recognising the importance of research on improving web-based interventions, due to a perceived gap in face-to-face services and some existing websites feeling unsafe. Many of these factors were also cited as facilitating retention in the trial, as well as factors such as text reminders about follow-ups, and viewing the research team as sensitive, polite and not intrusive. Participants reported that the research process was well-managed, clearly explained, straightforward, and flexible, and they liked the shopping vouchers. Some participants believed completing the measures had changed their thinking about their mood and diagnosis. Barriers to retention included: procedural difficulties such as, remembering follow-up times and re-scheduling missed appointments, feeling 'weird' to have interviews only on the phone and difficulties finding private space for the phone calls; issues with measures, some of which were too long (CSRI) and could be tiring, distressing, and required recall over long periods of time; and technical difficulties with online questionnaires. Some reported feeling disappointed to be in the waitlist control arm, although had remained in the trial.

Additional key data collection lessons we learnt included: the importance of checking electronic communication is received (some of our reminder emails were initially going into junk folders); the need to accommodate the high demand for evening and weekend telephone appointments; the importance of text reminders for telephone appointments.

Feasibility and acceptability of ERPonline intervention

ERPonline is low cost at an estimated £19,340 to create, and approximately £2176 per year to host and maintain the site. Development costs included: time to adapt content from the ERP manual; discussion and feedback with co-authors; web developer time to build the site; filming and producing videos; costs for the Service User Reference Group to feedback on early iterations. Hosting costs include software updates and technical issues (estimated at 2hrs per week) and space on a server. To keep costs low, ERPonline was delivered unsupported and without an interactive moderated forum, despite these being part of the intended design.

Activity levels were highly skewed. Two people allocated to ERPonline never visited the site. Mean number of page views per person was 259 (SD = 577), median was 85 (range 0 – 3203). Participants spent a mean of 259 minutes (SD 509), median 76 minutes (range 0 – 2770) accessing ERPonline

throughout the 48 week intervention period. The most frequently viewed modules were" Life Charting" (median views 11; range 0-990 per person) and "Mood Charting" (median views 13; range 1- 2519 per person), which is unsurprising as they offered an ongoing monitoring function. "Coping strategies for Low Mood" (median views 0: range 0-44 per person) and "Your Staying Well Plan" (median views 0; range 0-30 per person) were the least frequently visited, but also occurred towards the end of the listed modules (see Table 1 for number of visits and time spent on all modules).

Seventeen ERPonline participants (36%) responded to the online survey. Overall these participants were satisfied (13 people (76%) somewhat/very satisfied), found it somewhat/very helpful (n = 12, 71%), and very/extremely relevant (n = 13, 76%). Only one person said they would not recommend it to a friend. Most useful features were recognising early warning signs of relapse, shared experiences through videos, mood monitoring, ability to revisit and refresh skills, improved knowledge and self-management of BD, ease of use, and being able to use the site with the family. The key recommendation for improvement was additional support with working through the materials. The sample of questionnaire respondents described themselves as confident (n = 16, 94% very or extremely confident) and regular (n=12, 71% at least daily) internet users.

Nineteen people took part in qualitative interviews about their experience of the trial and use of the ERPonline site. The key finding was the importance of relationships that the individual developed with the ERPonline team in determining retention into the study and use of the site:

> "*I think the sort of general thoroughness and kindness of the people I dealt with that certainly contributed to, you know, me sort of staying in the study. Everybody's been really upbeat, very positive, very accommodating*." (P10)

This is particularly interesting when we consider there was no face to face contact. Sole direct contact was by telephone at 3 monthly interviews for SCID-LIFE interviews, which for some was preferable to face to face:

> *"…I think it being over the 'phone makes it a bit easier. If it's face-to-face I would have probably not been quite so comfortable answering. But yeah over the 'phone was definitely not so bad."* (P13)

Crucial to the strength of the alliance was the perceived trustworthiness of the team and being made aware of the extensive user involvement in design and content of the site :

> *"It's always available and also the information's on there has been put together by the people who do know what they're doing."* (P7)

> *"I suppose the prospect of the online study kept me quite interested and the fact that it was developed by other people with Bipolar and that was something that I was definitely interested in…"*(P17)

A key recommendation to improve the ERPonline site was to integrate human support to facilitate ongoing use of the site. This is consistent with previous studies in which adherence was higher in groups receiving a web intervention plus support as compared to web intervention only [31]. Participants felt websites should be used to support interventions delivered by real people and not as a cheaper replacement:

> "*The cash strapped health service will rely heavily on these sort of techniques which I think only fill one part of the market. I think they only really deal with, you know, and a comparatively narrow field of potential patients. I think they're very useful but I do think the gold standard involves some sort of face-to-face psychological therapy. And I think the clinical literature bears that out so, I want more jobs for psychologists basically*." (Henry: 23.893-898)

Estimate of impact on outcome & process measures

Descriptive statistics on process and outcome measures at each time point are shown in Table 3. Comparison between WL and ERPonline on process and outcome measures at 12, 24 and 48 week follow-ups are shown in Table 4. Models adjusting for baseline demographic and clinical variables were also are shown in Table 5.

Table 3 – Descriptive statistics on outcome and process measures at 24 and 48 week followups.

Variable	**arm**	**Baseline n WL=49(I); 49(O) ERP=47(I);47(O)**	**12 weeks WL=41(I) ERP= 43 (I)**	**24 weeks WL=42(I); 43(O) ERP=39(I);34(O)**	**36 weeks WL=41(I) ERP=36 (I)**	**48 weeks WL=45(I);42(O) ERP=36(I);31(O)**
Process Measures						
Early Warning Signs monitoring frequency – depression (O) N (%)	WL never	3 (6)		8 (19)		4(10)
	occasionally	18 (37)		13(30)		11(26)
	fairly regularly	18 (37)		17(40)		19(45)
	very regularly	10 (20)		5 (12)		6(14)
	ERP never	3(6)		1(3)		1(3)
	occasionally	11(23)		11(32)		6(19)
	fairly regularly	20(43)		15(44)		10(32)
	very regularly	13(28)		7(21)		14(45)
Early Warning Signs monitoring frequency – (hypo)mania (O) N (%)	WL never	6(12)		11(26)		4(10)
	occasionally	21(43)		17(40)		18(43)
	fairly regularly	16(33)		9(21)		11(26)
	very regularly	6(12)		6(14)		7(17)
	ERP never	5(11)		2(6)		1(3)
	occasionally	14(30)		10(29)		8(26)
	fairly regularly	18(38)		15(44)		11(35)
	very regularly	10(21)		7(21)		11(35)
BIPQ- total (O) Mean (SD)	WL	60.6 (10.5)		49.4 (22.6)		49.4 (24.6)
	ERP	60.7 (9.9)		39.3 (27.0)		36.2 (29.1)
MARS (O) Mean (SD)	WL	6.9 (2.2)		6.7 (2.6)		6.6 (2.5)
	ERP	7.0 (2.1)		6.8 (2.7)		7.0 (2.2)
Outcome measures						

HAM-D (I) Mean (SD)	WL	4.5 (5.3)	7.5 (7.4)	7.3 (8.6)	6.8 (8.6)	8.2 (9.0)
	ERP	3.5 (4.2)	6.6 (6.7)	6.9 (8.0)	6.0 (8.3)	7.1 (9.3)
MRS (I) Mean (SD)	WL	1.3 (2.4)	2.7 (3.7)	2.2 (4.1)	1.7 (2.9)	1.7 (2.2)
	ERP	1.0 (1.7)	2.5 (4.4)	2.4 (3.9)	2.0 (4.0)	1.4 (2.4)
PSP (I) Mean (SD)	WL	79.7 (11.2)	75.0 (15.1)	76 (16.4)	79.8 (14.8)	78.4 (15.6)
	ERP	79.1 (13.1)	77.8 (15.1)	76.7 (15.4)	77.8 (16.1)	80.7 (16.1)
MDSIF-global (frequencies for scores categories 1, 2, 3, 4,5,6) (I) N (%)	WL 1	25 (51)	24 (59)	20 (48)	25 (61)	28 (62)
	2	14 (29)	8 (20)	13 (31)	10 (24)	9 (20)
	3	8 (16)	4(10)	5 (12)	3 (7)	6 (13)
	4	2 (4)	5 (12)	3 (7)	1 (2)	1 (2)
	5	0 (0)	0 (0)	1 (2)	2 (5)	0 (0)
	6	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
	ERP 1	21 (45)	26 (60)	18 (46)	20 (56)	22 (61)
	2	16 (34)	10 (23)	12 (31)	9 (25)	9 (25)
	3	6 (13)	3 (7)	6 (15)	5 (14)	4 (11)
	4	2 (4)	3 (7)	2 (5)	0 (0)	1 (3)
	5	2 (4)	1 (2)	1 (3)	2 (6)	0 (0)
	6	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
WSAS (I) Mean (SD)	WL	11.4 (9.4)		12.4 (10)		12.9 (10.6)
	ERP	12.8 (8.7)		14.3 (9.1)		14.8 (10.3)
QoLBD (O) Mean (SD)	WL	162.7 (33.5)		161.2 (39.7)		154.9 (36.1)
	ERP	162.5 (22.8)		156.5 (33.4)		151.8 (41.7)
BRQ (O) Mean (SD)	WL	2332 (394)		2309 (504)		2336 (468)
	ERP	2342 (383)		2451 (430)		2414 (577)

(I) = interviewer rated by telephone
(O) = completed online
SD = standard deviation
BIPQ = Brief Illness Perception Questionnaire (score 0-110 higher score = more negative beliefs)
MARS = Medication Adherence Rating Scale (0-10 higher score = higher compliance)
HAMD =Hamilton Depression Rating Scale (scores above 7 indicate mild depression, above 13 moderate, and above 18 severe)
MRS = Mania Rating Scale (scores of 11 and above indicate hypomania)
PSP = Personal and Social Performance Scale (scores 70-80 indicate mild difficulties, above 80 is good functioning)
MDSIF = Multidimensional Scale of Independent Functioning (Likert scale 1 = normal functioning, to 7 = total disability)
WSAS = Work and Social Adjustment Scale (less than 10 = subclinical; 10-20 some functional impairment; above 20 moderate psychopathology)
QoLBD = Quality of Life in Bipolar Disorder (range 48-240 with high score = higher quality of life)
BRQ = Bipolar Recovery Questionnaire (score 0-3600 high score = higher recovery)

Table 4 –Comparison of linear models with correlated errors to test for differences between Wait List and ERPonline on outcome and process measures at 12, 24 and 48 week followups. Unadjusted model showing estimates of difference between Beta estimates at each time point.

	Model 1 – unadjusted analysis							
Variable	**12wk FU estimate**	**95% CI (*P* value)**	**24wk FU Estimate**	**95%CI (*P* Value)**	**36 week FU Estimate**	**95%CI (*P* value)**	**48wk FU**	**95%CI (*P* Value)**
Early Warning Signs monitoring frequency – depression			**0.73**	**-1.86, 0.40 (.20)**			**-1.39**	**-2.61, -.163 (.03)**
Early Warning Signs monitoring frequency – (hypo)mania			**-1.72**	**-2.98, -.47 (.01)**			**-1.61**	**-2.92, -.30 (.02)**
Brief Illness Perception Questionnaire-total			**10.70**	**0.90-20.5 (.03)**			**13.18**	**2.44 – 23.93 (.02)**
Medication Adherence Rating Scale			**-.102**	**-1.07, 0.87 (.84)**			**-.327**	**-1.34, .685 (.53)**
Personal and Social Performance Scale	**-2.91**	**-9.19, 3.37 (.36)**	**-.198**	**-6.77, 6.38 (.95)**	**0.77**	**-5.87, 7.41 (.82)**	**-2.87**	**-9.27, 3.52 (.38)**
Multidimensional Scale of Independent Functioning - global (frequencies for scores categories 1, 2, 3, 4,5,6)	**.169**	**-.867, 1.20 (.75)**	**.029**	**-.959, 1.02 (.95)**	**-.074**	**-1.15, 1.00 (.89)**	**.281**	**-.785, 1.35 (.61)**
Work and Social Adjustment Scale			**-1.61**	**-5.67, 1.46 (.30)**			**-.53,**	**-3.90, 2.83 (.76)**
Quality of Life in Bipolar Disorder			**6.67**	**-5.73, 19.1 (.29)**			**3.99**	**-9.72, 17.7 (.57)**
Bipolar Recovery			**-52.3**	**-195,**			**-**	**-**

Questionnaire				**90.7 (.47)**			**38.09**	**208.58, 132.41 (.66)**

BIPQ total measures how negative a model the person has – so high score = more negative model.

Table 5 –Comparison of linear models with correlated errors to test for differences between Wait List and ERPonline on outcome and process measures at 12, 24 and 48 week followups. Adjusted for any differences in baseline demographic (age, gender, ethnicity, employment, education) and clinical variables (number of previous episodes, and whether or not prescribed a mood stabiliser).

	Model 2 – adjusted analysis							
Variable	12wk FU Estimate	95%CI (*P* value)	24wk FU Estimate	95%CI (*P* Value)	36wk FU Estimate	95%CI (*P* value)	48wk FU Estimate	95%CI (*P* Value)
Early Warning Signs monitoring frequency – depression			-.721	-1.85, .413 (.21)			-1.38	-2.61, -.153 (.03)
Early Warning Signs monitoring frequency – (hypo)mania			-1.70	-2.96, -.452 (.01)			-1.60	-2.91, -.291 (.02)
Brief Illness Perception Questionnaire-total			11.06	1.25 – 20.9 (.03)			13.6	2.69 – 24.6 (.02)
Medication Adherence Rating Scale			-.128	-1.11, .855 (.80)			**-.**356	- 1.39, .674 (.50)
Personal and Social Performance Scale	-2.99	-8.84, 2.863 (.32)	-.430	-7.02, 6.16 (.90)	.704	-6.06, 7.47 (.84)	-3.21	-9.69, 3.26 (.33)
Multidimensional Scale of Independent Functioning – global (frequencies for scores categories 1, 2, 3, 4,5,6)	.092	-.907, 1.09 (.86)	-.075	-1.03, .878 (.88)	-.084	-1.12, 0.95 (.87)	.275	-.743, 1.29 (.60)
Work and Social			-1.46	-4.53,			-.40	-3.84,

Adjustment Scale				1.64 (.36)				3.03 (.82)
Quality of Life in Bipolar Disorder			6.23	-6.13, 18.6 (.32)			3.58	-10.4, 17.5 (.62)
Bipolar Recovery Questionnaire			-63.29	-206.47, 79.88 (.39)			-35.84	-209.78, 138.10 (.69)

BIPQ total measures how negative a model the person has – so high score = more negative model.

Process Measures

ERPonline increased the frequency of monitoring early signs of mood change (EWS – depression and EWS- (hypo)mania), evident for (hypo)mania at 24 weeks (-1.72 (-2.98, -0.47 95%CIs), and for both at 48 weeks (depression -1.39 (-2.61, -.163 95%CIs); (hypo)mania -1.61 (-2.92, -0.30 95%CIs)), and improved working model of mood changes (BIPQ – high score indicates more negative model) at both 24 weeks (10.70 (0.90 – 20.5 95% CIs) and 48 weeks follow ups (13.18 (2.44 – 23.93 95%CIs) (Table 4). All differences are robust to adjustments in model 2 for baseline differences between the groups (Table 5). Medication adherence was high (indicated by high score on the MARS) throughout the study and did not differ between groups.

Mood and Functioning

Depression and hypomania were low at all time points suggesting a generally stable and euthymic group. Similarly, functioning on WSAS, PSP and MSIF at baselines were suggestive of very mild impairment in work and social performance and remained so throughout. Time spent in euthymic, subsyndromal and relapse mood states respectively in WL were: 93% (SD 8%); 5% (SD 7%); and 3% (SD 15%), and in ERP online: 95% (SD 8%); 4% (SD 6%); and 2% (SD 4%). There were no notable differences between the two groups in any of the outcome measures at any of the time-points.

Relapse

Of the 96 participants, one provided no SCIDLIFE data at follow-up. Only 15 (16%) participants experienced a relapse over the 48 week follow-up; 11 (11%) depressive and seven (7%) mania-type. There were no notable differences between groups on time to any relapse (unadjusted hazard ratio (HR) 1.67 (95% CI: 0.60, 4.71), p=0.33; time to depressive episode (HR 1.53 (95% CI 0.49,

4.83),p=0.47; time to mania type episode HR 2.87 (95% CI 0.56, 14.8), p=0.12. Given the low level relapses, no Kaplan Meier curves are presented.

Adverse Events

During the trial, one participant completed suicide prior to randomisation. Eleven participants (11% of those randomised) reported suicidality and/or self-harm, and one made a suicide attempt (prior to withdrawing from the study). Six were in the WL arm, and five were receiving ERPonline. None of the SAEs were deemed study related by an independent TSC.

Discussion

ERPonline is a novel web intervention for improving relapse prevention and providing NICE congruent information to people with BD. This study indicates that the development and evaluation of this type of approach in a rigorous RCT using telephone and online assessments is both feasible and acceptable. Important lessons were learnt relevant to each of our study aims, but which also have relevance to the wider development and evaluation of remote-access approaches for other health problems.

With the help of our Service User Reference Group, we were able to develop an online version of an existing Enhanced Relapse Prevention intervention for people with Bipolar Disorder at very low cost that received largely positive feedback, and led to no evident adverse events. Activity was highly skewed but over 90% of our sample visited the site more than once, which can be compared to MyRecoveryPlan [17] which reported site returns for 71% in a coached group, and only 44% in an unsupported group. Based on levels of use of the different modules, and direct participant feedback, engagement could be enhanced by making the intervention more interactive and providing support to use it.

Recruitment, retention and data completion strategies were largely successful. Retention was higher than demonstrated in previous online trials with people with BD [14, 15, 17].Key features of the trial design that facilitated this included payment for completing assessments, text and email reminders, a waitlist control design, and a friendly flexible research team who were willing to offer telephone appointments at times to suit participants including out of office hours. However, to reach the sample size required for large scale clinical and cost effectiveness trials, paying for advertising through popular websites such as Google and Facebook may be necessary [36].

Feedback about the experience of taking part in a primarily online trial was mixed. Some participants reported difficulties finding a private space to take telephone calls or finding the online difficult, tiring or distressing, whilst others valued the flexibility, convenience and felt more able to be open about the problems they had experienced than in a face to face interview. This suggests that trials which offer a choice of data collection options may be most effective in achieving recruitment and retention targets.

However, further work is needed to test the validity and reliability of these data collection approaches. Our data showed that whilst, the hypothesised increase in early warning signs monitoring and development of more positive beliefs about mood swings did occur in those receiving ERPonline compared to waitlist control group, we did not see any benefit of ERPonline on any of the clinical outcome measures. This was largely due to the ceiling effect on our outcome measures. Only 16% of the total sample experienced any relapse, compared to expected levels of 50-70% [37].

This ceiling effect was consistent across all outcome measures, and all assessors. Therefore the most likely explanations are either that the method of data collection is leading to underreporting of problems, or that the participating sample reflect a different population from those taking part in more traditionally designed face to face clinical studies.

With regards to the first possibility, whilst we did not directly test the reliability of the data compared to a face to face interview, other studies have done this comparing telephone and face to face interview data of SCID assessments found high levels of agreement [38]. Our team have also carried out a parallel online randomised controlled trial which included the same online and telephone assessments, delivered through researchers trained by the same methods, and which will report relapse rates of 47% which are akin to those expected from previous research data and much higher than in this study [39].

The second possible explanation can be explored by examining the characteristics of our participants. Compared to bipolar samples recruited to other face to face trials [37] including one evaluating clinician delivered ERP [7], and samples in other online trials which all show higher relapse rates [14, 15, 17], our sample are more euthymic, highly educated, likely to be in employment, and have had surprisingly high levels of access to previous psychological therapy. Further work is needed to better understand how using a primarily online trial design may impact on sample characteristics, and the information they provide.

The future for ERPonline

ERPonline offers a cheap and easily accessible option for people who are seeking ongoing support following successful treatment, which is currently unavailable. However, given the high functioning and low relapse rates evident in this study, testing the clinical effectiveness of ERPonline for this population would require very large sample sizes. Alternatively, ERPonline could target people at an earlier stage of treatment, who have had not yet received more expensive face-to-face psychological therapy, and need support to understand their mood swings, consider the pros and cons of medication use, and explore the usefulness of monitoring and managing early warning signs of relapse. For this group, ERPonline may offer a way to reduce the need for expensive individual therapy. Consistent with participant recommendations and previous research we also need to consider how best to integrate support mechanisms to facilitate use of the intervention, either by integrating the online resource with clinician delivered relapse prevention, or through online peer support as described in other online interventions for BD [10, 11, 13]. This study highlights the importance of the relationship users have with online interventions and how this develops as an extension of the relationship with the humans perceived as offering and supporting its use. Online interventions offered in isolation in this context seem unlikely to engage people in the same way and may be perceived negatively as attempts to save money rather than improve care. Our study has explored the feasibility and acceptability of a specific online intervention (ERPonline), but does not address the broader social issue of how acceptable the increasing use of digital health technology is to people with mental health problems [40].

Strengths of study

Extensive user involvement improved the content of the ERPonline website, identified recruitment sources, and ensured the measures were appropriate and not too burdensome. The sample was sufficiently large to be able to comment on patterns in the data likely to be indicative of effects on process and outcome measures in a larger trial. Independent randomisation, trained blind assessors and the use of well-established outcome and process measures ensured the data are reliable and valid. Extensive reflection and learning around feasibility was built into the design process using face to face meetings and an online reflection log.

Limitations

Despite 280 unique site registrations, only 145 people consented, and due to ineligibility and drop out, only 96 were randomised. We have no data on why nearly half the sample registering an interest, then chose not to take part, though for some it may have been delay between prestart expression of interest and randomisation. During the trial, we had higher dropout in the ERPonline

arm, which is common in trials with a waitlist control arm and is likely due to the perceived reward of the intervention retaining people through waitlist. Survey responses were incomplete for feedback on trial participation (22 out of 49 in waitlist group (45%)) and for feedback on the ERPonline intervention (17 out of 47 in ERPonline arm (36%)). The bias in responders is likely to skew the nature of the feedback which on the whole was very positive.

In summary we were able to successfully adapt and deliver online a relapse prevention intervention for BD previously used face-to-face. The intervention was successfully evaluated against a waitlist control group using a RCT design with high levels of retention and data completeness over 48 weeks. Participants had high rates of previous bipolar episodes but had accessed previous psychosocial interventions (where specified, most commonly described as CBT) for BD. Online interventions may prove an important cheap, feasible and acceptable step forward in creating a choice of evidence-based interventions for people with BD at different stages of recovery, but may be more appropriately designed with built-in support and targeted at those with less prior experience of effective care.

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Author Contributions

FL was the study Chief Investigator, leading the design of the trial and ERPonline intervention, study conduct and write up of the study. AD managed day to day management of the trial and data collection. OA and PD did the statistical analysis. AS, MG, DK collected the data. MH analysed the

web usage data. RL Chaired the SURG, ensuring continued service user input throughout the study. RP developed the ERPonline website. RM and SJ contributed to the design analysis and interpretation of data, and edited drafts of the paper. DD facilitated recruitment through NHS Trusts. All authors were involved in drafting and final approval of this paper.

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