Clinical effectiveness of a web-based peer-supported self-management intervention for relatives of people with psychosis or bipolar (REACT): online, observer-blind, randomised controlled superiority trial

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Abstract

Background: The Relatives Education And Coping Toolkit (REACT) is an online supported self-management toolkit for relatives of people with psychosis or bipolar designed to improve access to NICE recommended information and emotional support.

Aims: Our aim was to determine clinical and cost-effectiveness of REACT including a Resource Directory (RD), versus RD-only.

Methods: A primarily online, observer-blind randomised controlled trial comparing REACT (including RD) with RD only (registration ISRCTN72019945). Participants were UK relatives aged ≥ 16, with high distress (assessed using the GHQ-28), and actively help-seeking, individually randomised, and assessed online. Primary outcome was relatives’ distress (GHQ-28) at 24 weeks. Secondary outcomes were wellbeing, support, costs and user feedback.

Results: We recruited 800 relatives (REACT = 399; RD only = 401) with high distress at baseline (GHQ-28 REACT mean 40.3, SD 14.6; RD only mean 40.0, SD 14.0). Median time spent online on REACT was 50.8 min (IQR 12.4–172.1) versus 0.5 min (IQR 0–1.6) on RD only. Retention to primary follow-up (24 weeks) was 75% (REACT n = 292 (73.2%); RD-only n = 307 (76.6%)). Distress decreased in both groups by 24 weeks, with no significant difference between the two groups (−1.39, 95% CI -3.60, 0.83, p = 0.22). Estimated cost of delivering REACT was £62.27 per person and users reported finding it safe, acceptable and convenient. There were no adverse events or reported side effects.

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Background
Relatives and friends of people experiencing psychosis or bipolar provide much unpaid care [1, 2], but at high personal cost emotionally and financially [3–5]. Sample estimates of levels of clinically significant distress and burden in relatives of people with psychosis range from a third [4], to more than 60% of those in early intervention in psychosis (EIP) services [6, 7], with almost half reporting post-traumatic stress symptoms associated with their caring roles [8], particularly linked to episodes of violence, disruptive behaviour and forced admission [9]. Key factors that increase the negative impact of psychosis on carers include: being a female carer [10]; living with the person with psychosis; young patient age and awareness of suicidal ideation [11]; reduced social support and family resources [11, 12]; use of emotion-focused coping strategies [13]; and beliefs that relatives hold about the psychosis, particularly those concerning cause and control [14–16]. Particular challenges for relatives of people with bipolar experiences include high risk of suicide attempts [17], mania related extravagant spending, irritability and disinhibited behaviour [18–20], all of which are associated with feelings of helplessness, anger, and anxiety in their relatives [21, 22]. Historically, the impact of severe mental health problems on relatives has been neglected [23]. However, there is now good evidence that interventions that support relatives can improve both service user [23–25] and carer [26–29] outcomes. The UK Government recognises the need to support carers [30], and the National Institute for Health and Care Excellence (NICE) recommends that all relatives of people with psychosis or bipolar be given carer-focused education and support, and offered structured family intervention to enhance family coping and communication [31, 32]. Despite this, a recent national audit of community mental health services in the UK showed poor implementation, with only 50% of relatives receiving carer-focused education and support and only 12% receiving structured family intervention [33].

Within this context, our aim was to test the clinical and cost effectiveness of an online self-management intervention, based on the principles of psychoeducation and family intervention [34]. The Relatives Education And Coping Toolkit (REACT) was developed with extensive input from relatives and clinicians [35] initially in paper form, supported by staff in EIP services and tested in a feasibility trial which showed a significant reduction in distress for relatives receiving REACT in addition to usual treatment, when compared to those receiving usual treatment only [6]. To increase accessibility, REACT was adapted for this study to be available online and supported by trained relatives with lived experience of supporting someone with a severe mental health problem (REACT Supporters) [36]. REACT included a comprehensive Resource Directory (RD), signposting relatives to other freely available relevant support. We tested REACT including the RD, against the RD only to determine the impact of REACT on relatives’ distress, wellbeing, and support, and to test hypothesised mediators of change including relatives’ beliefs, perceived coping, and amount of use of REACT. We also report the costs of the development and delivery of REACT and the RD, and user experience of REACT. A comprehensive cost effectiveness analysis will be reported elsewhere. A separate study has examined the factors impacting on implementation of REACT in NHS services [37].

Methods
Study design
We conducted an online, two-arm, pragmatic, observer-blind, randomised controlled superiority trial open to relatives of people with psychosis or bipolar across the UK. Inclusion criteria were broad and relatives could self-refer into the trial. A nested qualitative study examined user experiences of REACT. Prior to the end of data collection, a trial protocol [38] and a comprehensive statistical analysis plan were published [39, 40]. Reporting follows CONSORT guidance [41].

Participants
Inclusion criteria were (according to self-report):

- Aged 16 or over
- Living in the UK
- Relative or close friend of someone with psychosis or Bipolar
- Currently experiencing distress (selecting “rather more than usual” or “much more than usual” on GHQ-28 item “Have you recently been feeling
nervous and strung up all the time”). This was included to avoid a distress floor effect at baseline (selected item was the most highly correlated most with GHQ total score in the REACT feasibility trial [6].

- Currently seeking help (self-identified)
- Internet access
- Sufficient English fluency to comprehend intervention content

Exclusion criteria were:

- Living in any of six geographical areas by postcode taking part in a parallel implementation study of the same intervention (IMPART) [42].
- Only one relative per service user was allowed to participate, to avoid a clustering effect.

Recruitment took place from 22 April 2016 to 30 September 2017. We used a range of online (Facebook, twitter, charity websites) and offline recruitment strategies (clinical services, third sector providers), all directing potential participants to the study home page, including information about how to take part. At registration, all participants gave online written informed consent, indicated how they had found out about REACT, and provided postal, email and telephone contact details. A convenience sub-sample (n = 55) of relatives in the REACT arm who had completed the 24-week follow-up at the time of interviewing were invited to take part in qualitative interviews about their experiences of using REACT, with the aim of recruiting approximately 25 interviewees.

Randomisation and masking

Eligible participants were randomised using a 1:1 ratio to “REACT (including RD) plus Treatment As Usual (TAU)” or “RD only plus TAU” using web-based variable block randomisation, in which the unit of randomisation was the relative. Participants then received an email indicating which arm of the trial they had been allocated to, and a link to the REACT website, with their username and password. Those in the RD-only arm had access only to the directory pages. All participants were aware that the RD was one component of the REACT intervention, and therefore were likely to have perceived REACT as the “intervention of interest” and the RD as the comparator.

All data were self-reported and predominantly entered online by participants. Data sets submitted by post at follow-up were inputted by the trial manager, blind to allocation. Data were uploaded directly to the Clinical Trials Research Centre (CTRC) database. To prevent bias, the chief investigator, trial manager (TM) and statisticians were blinded to treatment assignment. REACT supporters, clinical supervisors, qualitative interviewer, one CTRC analyst of web usage data and technical staff were unblinded. To minimise unwanted unblinding, all contact with participants was prefaced by a reminder not to disclose trial arm. If the TM was unblinded regarding a particular participant, another blind team member delivered any non-automated reminders and carried out any data entry for that participant.

Procedures

Interventions

React The REACT intervention was built in WordPress, hosted and maintained at Lancaster University, and included: 12 psychoeducation modules; peer support through a moderated group forum; a confidential direct messaging service; and the RD, which pointed relatives to other available resources. The modules addressed important questions relatives have highlighted, and included videos of experts by experience and clinical experts; evidence-based education and strategies; and self-reflection tasks that help users apply the content to their personal circumstances. Module titles were: ‘What is psychosis?’; ‘What is bipolar disorder?’; ‘Managing “positive” symptoms’; ‘Managing “negative” symptoms’; ‘Managing mood swings’; ‘Dealing with difficult situations’; Managing stress – doing things differently; ‘Managing stress – thinking differently’; ‘Understanding mental health services’; ‘Treatment options’; ‘Dealing with crisis’; The future and recovery’. A detailed description of each module is presented in the protocol paper, along with screenshots showing the look and feel of the website, [38], and the modules can be freely accessed by visiting reacttoolkit.uk [43].

A “Meet the Team” page informed relatives about who was delivering the content of the site. “Mytoolbox” provided a confidential space for users to save links to information they might find useful in the future including external web links. A blog page offered a flexible space for additional communication with site users, which was editable by the REACT supporters.

REACT Supporters were relatives with lived experience of supporting someone with a mental health problem who were trained to moderate the forum, respond to confidential direct messages from users, and guide users to relevant parts of the toolkit and/or other resources as appropriate. REACT Supporters were hosted by one National Health Service (NHS) mental health trust in England but available to relatives across the UK. They were trained to identify and report risk, and were supervised by two clinical psychologists and an expert relative. A supervision manual, supporter manual and
risk protocol were developed for the study and are available on request.

Relatives could access REACT whenever they wished throughout the trial (minimum of 24 weeks to last follow-up for final participant). REACT supporters were available on weekdays 9 am to 4.30 pm excluding public holidays and university closures. Participants were advised to use the intervention as they needed, and emailed reminders (which they could turn off) to visit the website after a week of inactivity.

**Resource directory (RD)** The resource directory (RD) contained a comprehensive list of national organisations supporting people with psychosis or bipolar and their relatives (such as Rethink, Mind, Carers UK and Bipolar UK), and those for related conditions (such as Anxiety UK and Samaritans (voluntary crisis helpline for people feeling suicidal)). The RD also listed UK government websites offering information and guidance about mental health and related topics, such as NHS Choices, Care Quality Commission, NICE Guidelines and the Department of Work and Pensions, and gave contact details for emergency services, including local NHS mental health services out-of-hours crisis teams. At the end of the study the RD-only participants were given access to the modules, without the forum or direct messaging.

**Costing the interventions**

We assessed all costs relevant to content development for REACT and the RD.

Development costs included: Conception and design of the toolkit; Consultation with service users, relatives and professionals to identify user requirements; Staff time to develop content; Production of videos and images; Design and development of the website; Website infrastructure during development. Delivery costs were computed for a 6-month period (time spent in the trial) and included general infrastructure for hosting the REACT website and the costs of training, supervision, and employment of REACT supporters for 6 months. The costs of developing and delivering the RD were also calculated and half allocated to the intervention arm, and half to the comparator arm.

**Data collection process**

At baseline, participants completed all measures before being randomised. Participants were sent £10 shopping voucher on completion of measures at baseline and 12 week follow up, and £10 or £20, conditional or unconditional on completion at 24 week follow up (secondary randomisation as part of study within a trial SWAT65 [https://bit.ly/2WCDMqU](https://bit.ly/2WCDMqU)).

Partway through the study (8th of September 2017 to 23rd of February 2018), a subgroup of participants were invited to take part in topic guided qualitative interviews (conducted by telephone / video-conferencing) to understand their experiences of using REACT. This sample was randomly selected from a pool of 76 people who had a) been randomized to the intervention arm, b) completed 24 week follow-up at the point of data collection, and c) had consented to be contacted about further research across different levels of use of REACT. All interviews were recorded and transcribed for analysis. A diagram of pathway through the study is given in the protocol [38].

**Outcomes**

All outcomes were validated self-report questionnaires collected online using a closed system, presented in order of priority (primary outcome first) at baseline, 12 and 24 week follow-ups. The primary outcome was relatives’ distress at 24 weeks, assessed using the GHQ-28 with Likert scoring (0–3) [44]. Subscales include somatic symptoms, anxiety / insomnia, social dysfunction, and severe depression. Higher score indicates greater distress (score range 0–84).

Secondary outcomes included the relatives’ experience of caring, assessed online at 24-week follow-up using the Carer Wellbeing and Support (CWS) questionnaire [45]; and distress (GHQ-28) and carer experience (CWS) assessed online at 12-week follow-up. CWS provided total wellbeing scores (possible range 0–128), based on levels of concern over the previous 4 weeks about the impact of caring responsibilities on: day-to-day life (e.g. ‘During the past 4 weeks how concerned were you that your caring responsibilities stopped you from having enough time to yourself?’); relationship with the person being cared for; relationship with family and friends; financial situation; physical health; emotional wellbeing; stigma and discrimination; their own safety; the safety of the person they care for. CWS also provided total satisfaction with support from services (possible range 0–51), which assessed how satisfied the relatives were with the information and advice they have received (e.g. ‘In general, how satisfied are you that you have enough information about the condition/illness of the person you care for/support to enable you to feel confident in caring for them/providing support?’); involvement in treatment and care planning; and support from staff. Higher scores indicate better outcome.

Website usage data for each participant was downloaded from the intervention site and summarised for participants in each intervention group.

Participants in the REACT intervention group were asked to rate the following statements at 12 and 24 weeks post-randomisation (based on previously published studies) [46].
• “I always feel supported by the REACT supporters”
• “I always feel supported by the REACT group”
• “I always feel the REACT site was a safe and confidential environment”.

Options for each answer were “strongly disagree”, “disagree”, “agree”, and “strongly agree”.

Qualitative interviews
Open questions explored relatives’ general experiences of REACT, factors influencing levels of use, which parts of REACT were used, experience of peer support from REACT and any suggestions for improvements.

Safety and adverse events
We assessed the number of low-risk (clear evidence of distress or concerns of risk of harm or abuse towards participants or others, but no immediate or serious threat of severe harm, risk to life or child welfare) and high-risk events (clear evidence of immediate risk to life or child welfare). Risks were identified via online questionnaire red flag items, posts on the REACT forum, direct messages to REACT supporters and by the trial manager during email or telephone participant contact. High-risk events were classed as study adverse events.

Statistical analysis
Based on data from a feasibility study [6], and in accordance with the rationale detailed in the protocol paper [47], we aimed to recruit 666 relatives of people with psychosis or bipolar to test the primary hypothesis of a mean difference $\geq 5.0$ in GHQ score between arms, assuming a standard deviation of 16.6 units ($p < 0.05$) at 24-weeks follow-up, and with 70% retention.

Mean scores were compared between groups using analysis of covariance (ANCOVA) adjusting for baseline scores and including all participants according to the randomisation scheme. A joint modelling approach was used to assess differences in longitudinal outcomes between the randomised arms adjusted for missingness (at 12-week or 24-week follow-up).

Additional multivariable analyses, using forward step-wise selection and adjusting for baseline GHQ-28 were conducted to identify significant baseline predictors of outcome.

Instrumental variable regression was carried out to estimate the impact of intervention use (number of web page downloads) on outcome. A two-stage least squares estimator (2SLS) was used: the first stage was to fit a model regressing web page downloads on randomisation and the second stage was to regress GHQ-28 at 24 weeks on the fitted values of web page downloads predicted in the previous step. The model was adjusted for baseline GHQ-28 score. All analyses were done using SAS statistical analysis software, version 9.4 and Stata version 14.

Qualitative analysis
Following the framework approach described by Ritchie and Spencer [48], broad themes were created a priori, based on the research team’s interest in understanding how participants experienced the REACT toolkit, including patterns of use and experience of the website, and how the toolkit could be improved. The framework evolved during familiarisation and indexing to incorporate additional issues raised by participants.

Results
The flow diagram (Fig. 1) shows recruitment and retention throughout the study. There were 4348 registration page visits. Of 3287 people who completed eligibility screening, 1416 failed on at least one criterion, with 1146 (81%) of these failing to report higher than usual levels of distress. Of the 1528 (46%) who subsequently provided consent for the study, 807 completed baseline measures and 800 (52% of those consenting) were randomised. Unfortunately due to an administrative error, detailed web usage data was not collected from the outset and so was only available for 700 of the 800 participants (REACT = 348; RD only = 352). There were nine instances of unblinding in total.

Baseline demographic and situational characteristics of the participants are presented in Table 1.

Participants were typically middle aged (53% aged 40–60), white British (91%), female (81%), mothers (48%), and highly educated (55% to university level). The majority were supporting young adults aged 35 or less (61%), more than half of whom (58%) had a diagnosis of bipolar. Most were supporting only one person with a mental health problem, but 26% reported supporting two or more people, and 57% had other dependents. Some 61% were married or in a civil partnership. Most were in full-time, part-time or voluntary work (64%) but 8% reported being unable to work specifically due to their caring responsibilities. All except four participants had home internet access.

Baseline, 12 and 24 week scores are presented in Table 2. Relatives reported very high levels of distress at baseline (mainly due to the inclusion criteria on GHQ-28 score). 784 of the 800 (89%) scored at or above 24, generally considered to be a screening threshold for psychiatric caseness [49, 50]. Highest scores were on the anxiety/insomnia subscale.

Mean wellbeing scores on CWS were in the 50s at baseline (possible range is 0–128, higher scores indicate greater wellbeing). Mean support scores at baseline were below 20 in each group (possible range 0–51, higher scores indicate greater support). Although there are no
clinical thresholds for CWS, wellbeing and support scores were very low compared to other studies of groups of relatives of people with psychosis [6, 51, 52].

Taking into account full costs of development and delivery (shown in Table 3), REACT cost £142.95 per person, and RD only £0.84. Most of these costs were development; ongoing delivery would cost £62.27 for REACT and £0.43 for RD.

The median time spent online on REACT was 50.8 min (IQR 12.4–172.1) compared to 0.5 min (IQR 0–1.6) on RD only. REACT was accessed more outside traditional working hours (9 am–5 pm Monday to Friday excluding public holidays) (median 33.6 min (IQR 7.2–10.2)) than during (median 24.5 min (IQR 4.8–64.9)). The most popular module was the online forum (60% REACT participants visited at least once). However, of the 207 visitors, only 67 were actively posting, with a mean number of 9.8 (SD 25.9) posts each. The least popular were “Recovery: looking to the future” and “Managing stress; thinking differently” (31% visited). Detailed descriptions of REACT module levels of use are shown in Table 4.

Retention to the primary outcome was 74% at 12 weeks, and 75% at 24 weeks (REACT n = 292 (73.2%); RD-only n = 307 (76.6%)). Similar numbers of participants dropped out in each arm, but those who dropped out in the REACT arm were more distressed than those who remained. The joint model estimates that the REACT arm participants who dropped out were on average 0.33 (95% CI -0.27–0.93, p = 0.279) GHQ units more distressed than those who did not drop out; note however that this is the average over the entire 24-week period, i.e. this model assumes that the difference in distress between those REACT participants who did and did not drop out was constant over the entire period. In the RD only arm, the equivalent result for those who...
## Table 1 Demographic and situational characteristics of participants

|                     | REACT n = 399 | RD n = 401 | Overall n = 800 |
|---------------------|--------------|------------|-----------------|
| **Age (years)**     |              |            |                 |
| < 30                | 39 (9.77)    | 36 (8.98)  | 75 (9.38)       |
| 30–39               | 50 (12.53)   | 73 (18.20) | 123 (15.38)     |
| 40–49               | 95 (23.81)   | 104 (25.94)| 199 (24.88)     |
| 50–59               | 111 (27.82)  | 112 (27.93)| 223 (27.88)     |
| 60–69               | 88 (22.06)   | 61 (15.21) | 149 (18.63)     |
| ≥ 70                | 16 (4.01)    | 15 (3.74)  | 31 (3.88)       |
| **Mean (SD)**       | 49.4 (13.3)  | 47.9 (12.7)| 48.6 (13.00)    |
| **Range (min–max)** | 16–84        | 18–86      | 16–86           |
| **Gender**          |              |            |                 |
| Male                | 82 (20.55)   | 69 (17.21) | 151 (18.88)     |
| Female              | 317 (79.45)  | 331 (82.54)| 648 (81.00)     |
| Missing             | 0 (0.00)     | 1 (0.25)   | 1 (0.13)        |
| **How many people do you support?** | | | |
| 1                   | 296 (74.19)  | 295 (73.57)| 591 (73.88)     |
| 2                   | 68 (17.04)   | 72 (17.96) | 140 (17.50)     |
| 3                   | 20 (5.01)    | 21 (5.24)  | 41 (5.13)       |
| ≥ 4                 | 15 (3.76)    | 13 (3.24)  | 28 (3.50)       |
| **Relationship to service user** | | | |
| Mother              | 187          | 200        | 387             |
| Father              | 17           | 10         | 27              |
| Partner             | 149          | 143        | 292             |
| Daughter            | 56           | 62         | 118             |
| Son                 | 6            | 1          | 7               |
| Sibling             | 41           | 38         | 79              |
| Friend              | 31           | 26         | 57              |
| Grandparent         | 8            | 2          | 10              |
| Wider family member | 17           | 17         | 34              |
| Other               | 10           | 12         | 22              |
| Undefined           | 38           | 52         | 90              |
| **Ethnicity**       |              |            |                 |
| White British       | 361 (90.48)  | 366 (91.27)| 727 (90.88)     |
| White Irish         | 5 (1.25)     | 6 (1.50)   | 11 (1.38)       |
| Any other white background | 15 (3.76) | 13 (3.24) | 28 (3.50) |
| Mixed               | 6 (1.50)     | 6 (1.50)   | 12 (1.50)       |
| Asian or Asian British | 11 (2.76)  | 3 (0.75)   | 14 (1.75)       |
| Other Ethnic group  | 1 (0.25)     | 5 (1.25)   | 6 (0.75)        |
| Rather not say      | 0 (0.00)     | 2 (0.50)   | 2 (0.25)        |
| **Marital status**  |              |            |                 |
| Single              | 88 (22.06)   | 77 (19.20) | 165 (20.63)     |
| Married             | 219 (54.89)  | 239 (59.60)| 458 (57.25)     |
| Civil partnership   | 14 (3.51)    | 13 (3.24)  | 27 (3.38)       |
| Separated           | 8 (2.01)     | 15 (3.74)  | 23 (2.88)       |
| Divorced            | 47 (11.78)   | 40 (9.98)  | 87 (10.88)      |
did/not drop out = 0.12 (95% CI -0.52–0.77, \( p = 0.707 \)). This meant that data could not be assumed to be missing at random.

Relatives’ distress decreased significantly in both groups by 24 weeks (GHQ-28; average daily reduction = \(-0.06\), 95% CI = \(-0.06, -0.05\), \( p < 0.001 \)). The estimated mean difference between the two groups on the primary outcome at 24 weeks favoured REACT but was small (\(-1.39\), 95% CI = \(-3.60, 0.83\)) and not statistically significant (\( p = 0.2189 \)). At 12 weeks’ follow-up, GHQ-28

| Table 1 Demographic and situational characteristics of participants (Continued) |
|-----------------------------------------|-----------------|-----------------|
|                                        | REACT n = 399   | RD n = 401      | Overall n = 800 |
| Widowed                                 | 10 (2.51)       | 8 (2.00)        | 18 (2.25)       |
| Rather not say                          | 13 (3.26)       | 9 (2.24)        | 22 (2.75)       |
| Living arrangements                      |                |                |
| Spouse or partner                       | 275 (68.92)     | 289 (72.07)     | 564 (70.50)     |
| Living alone                            | 82 (20.55)      | 80 (19.95)      | 162 (20.25)     |
| Parent(s)                               | 17 (4.26)       | 11 (2.74)       | 28 (3.50)       |
| Other                                   | 20 (5.01)       | 17 (4.24)       | 37 (4.63)       |
| Rather not say                          | 5 (1.25)        | 4 (1.00)        | 9 (1.13)        |
| Dependents                               |                |                |
| None                                    | 168 (41.90)     | 175 (43.86)     | 343 (42.88)     |
| 1                                       | 99 (24.69)      | 117 (29.32)     | 216 (27.00)     |
| 2                                       | 91 (22.69)      | 57 (14.29)      | 148 (18.50)     |
| 3                                       | 30 (7.48)       | 28 (7.02)       | 58 (7.25)       |
| ≥ 4                                     | 13 (3.26)       | 22 (5.49)       | 35 (4.38)       |
| Highest education level                 |                |                |
| School level                            | 65 (16.29)      | 73 (18.20)      | 138 (17.25)     |
| Further education (college)             | 108 (27.07)     | 117 (29.18)     | 225 (28.13)     |
| Higher (University)                     | 226 (56.64)     | 211 (52.62)     | 437 (54.63)     |
| Employment status                       |                |                |
| Employed full-time (35 h + a week)      | 150 (37.59)     | 151 (37.66)     | 301 (37.63)     |
| Employed part-time                      | 92 (23.06)      | 96 (23.94)      | 188 (23.50)     |
| Unable to work due to caring responsibilities | 33 (8.27) | 33 (8.23) | 66 (8.25) |
| Unable to work due to ill health/disability | 30 (7.52) | 20 (4.99) | 50 (6.25) |
| Unemployed                              | 10 (2.51)       | 8 (2.00)        | 18 (2.25)       |
| Student                                 | 7 (1.75)        | 8 (2.00)        | 15 (1.88)       |
| Retired                                 | 53 (13.28)      | 58 (14.46)      | 111 (13.88)     |
| Voluntary work                          | 12 (3.01)       | 11 (2.74)       | 23 (2.88)       |
| Housewife/house husband                 | 12 (3.01)       | 16 (3.99)       | 28 (3.50)       |
| Home internet access                    |                |                |
| Yes                                     | 395 (99.00)     | 400 (99.75)     | 795 (99.38)     |
| No                                      | 1 (0.25)        | 0 (0.00)        | 1 (0.13)        |
| Intermittent or poor quality            | 3 (0.75)        | 1 (0.25)        | 4 (0.50)        |
| Paid work affected by caring role       |                |                |
| No, I didn’t have paid work before      | 120 (30.08)     | 125 (31.17)     | 245 (30.63)     |
| No, I still perform the same amount of paid work | 198 (49.62) | 195 (48.63) | 393 (49.13) |
| Yes, I stopped work completely          | 40 (10.03)      | 33 (8.23)       | 73 (9.13)       |
| Yes, I reduced my working hours         | 41 (10.28)      | 48 (11.97)      | 89 (11.13)      |
| Mean (SD)                               | 13.5 (9.3)      | 11.4 (6.6)      | 124 (8.0)       |
| Min–max                                 | 2–48            | 1–30            | 1–48            |
scores were lower in REACT than in RD (−2.08, 95% CI = −4.14, −0.03), and although statistically significant (p = 0.027), this was likely to be of limited clinical significance. After accounting for missing data in a longitudinal model, there was no significant difference between the REACT and RD arms over the 24-week follow-up period (−0.56, 95% CI = −2.34, 1.22, p = 0.51).

When adjusting for baseline GHQ-28, being male, single, and unemployed (or in unpaid work) were all significantly associated with greater levels of distress at 24 weeks (Table 5).

Table 2 Baseline, 12 and 24 week scores: values are mean (SD) unless stated otherwise

| GHQ-28 | REACT | RD | Total |
|--------|-------|----|-------|
| Baseline | 40.3 (14.6) | 40.0 (14.0) | 40.2 (14.3) |
| 12 weeks | 30.6 (15.2) | 32.9 (15.4) | 31.8 (15.3) |
| 24 weeks | 29.6 (15.9) | 31.3 (15.2) | 30.5 (15.6) |

| GHQ-28 subscales | Somatic symptoms | Anxiety/insomnia | Social dysfunction: note that values are median (IQR) | Severe depression: note that values are median (IQR) | CWS - wellbeing | CWS - support |
|------------------|-----------------|-----------------|---------------------------------|------------------|----------------|----------------|
| Baseline | 10.3 (4.4) | 13.0 (4.1) | 11 (8–13) | 4 (1–9) | 55.9 (25.9) | 19.5 (11.6) |
| 12 weeks | 8.1 (4.3) | 9.5 (4.7) | 8 (7–11) | 2 (0–7) | 72.0 (27.0) | 26.0 (12.0) |
| 24 weeks | 7.9 (4.7) | 9.2 (4.9) | 8 (7–11) | 2 (0–6) | 77.0 (26.6) | 25.7 (11.7) |

The proactive support from REACT supporters was appreciated, as was the opportunity to learn through a variety of different media (text, video, forum).
### Table 3 Development costs for REACT and RD

| REACT Development | Type of cost | Total no. of hours or units | Cost per hour or unit | Total      |
|-------------------|--------------|----------------------------|-----------------------|------------|
| Content generation| Staff        |                            |                       |            |
|                   | Professor of clinical psychology | 54 h                   | £55.81                | £3013.74   |
|                   | Clinical psychologist            | 17 h                   | £29.66                | £504.22    |
|                   | Research assistant               | 18 h                   | £10.08                | £181.44    |
|                   | Relatives                        |                        |                       |            |
|                   | Relative co-applicant             | 29 h                   | £20                   | £580       |
|                   | Relatives in focus groups and advisory role | 118 h | £10 | £1180 |
|                   | Relatives travelling              | 23 persons             | £5                    | £115       |
| Producing videos and images | Staff        |                            |                       |            |
|                   | Research fellow                  | 450 h                  | £23.76                | £10,692    |
|                   | Research assistant               | 157.5 h                | £15.83                | £2493      |
|                   | Information officer              | 37.5 h                 | £30.43                | £1141.13   |
|                   | Communications and information manager | 56.25 h | £31.36 | £1764 |
|                   | Actors                            |                        |                       |            |
|                   | Relatives                         | 11 persons             | £20/person            | £220       |
| Developing and designing the website | Staff        |                            |                       |            |
|                   | Professor of clinical psychology | 36 h                   | £55.81                | £2009.16   |
|                   | Professor of clinical psychology | 26 h                   | £69.80                | £1814.80   |
|                   | Professor of psychiatry           | 26 h                   | £68.00                | £1768.00   |
|                   | Research assistant               | 10 h                   | £12.29                | £122.90    |
|                   | Digital technologist/web developer | 225 h | £23.05 | £5186.25 |
|                   | Relatives                         |                        |                       |            |
|                   | Relatives’ focus groups           | 56 h                   | £20                   | £1120.00   |
|                   | Other relatives                   | 8 h                    | £59.81                | £478.48    |
| Website infrastructure during development (until going live) | |                        |                       |            |
|                   | Domain name                       |                        | £9                    | £9         |
|                   | SSL certificate fees              |                        | £30                   | £30        |
|                   | Web hosting and exclusive IP address |                 | £100                 | £100       |
|                   | Website development               |                        | £27,900               | £27,900    |
|                   | Total                             |                        | £64,535.99            | £64,535.99 |

| REACT Delivery | Type of costs | Total no. of hours or units | Cost per hour or unit | Total      |
|----------------|--------------|----------------------------|-----------------------|------------|
| General infrastructure for hosting REACT | | | | £5119 |
| Digital technology/web developer | | 180 h | £23.05 | £4149 |
| Secure web hosting and exclusive IP address | | 6 months | £100 | £600 |
| Software for bulk emails | | 2 blocks | £185 | £370 |
| Training, supervision and employment (6 months) of REACT supporters | | | | £20,813.05 |
| REACT supporters | | 756 h | £15.83 | £11,967.48 |
| Back-up REACT supporter | | 94 h | £13.52 | £1270.88 |
| Expert relative REACT supporter | | 47 h | £20 | £940 |
| Supervision | | 33 h | £64.71 | £2135.52 |
Mother, 65: So I got the responses from the REACT supporters about ... how to navigate the system differently and language to use and so on and so forth, and then [from] people who had had much worse experiences than my experience. So it was that ability to connect with people who kind of have some empathy with what’s going on in your life and how difficult it can be in those moments.

Sister, 26: The videos were really helpful because it wasn't constant reading so I like that. I loved the depth of information that was available. The layout itself was absolutely great as well, it was easy to read, it was eye-catching enough and quite interactive as well ... The opportunity for me to be able to write notes and things like that, I thought that was really, really good.

A consistent message was that REACT would be most useful to relatives early in the recovery journey, when they were likely to be seeking information and strategies.

Female partner, 43: We only had a diagnosis last year, so actually I was really desperate for any resources and any further information that I could find, so I was literally soaking everything up as much as I could, and I found REACT through Bipolar UK and ... it has been really helpful because I think what I really struggled to find was anybody else in a similar situation who had a recent diagnosis, you know early forties and [with] a young family

Some relatives found seeking help for their own needs difficult, and most relatives found prioritising time to use REACT difficult.

Mother, 57: I was engaging with it [REACT] and then he then went into crisis and then went into hospital and in fact he was in hospital until the following January, and I was then caught up in that. And then you know after that I needed reminders. So I think that’s your difficulty really, is that the very people that you’re trying to help have so much on their plates really.
| Module | Topic | Total time spent on page per person (mins) | Number of people who accessed page | Total time (across all participants) | Mean time on page per person (STD) | Median time on page per person (IQR) | Min – max time spent on page |
|--------|-------|------------------------------------------|-----------------------------------|--------------------------------------|-----------------------------------|-----------------------------------|-----------------------------|
| MODULE 1 - What is psychosis | | | 205 | 188.4 | 11.4 (13.1) | 1.4 (0.5, 5.5) | 0, 55.8 |
| MODULE 2 - What is bipolar disorder | | | 203 | 158.7 | 14.6 (17.4) | 8.2 (2.3, 20.4) | 0.1, 97.4 |
| MODULE 3 - Managing positive symptoms | | | 163 | 167.1 | 13.1 (15.6) | 5.7 (1.8, 20.4) | 0, 75.8 |
| MODULE 4 - Managing negative symptoms | | | 153 | 127.5 | 14.2 (23.2) | 4.6 (1.2, 18.1) | 0.1, 167.3 |
| MODULE 5 - Managing mood swings | | | 134 | 64.3 | 7.3 (10.4) | 3.4 (0.8, 8.6) | 0.1, 59.1 |
| MODULE 6 - Dealing with difficult situations | | | 145 | 117.6 | 11.8 (14.5) | 6.3 (1.6, 16.3) | 0.1, 75.3 |
| MODULE 7 - Managing stress - doing this differently | | | | | | | |
| MODULE 8 - Managing stress - thinking differently | | | 108 | 78.9 | 11.7 (22.6) | 3.9 (0.4, 14.4) | 0, 136 |
| MODULE 9 - Understanding mental health services | | | | | | | |
| MODULE 10 - Treatment options | | | | | | | |
| MODULE 11 - Dealing with crises | | | | | | | |
| MODULE 12 - Recovery: looking to the future | | | | | | | |
| FORUM | | | | | | | |
In the first randomised controlled trial of a digital intervention to support relatives of people with psychosis or bipolar, the Relatives Education And Coping Toolkit (REACT), including 12 psychoeducation modules, a moderated online forum, confidential direct messaging service, and a comprehensive Resource Directory was compared to the Resource Directory only. Relatives reported high levels of distress (GHQ-28 primary outcome) at baseline, which reduced significantly in both groups over the 24 weeks follow-up period, but there was no difference between the groups at follow up. Carer wellbeing and support scores (CWS) were very low at baseline and increased significantly in both groups, with no significant differences between groups. Changes over time may reflect regression to the mean. There were no adverse events: relatives using REACT reported feeling safe and supported, and qualitative experiences of using REACT were positive.

REACT offers an inexpensive, safe and acceptable way to deliver NICE recommended information and support to relatives of people with severe mental health problems, but there was no evidence that it reduces distress more effectively than a comprehensive resource directory. These findings are consistent with previous studies showing that in general, interventions designed to improve outcomes for relatives are less effective for those with higher levels of distress [26]. This may be due to the impact of other life challenges that cause distress and therefore impact on GHQ scores, but are unrelated to the caring role, including being male, single, and not in paid work, which were significant predictors of the primary outcome but which are unlikely to be addressed by carer interventions such as REACT. Targeting relatives with lower levels of generic distress or using a more specific measure of distress associated with caring may have led to different outcomes. Another possible explanation for lack of a significant clinical effect of REACT is low levels of website use compared to carer support delivered face-to-face. This pattern of use is consistent across digital health interventions and may paradoxically stem from their inherent flexibility of digital interventions [53]. REACT was accessible at any time, and relatives were given no expectations of times, levels, or order of use. The REACT Supporters proactively engaged with activity on the forum and direct messages, but use of the psychoeducational modules was unsupported. Clearer expectations of use and feeling accountable to a supporter may have enhanced engagement.

Strengths and limitations
This trial was rigorously conducted, with a large, broadly recruited sample, clearly defined and theoretically based supported intervention, an active control group, good follow-up rate for an online trial, web-based randomisation, robust blinding, and a pre-published analysis plan that appropriately addressed missing data. The key limitations were: failure to recruit more men and people from ethnic minority groups, which limits the generalisability of the findings; and (with hindsight) the inclusion of GHQ-28 minimal score as an inclusion criterion, which limited the sample to highly distressed relatives, increasing the likelihood of regression to the mean in both arms of the study over the follow-up period. Non-random dropout (greater in participants with higher baseline GHQ-28 scores) further limited the potential to identify group differences, though this was robustly dealt with using a joint modelling approach.

### Table 4

| Parameter                                      | Mean time on page per person (STD) | Median time on page per person (IQR) | Min – max time spent on page |
|------------------------------------------------|-----------------------------------|-------------------------------------|------------------------------|
| Mean time on page per person (STD)            | 65.0 (201.2)                      | 12.1 (2.2, 58.4)                    | 0, 2553.8                    |
| Median time on page per person (IQR)          | 12.1 (2.2, 58.4)                  | 0.7 (0.2, 7.2)                      |                              |
| Min – max time spent on page                  | 0, 2553.8                         | 0, 260.7                            |                              |

### Table 5

| Covariate                                      | Coefficient (95% CI) | p-value |
|------------------------------------------------|----------------------|---------|
| Treatment                                      | –1.48 (–3.80, 0.85)  | 0.2121  |
| Baseline GHQ-28                                | 0.51 (0.42, 0.59)    | <.0001  |
| Gender (Male vs. reference category: Female)   | 3.39 (0.27, 6.51)    | 0.0334  |
| Marital status (Married/civil partnership vs. reference category: Single/divorced/separated/widowed) | –3.65 (–6.11, –1.18) | 0.0038  |
| Employment (reference category: None/unpaid)   | –2.10 (–5.11, 0.91)  | 0.0039  |
| Part-time                                      | –4.60 (–7.30, –1.90) |         |

Number included in analysis - REACT: N = 292; RD: N = 307
Implications for future research

The findings highlight two key lessons for research in digital health interventions. The first is that we cannot assume that online interventions adapted from those delivered face-to-face will be equally effective. REACT draws on evidence based cognitive behavioural interventions [34], and was shown to be effective in reducing distress when offered in paper form and supported by telephone by staff linked to the relevant clinical team [6]. It is not possible to determine in this study whether the lack of an effect is due to delivering REACT online, supporting REACT online with trained relatives, or the higher levels of relatives’ distress at baseline.

The second is that we need new methodologies appropriate to the rigorous evaluation of digital health interventions. They must be controlled: without an active control group, a post-evaluation of REACT would have made it appear very effective. They must account for higher levels of dropout and missing data: without accounting for non-random missing data, REACT would have appeared a more effective intervention than REACT only in improving relatives’ support. However, they also need to allow a more flexible iterative development of the technology in response to feedback, to test the technology as one component of a much broader care package within context, and to establish which part of an intervention has what effect on which people. In this study, REACT remained relatively fixed throughout the trial (excluding updating directory for accuracy), despite ongoing feedback about ways it could have been improved, and general advances in website design. We also do not understand exactly what relatives did in response to using REACT or the RD. In particular, whether or not they sought support from organisations recommended in the RD or how effective this was. Alternative methodologies such as iterative testing and adaptation suggested by Mohr et al., [54] or those based on realist approaches [55] may offer useful ways forward.

Conclusions

 Relatives need access to information and emotional support. REACT offers an inexpensive, safe and acceptable way to deliver this, even if it does not reduce their distress. Therefore, REACT should continue to be developed in light of user feedback, and offered and evaluated as one component of a comprehensive care package, which includes face-to-face support.

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Authors’ contributions

The first author (FL) is the study Chief Investigator who led the study and writing of this paper. All other authors are listed alphabetically and their role described. SJ1, SJ2, EM, and PW were co-applicants and designed, and managed the study including securing funding. SD led the design of the statistical analysis and oversaw the work of AR-H and NR to carry out the data management and analysis processes. SJ2, WS and LM supervised the REACT Supporters (SF, LC, NA). DA and AW designed and maintained IT systems for the trial including delivery of REACT and collection of data online. HR was the trial manager; BM and NA supported the administration and trial management. CM developed and carried out the Health Economics analysis for the trial, supported by LH. KP conducted and analysed qualitative interviews. All authors contributed to the writing of the paper and approved the final version.

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Availability of data and materials

The CTRC trial statisticians had access to the data throughout the trial. A de-identified version of the dataset will be transferred to the sponsor (Lancaster University) by March 31 2020. Ownership of copyright and intellectual property rights for all research conducted for the REACT study will ultimately be held by Lancaster University. We intend to make available individual participant data that underlie the results reported in this article, after de-identification. Data will be made available on request 12 months following article publication, and only to researchers who provide a methodologically sound proposal and where the proposed use of the data has been approved by an independent ethics review committee (“learned intermediary”) identified for this purpose. Proposals should be directed to rdm@lancaster.ac.uk. Data will be available for 10 years at Lancaster University’s Research Directory (https://doi.org/10.17635/lancaster/researchdata/306).

Ethics approval and consent to participate

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All participants gave written informed consent and all procedures were approved by Lancaster National Research Ethics Service committee (15/NW/0732).

Consent for publication

Not applicable.

Competing interests

Some members of the applicant team (FL, SJ1, SJ2, LC) were involved in developing REACT. This study is therefore not an independent evaluation. BH has been a NIHR HS&DR commissioned board member and PW reports additional grants from NIHR for other studies, and NIHR funding for The Clinical Trials Research Centre during conduct of this study.

Abbreviations

REACT: Relatives’ Education And Coping Toolkit; RD: Resource Directory; GHQ: General Health Questionnaire; NICE: National Institute for Health and Clinical Excellence; NHS: National Health Service; TM: Trial Manager; CWS: Carer Wellbeing & Support scale
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