Online randomised controlled trial to evaluate the clinical and cost-effectiveness of a web-based peer-supported self-management intervention for relatives of people with psychosis or bipolar disorder: Relatives' Education And Coping Toolkit (REACT)

Keywords

Mental health, relatives, carers, digital, online, psychoeducation, peer support

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Competing interests

Fiona Lobban reports grants from NIHR Health Technology Assessment (HTA) during the conduct of the study. The study evaluates the clinical and cost effectiveness of REACT; Fiona Lobban and Lesley Chapman were involved in the design and development of REACT and hence this is not an independent evaluation. Bruce Hollingsworth reports he was an NIHR HS&DR commissioned board member (term complete). Paula Williamson reports grants from NIHR, other funding from NIHR, during the conduct of the study.

The background intellectual property (IP) for the content of the paper-based version of REACT was originally held by Lancashire Care NHS Foundation Trust, which sponsored the feasibility trial. This IP was given freely to Lancaster University to develop the foreground IP for the online REACT site, with the understanding that, should the intervention be shown to be effective, further collaboration for delivery of REACT would first be explored with them as clinical host.

Abstract

Background Relatives caring for people with severe mental health problems find information and emotional support hard to access. Online support for self-management offers a potential solution.

Objective To determine the clinical and cost-effectiveness of an online supported self-management tool for relatives, the Relatives' Education And Coping Toolkit (REACT).

Design A primarily online, single-blind, randomised controlled trial, comparing REACT plus a resource directory (RD) and treatment as usual (TAU), against the RD and TAU only, by measuring user distress and other wellbeing measures at start, 12 and 24 weeks.

Participants 800 relatives across UK, aged 16 or over, with high levels of distress, access to Internet, and actively seeking help.

Intervention REACT comprised 12 psychoeducation modules, peer support through a group forum, confidential messaging, and a comprehensive RD of national support. Trained relatives moderated the forum and responded to messages.

Main outcome measure Participants' distress, measured by the General Health Questionnaire (GHQ-28).

Results Recruitment was via study website. Various online and offline strategies including social media directed potential participants to the site. Participants were randomised into two groups: REACT plus RD (n=399) or RD only (n=401).

Retention at 24 weeks was 75% (REACT n=292; RD-only n=307).

Mean GHQ-28 scores fell substantially across both groups over 24 weeks, from mean 40.2, standard deviation (SD) 14.3 to mean 30.5, SD 15.6, with no significant difference between groups (-1.39, 95% CI -3.60–0.83, p=0.22).

At 12 weeks GHQ-28 scores were lower in the REACT arm than in RD-only (-2.08, 95% CI -4.14– -0.03, p=0.027), but of likely limited clinical significance. Accounting for missing data, which was associated with higher distress in the REACT arm (0.33, 95% CI -0.27–0.93, p=0.279), in a longitudinal model, there was no significant difference between groups over 24 weeks (-0.56, 95% CI–2.34–1.22, p=0.51).

REACT cost £142.95 per participant to design and deliver (£62.27 delivery only) against £0.84 for RD-only. Health economic analysis of NHS, health and personal social services outcomes found REACT to have higher costs of £286.77, slightly better GHQ scores (incremental GHQ adjusted for baseline, age and gender: -1.152, 95% CI -3.370–1.065), and slightly lower QALYs than RD-only; none of these differences was statistically significant.

Median time spent online was 50.8 minutes for REACT (IQR 12.4–172.1) with no significant association against outcome. Participants reported finding REACT a safe, confidential environment (96%), and feeling supported by the forum (89%) and REACT supporters (86%). No serious adverse events reported.

Limitations Predominantly white British female sample; 25% lost to follow-up; dropout in the REACT group was not random.

Conclusions An online self-management support toolkit with moderated group forum is acceptable to relatives and, compared to face-to-face programmes, offers inexpensive, safe delivery of NICE-recommended support to engage relatives as peers in care delivery. However, currently, REACT plus RD is no more effective in reducing relatives' distress than RD-only.

Future work Further research in improving the effectiveness of online carer support interventions.

Study registration ISRCTN72019945

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[495 words]

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Alphabetical list of abbreviations

ACME	Average causal mediated effect
ANCOVA	Analysis of covariance
Brief IPQ	Brief Illness Perception Questionnaire
CCG	Clinical commissioning group
CEAC	Cost-effectiveness acceptability curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHERRIES	Checklist for Reporting Results of Internet E-Survey
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CSRI	Client Service Receipt Inventory
CWS	Carer well-being and support questionnaire
DHI	Digital health intervention
DMEC	Data monitoring and ethics committee
EIP	Early intervention for psychosis
EQ-5D-5L	See glossary
GHQ-28	General Health Questionnaire (28 question version?)
HS&DR	Health services and delivery research
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IP	Internet protocol
IQR	Interquartile range

IV	Instrumental variable
ivreg	Instrumental-variable regression
Liverpool CTRC	Liverpool Clinical Trials Research Centre
MANOVA	Multivariate analysis of variance
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PIC	Participant identification centre
PPI	Patient and public involvement
QALY	Quality-adjusted life year
RAG	Relatives' advisory group
RCT	Randomised controlled trial
RD	Resource directory
REACT	Relatives' Education And Coping Toolkit
SD	Standard deviation
SE	Standard error
SSL	Secure sockets layer
SWAT	Study within a trial
TAU	Treatment as usual
TM	Trial manager
TMG	Trial management group
TSC	Trial steering committee

Glossary

Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject who has been administered a health intervention but which does not necessarily have a causal relationship with this treatment.

ANCOVA: A model that evaluates whether the means of a dependent variable (DV) are equal across levels of a categorical independent variable (often called the treatment), while statistically controlling for the effects of covariates – other continuous variables that are not of primary interest.

Bipolar disorder: A mood disorder characterised by periods of low mood (depression) and periods of elevated mood (hypomania, or mania).

Brief COPE: A shorter version of the COPE inventory, a questionnaire designed to assess a broad range of the subject's coping responses.

CONSORT-EHEALTH: A checklist designed to standardise the running of randomised controlled trials for digital health interventions.

Covariance: A measure of the joint variability of two random variables.

Digital health intervention: Interventions delivered via digital technologies such as smartphones, website, text messaging.

eHealth: Alternative term for digital health intervention.

EQ-5D-5L: Measure of health-related quality of life developed by the EuroQol Group (EQ). The latest version assesses five dimensions (5D): mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Ratings can be given for each across five levels of severity (5L).

Family intervention: Structured help and support for carers and family members of a person with a mental health problem, either individually or together, delivered by health professionals.

Instrumental variable: A variable measure used to estimate a causal relationship when a treatment is not delivered to every participant in a randomised controlled trial.

Likert scale: A psychometric scale used in research questionnaires, measuring levels of agreement or disagreement with a given statement.

Lurking: Spending time on an online forum or social media, reading posts without posting oneself.

Mediator: Variable measure posited to explain the relationship between an independent variable and a dependent variable, by investigating whether the influence of the independent variable on the mediator in turn influences the variable outcome.

Mental health trusts: Healthcare delivery organisations that provide specialist health and social care services for people with mental health problems in defined geographical areas in the UK.

mHealth: Mobile health, a form of digital health intervention accessed or delivered mainly by mobile phone or other mobile device.

Multiple imputation: Statistical process for replacing missing data in incomplete data sets, conducted multiple times and averaged to reduce noise in the data.

NHS trusts: Healthcare delivery organisations that cover defined geographical areas across England.

Participant identification centre: Identifies potential participants for off-site research studies through patient records, speaking to patients or other means.

Peer worker: Someone with lived experience of (usually) mental health problems providing support or services to others with mental health problems.

Patient and public involvement: Input from patients and members of the public into decisions about the design and delivery of health services or (in this instance) health research.

Psychoeducation: Evidence-based provision of information and support to help patients and their relatives better understand and cope with illness, particularly serious mental illness,

Psychosis: A state in which people perceive or interpret the world around them very differently. Psychosis most frequently manifests as: having beliefs that are not shared by others and do not have a basis that is understandable to others (often called delusions); not being able to think clearly and so sounding muddled and hard to follow (often called thought

disorder); and experiencing, for example hearing or seeing, things that other people cannot (often called hallucinations).

Quality-adjusted life year: Generic measure of disease burden, including both the quality and the quantity of life lived, used to assess value for money of medical interventions. One QALY equates to one year in perfect health.

Randomised controlled trial: Scientific investigation method whereby participants are allocated randomly either to a group receiving the treatment under investigation or to a control group receiving standard treatment.

REACT: The Relatives' Education And Coping Toolkit. An online supported self-management toolkit for relatives or friends of people with psychosis or bipolar disorder.

Relative/carer: Family member or other close person providing unpaid care and support to a person with psychosis or bipolar disorder.

Technology-enabled service: Health service in which technology plays a role alongside many other face-to-face components.

Triangle of care: The three-way collaboration of health professional, mental health service user and their carer to provide therapeutic care.

Plain English Summary

Relatives of people with severe mental health problems need better access to information and emotional support. The Relatives' Education And Coping Toolkit (REACT) is a website designed to do this. It includes lots of information presented in text and video, an online forum for relatives to share knowledge and experience, a messaging system where they can ask questions in confidence, and a comprehensive directory of contact details for national organisations offering relevant support. Trained relatives support the forum and messaging.

We recruited 800 relatives in the UK, all aged over 16, with high levels of distress, access to the Internet, and wanting help. We divided them into two equal groups: one group got REACT (including the directory), while the group got just the resource directory. To ensure there were no differences between groups at the start, relatives were allocated to the two groups randomly, so they had an equal chance of being in either group. We followed up with both groups at 12 weeks and finally at 24 weeks, and received data from approximately three-quarters of the participants.

Our study found that REACT was acceptable, safe, inexpensive to deliver (£62.27 per relative), compared to face-to-face interventions and that relatives using it felt well supported.

However, once we accounted for missing data (relatives who dropped out of the trial or did not complete the follow-up questionnaires) there were no significant differences between the groups. There was no evidence that REACT increased relatives' quality of life or saved money for the NHS.

[250 words]

Scientific summary

Background

Relatives supporting people with a severe mental health problem such as psychosis or bipolar disorder (BD) face many challenges and report high levels of distress. Psychoeducation and emotional support through peer interactions are effective, beneficial and recommended by the National Institute for Health and Care Excellence (NICE). However, evidence shows that many relatives are unable to access these services. The Relatives' Education And Coping Toolkit (REACT) was an online supported self-management package designed to improve availability and access to support for relatives. It included a comprehensive online resource directory (RD).

Objectives

The aim of the study was to determine the clinical and cost effectiveness of REACT with RD and treatment as usual (TAU), compared to only the RD and TAU. This was the first definitive randomised controlled trial (RCT) to test an online digital health intervention (DHI) for relatives of people with severe mental health problems.

Objectives were to determine the:

- Impact of REACT on relatives' distress
- Impact of REACT on relatives' wellbeing and support
- Impact of REACT on hypothesised mediators of change including relatives' beliefs, perceived coping, and amount of use of REACT
- Costs associated with delivery and maintenance of REACT
- Incremental cost-effectiveness ratio (ICER) of REACT.

The primary hypothesis was that there would be a significant difference ($p<0.05$) between the two arms of the trial in levels of relatives' distress at 24-week follow-up.

Methods

Our design was an online, single-blind two-arm RCT.

Eligible participants were relatives or close friends engaged in caring for a person with psychosis or BD. Inclusion criteria were: aged 16 or over; living in the UK; currently experiencing high levels of distress as a result of their caring role (assessed using a single item from GHQ-28, “Being strung up and nervous all the time”, and requiring a response of “rather more than usual” or “much more than usual”); actively seeking help; with access to an Internet-enabled computer; and with sufficient command of English to use REACT (which was available only in English). Only one relative per family could take part, and relatives living in any of six geographical areas taking part in a parallel implementation study (IMPART study) of the same intervention were excluded by postcode.

The REACT toolkit included: 12 psychoeducation modules addressing key questions identified by relatives; peer support through a moderated group forum; a confidential direct messaging service; and the RD of contact details for national organisations offering relevant support.

Relatives with lived experience of supporting someone with a mental health problem were trained to moderate the forum, respond to confidential messages from users, and guide users to relevant parts of toolkit and/or other resources as appropriate. The toolkit was hosted by one National Health Service (NHS) mental health trust in England but available to relatives across the UK.

The comparator intervention was access to the same RD. All participants received TAU.

Participants were recruited through mental health services, charities, media, social media and online advertisements. After providing informed consent and completing baseline data, eligible participants were randomised using a 1:1 ratio to “REACT (including RD) plus TAU” or “RD plus TAU” using web-based variable block randomisation, in which the unit of randomisation was the relative. Following randomisation, participants received an email telling them to which arm of the trial they had been allocated. The email included a link to the REACT website, and their username and password. All accounts were set up on the same website, but those in the RD only arm had access only to the directory. 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 outcomes were validated self-report measures, collected online using a closed system available only to participants with an account on the REACT site. We gave participants shopping vouchers at each time point as an incentive to completion of follow-up measures.

The primary outcome was relatives' distress at 24 weeks, assessed using an online version of the GHQ-28 with Likert scoring. Based on our previous feasibility trial, and accounting for design changes and dropout, we aimed to recruit 666 relatives to provide 90% power to reject the null hypothesis ($p<0.05$), assuming an estimated mean difference of 5.0 units on the GHQ-28 (standard deviation (SD) 16.60) and 30% dropout by 24 weeks.

Secondary outcomes included the relatives' wellbeing and experience of support, assessed online using the Carers' Well-Being and Support measure (CWS) at 12 and 24 weeks, and distress (GHQ-28) at 12 weeks' follow-up. Illness perceptions (assessed using a modified version of the Brief Illness Perception Questionnaire) and coping (assessed using the Brief COPE) were hypothesised mediators of the intervention effect. Costs of health and personal social care use and quality of life were assessed using a modified version of the Client Service Receipt Inventory and the EQ-5D-5L respectively at baseline, 12, and 24 weeks.

Mean scores were compared between groups using analysis of covariance (ANCOVA) adjusting for baseline scores. 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). Multivariate ANCOVA was used for exploratory analyses of the impact of intervention group on each subscale of the mediator measures, while taking into account correlation between the subscales. Instrumental variable regression was used to estimate the impact of intervention use on outcome. Further exploratory analyses assessed the impact of reading but not posting (known as "lurking") on the REACT forum.

Participants' experiences of using REACT were explored quantitatively (all REACT group) and qualitatively (purposive sample n=24). Adverse events were closely monitored. A full statistical analysis plan was published prior to any data analysis

Results

The total number of visits to the REACT study page during the trial was 51,832. The total number of visits to the registration page was 4,348. Of the 3,287 people who completed the eligibility screening, 1,416 people failed on at least one of the eligibility criteria, with 1,146 (81%) of these failing to report higher than usual levels of distress. Of the 1,528 (46%) who subsequently provided consent for the study, 807 completed baseline measures and 800 (52% of those consenting) were randomised. Of these, 424 (53%) were recruited through primarily online strategies (Facebook being the most successful) and 376 (47%) through primarily offline strategies (mainly mental health services).

Participants were typically middle-aged (40–60 years: 422, 53%), white British (727, 91%), female (648, 81%), mothers (387, 48%), highly educated (university level: 437, 55%), and supporting an adult under 35 years old (485, 61%). More than half of participants (462, 58%) were supporting someone with BD. Most were supporting only one person, but 209 (26%) reported supporting two or more people, and the majority (457, 57%) also had other dependents. Some 485 (61%) were married or in a civil partnership. The majority of relatives were in full-time, part-time or voluntary work (512, 64%) but 66 (8.5%) reported being unable to work specifically due to their caring responsibilities. The vast majority had home Internet access (795, 99%). Retention was 74% at 12 weeks, and 75% at 24 weeks.

Taking into account full costs of development and delivery, 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 on REACT in the REACT arm was 50.8 minutes (IQR 12.4–172.1, range 0.1–4505.5). The median time spent on the RD was 0.5 minutes (IQR 0–1.6, range 0–42.9). Both online interventions (REACT and RD) were accessed considerably more outside the working week (9am–5pm Monday to Friday excluding public holidays) than during working hours, suggesting a need for online interventions to be available 24 hours a day. The most popular module (with most people visiting at least once) was the online forum.

Relatives had high levels of distress (GHQ-28) at baseline (mean 40.2, SD 14.3), which decreased in both groups by 24-week follow-up (overall mean 30.5, 15.6), but there was no significant difference between the two groups (-1.39, 95% CI -3.60–0.83, p=0.22). At 12 weeks' follow-up, GHQ-28 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). Participants in the REACT arm who dropped out were on average 0.33 GHQ units (95% CI -0.27–0.93, p=0.279) more distressed than those who remained. Being male, single, and unemployed (or in unpaid work) were all associated with greater levels of distress.

Carer wellbeing and support both increased significantly over time in both groups. There were no significant differences between groups in wellbeing at either 12 weeks (1.53, 95% CI -2.21–5.27, p=0.42) or 24 weeks (2.39, 95% CI -1.76–6.54, p=0.26). Relatives in REACT reported higher levels of support at 12 weeks (2.50, 95% CI 0.87–4.12, p<0.0001) and at 24 weeks (1.65, 95% CI 0.04–3.27, p=0.045). However, after accounting for missing data in a

longitudinal model, the mean difference (1.51, 95% CI -0.005–3.01) was no longer statistically significant (p=0.051) and was likely to be of limited clinical significance.

This within-trial health economic analysis of NHS, health and personal social services outcomes found the REACT toolkit to have higher costs of £286.77 (95% CI -£858.81–£1432.36, p=0.624), slightly better GHQ scores (incremental GHQ adjusted for baseline GHQ score and age and gender = -1.152, 95% CI -3.370–1.065), and slightly lower QALYs (incremental QALYs adjusted for baseline EQ-5D-5L index score, age and gender = -0.0024, 95%CI -0.0088–0.0039) compared to RD only, but none of these differences was statistically significant.

Illness perceptions and perceived coping improved over time. However, neither had a significant mediation effect on outcome. There was no evidence of a causal association between amount of use of REACT and impact on outcomes. REACT forum users were estimated to have lower GHQ-28 scores at 24 weeks compared to non-users (-2.0, 95% CI -5.9–1.9) who had similar outcomes to people reading but not posting ("lurkers") (-0.1, 95% CI -3.2–2.9); however there was no evidence of a significant difference (p=0.59).

The intervention appeared highly acceptable. Participants reported finding REACT a safe and confidential environment (96%), feeling supported by the REACT group (89%) and by REACT supporters (86%).There were no serious adverse events (immediate and serious risk to life or to child welfare). Qualitative feedback was extremely positive. REACT was particularly valued by relatives for being comprehensive, relevant, easy to access, private and anonymous. The proactive support from REACT supporters was appreciated, as was the opportunity to learn through a variety of different media (text, video, forum) how best to support someone with a mental health problem. However, 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. Some relatives found seeking help for their own needs difficult, and most relatives found prioritising time to use REACT difficult. The advantage of online interventions is that they are conveniently accessible at any time, but the challenge is to make time to use them.

Conclusions

Relatives felt safe and well-supported using REACT, which might facilitate better engagement with other aspects of the service. Key developments should include: redesigning the content and presentation using feedback from participants; making the technology more interactive and user friendly; increasing the role of REACT supporters to

include support to use the modules; specifying recommended levels of use; and offering REACT to relatives earlier in the recovery journey, alongside other components of care, particularly for those with high levels of distress.

Recommendations for further research

1. Given the apparent unmet need and high acceptability of REACT, further work is needed to make the content of REACT more effective.
2. Psychoeducation and support are important and valued by relatives, but distress (GHQ-28) may not be the most appropriate outcome for evaluating their effectiveness. Understanding more about a chronic health problem for which there is no immediate cure is important, but unlikely to reduce distress without additional therapeutic input. Therefore, the effectiveness of psychoeducation interventions may be better tested against alternative outcomes such as supporting relatives to feel more knowledgeable, more empowered, better able to cope, and more engaged with services, rather than on reducing distress.
3. Research is needed to understand how to increase engagement and use of REACT (and other DHIs) to maximise their potential to improve outcomes.
4. Research is needed to understand how to improve uptake and reach of REACT (and other DHIs) by groups that currently show low levels of use of mental health and support services, including ethnic minority groups and men.
5. The impact of psychoeducation interventions for relatives on service-user outcomes needs to be tested.
6. RCTs can be delivered online at lower cost. However, this methodology presents new challenges in keeping participants engaged throughout long-term follow-ups, and in managing high-quality patient and public involvement. Both require further research.

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Funding details and study registration details

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The study is registered at ISRCTN72019945

The online version of REACT was developed and tested by our research team. Thus, this trial is not an independent evaluation.

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[2319 words]

Chapter 1 Introduction

This chapter provides the background and rationale for the present study. We have presented an overview of the challenges faced by relatives of people with psychosis, or bipolar disorder, described what support is currently available for this group, and outlined why we developed the Relatives' Education And Coping Toolkit (REACT). We have briefly described previous work in developing REACT and explained the context for the current study. The chapter draws on some material previously published by the report's authors during the course of the study,[1-3] and reproduced here under a Creative Commons licence (https://creativecommons.org/licenses/by/4.0/, last accessed 29 October 2019).

Challenges faced by relatives of people with psychosis or bipolar disorder

Psychosis is an umbrella term that covers many different conditions, the common feature of which is that people perceive or interpret the world around them very differently. The most frequent ways this manifests are: having beliefs that are not shared by others and do not have a basis that is understandable to others (often called delusions); not being able to think clearly and so sounding muddled and hard to follow (often called thought disorder; or experiencing, for example hearing or seeing, things that other people cannot (often called hallucinations).

As well as the presence of these unusual experiences, many people with psychosis also report a loss of valued experiences, most notably pleasure in everyday activities (anhedonia) and loss of motivation (apathy). These losses are sometimes referred to as "negative symptoms" and are particularly challenging for relatives: not least because they are hard to differentiate from normal "teenage angst", side effects of medication, or depression. It is difficult to report exact figures on the exact number of people who will experience psychosis as many may never have contact with mental health services, but most recent estimates include worldwide incidence at approximately 1 in 13 people (7.7 per cent)[4] and up to 10 per cent in the UK of people reporting some kind of psychotic experiences.[5] Only a fraction of these people (approximately 1 per cent of the general population) will ever come into contact with mental health services and receive a diagnosis of a mental health condition. In general, these are likely to be people for whom these experiences are particularly distressing or cause significant changes in behaviour.

Bipolar disorder (BD) is the 3rd most common mental health cause of disability globally,[6] affecting 1%–4.5% of adults[7] and costing the English economy £5.2 billion annually, largely due to inadequate treatment.[8] BD is characterised by episodes of extreme low mood (depression) and extreme high or irritable mood (mania, or hypomania in its milder form). Challenging behaviours such as increased self-harm and suicidal behaviour, excessive spending, sexual disinhibition and heightened irritability can all occur during mood episodes, which are often accompanied by psychotic symptoms. Between episodes, functioning may return to normal levels, though many people report problematic sub-syndromal levels of depression which impact on their functioning and relationships.[9]

Psychosis and BD present significant challenges to relatives, particularly in recognising and understanding what is happening, living with the elevated risk of suicide, the impact on relationships within the family, and having to balance caring, work and other family commitments. These challenges are exacerbated by difficulties in accessing mental health services, which delay access to effective treatment, leading to worse long-term outcomes.[10, 11] It has been estimated that over a third of relatives of people with psychosis experience clinically significant levels of distress and burden,[12] and estimates from more recent studies with relatives from early intervention in psychosis (EIP) services are even higher at more than 60 per cent.[2, 13]

Almost half of relatives of people with psychosis experience post-traumatic stress symptoms associated with their caring roles,[14] particularly linked to episodes of violence, disruptive behaviour and forced admission.[15]

Key factors that increase the negative impact of psychosis on carers include: being a female carer;[16] living with the person with psychosis; young patient age and awareness of suicidal ideation;[17] reduced social support and family resources;[17, 18] use of emotion-focused coping strategies;[19] and beliefs that relatives hold about the psychosis, particularly those concerning cause and control.[20-22]

In BD, symptoms associated with depressive episodes result in increased burden of caring, poorer general health, and depressive symptoms in carers.[23-25] The frequency of suicide attempts within the BD population is higher than in many other populations affected with mental health issues, creating a distressing situation for carers.[26] During periods of mania, extravagant spending, irritability and inappropriate and disproportionate behaviour become more frequent and extreme.[27-29] The challenge of learning to cope with symptoms associated with manic and depressive episodes can not only negatively affect the service user, but also

diminish carers and their family's quality of life, with carers expressing feelings of helplessness, anger, and anxiety.[30, 31]

Importantly, many relatives also report positive aspects of caring for someone with a severe mental health problem including identifying personal strengths, feeling a sense of love, caring and compassion, developing new insights about their lives and living, and greater intimacy with others as a result of their journey coping with mental illness.[32, 33]

We have chosen to focus on the needs of relatives of people with psychosis or BD together in the REACT project, as they face many common challenges. These include: how best to support someone in their recovery journey; how to deal with mental health crisis; how to manage difficult situations; how to manage stress; and how to understand and navigate mental health services and the treatments they offer. Mental health services are often structured such that people with a diagnosis of psychosis or bipolar disorder are managed within the same teams; e.g. community mental health teams, EIP teams etc. Therefore, having interventions to support relatives that work across these conditions also makes practical sense.

Support for relatives

Relatives of people with psychosis or BD provide a large amount of unpaid care,[34, 35] but at high personal cost in terms of distress and burden.[12, 36, 37] Without this unpaid care, the National Health Service would not be able to cope. Historically, the impact of severe mental health problems on relatives has been ignored, or included as a secondary outcome to service user outcomes.[38] However, more recently there has been increasing recognition of the importance of understanding the impact of supporting someone with a mental health problem, on the carer, and of the need for effective interventions to address this.[39]

There is now good evidence that interventions that support relatives can improve outcomes both for service users[38, 40, 41] and for carers.[39, 42-44] The exact nature of these interventions for carers varies. Some are psychoeducational, aiming to empower relatives with information and coping strategies.[45] Others are more systemic and, in addition to psychoeducation, work with the family on approaches to problem-solving and communication (e.g. Miklowitz 2010).[46] Interventions also vary in how many sessions are offered, over what period, whether or not the service user also takes part in the intervention, and whether the programme is offered to individual families, or in groups. To date, there are no good quality data sets that determine which content or format is most effective.

The exact mechanism underlying the improvements in carer outcomes as a result of family-focused support is not well understood. However, studies have identified several factors associated with improved outcomes for relatives, including:

- The development of an effective cognitive “working model“ of psychosis which increases empathy and understanding towards the service user;[47]
- A greater sense of being able to cope with problems they face (self-efficacy);[13, 48]
- A less emotionally charged relationship;[49-51] and
- A sense of feeling better supported by others.[32]

Implementing support for relatives

The UK Government recognises the need to support relatives in a caring role,[52] and the National Institute for Health and Care Excellence (NICE) recommends that all relatives be given carer-focused education and support, and offered structured family intervention to enhance family coping and communication.[53, 54]

However, a recent national audit of EIP services in the UK showed poor implementation, with only 50% of relatives receiving a carer-focused education and support programme and only 31% being offered a structured intervention (of whom only 12% took up the offer).[55] A survey of more than 1,100 families across 22 European countries showed that half were dissatisfied with how they were involved by mental health services,[56] suggesting that is unlikely that services are better elsewhere.

The challenges services face in providing structured family interventions are likely to include cost and the practicalities of delivery. Many require two trained therapists, available at the same time weekly for up to nine months with regular access to supervision, as well as a family whose members can all commit to attending face-to-face sessions, often during office hours – and have a sufficiently open and robust relationship with the service user.

However, these factors do not account for the lack of more straightforward psychoeducational approaches and emotional support for relatives. It is likely that additional organisational factors also play a role in poor implementation.

For example, staff workload is often measured in terms of number of service-user contacts, which may not adequately recognise time spent with family members. Under pressure, this may be the first thing to go. As well as highlighting the need for organisation-wide change, a study by Eassom *et al* (2014) identified staff reservations about the level of involvement family members should be given in the recovery process; fear of negative outcomes as a result of involving family members; and the need for an exclusive patient–professional relationship.[57]

Attempts have been made to improve access to support for relatives. *Achieving better access to mental health services by 2020*,[58] published in October 2014 by NHS England and the Department of Health, sets a key standard that "more than 50 per cent of people experiencing a first episode of psychosis will be treated with a NICE-approved care package within two weeks of referral". This includes carer-focused education and access to structured family interventions. Clinical commissioning groups (CCGs) have been directed to allocate funding to EIP teams to support efforts to meet this standard, the success of which is being audited by the College Centre for Quality Improvement (CCQI) within the Royal College of Psychiatrists.[55]

In addition to government policy, the Triangle of Care[59] has been developed by the Carers Trust and the Mental Health Development Unit as a "guide to best practice" to help mental health services improve collaboration and partnership with carers. The Triangle of Care sets out six key standards, which have already been adopted by a significant number of NHS trusts. However, the extent to which these are being met is currently monitored through self-audit only and this may limit their impact on practice.

Within this context, our aim was to develop a user-friendly, easily accessible self-management intervention, based on the principles of psychoeducation and family intervention, which could overcome some of the identified barriers to implementation, and be made available to all relatives of people with psychosis or bipolar disorder across the UK. Specifically we were keen that the intervention target key appraisals and coping strategies, be empowering for relatives, not require extensive staff time or training, and be low-cost and require little input from mental health services. Self-management interventions that have the flexibility to be used alongside other work and family commitments and augment other forms of support are ideally suited to meet the needs of relatives, and have the potential to be widely available in an increasingly resource-restricted health service.

Initial development of REACT

The Relatives' Education And Coping Toolkit (REACT) was first developed as a paper-based self-management intervention for relatives of people with psychosis in EIP services as part of a National Institute for Health Research (NIHR) Research for Patient Benefit-funded study.[60] The content was informed[3] by:

1. Our systematic review of interventions for relatives of people with psychosis,[39] highlighting the distinguishing features of effective interventions;
2. Focus groups of relatives;[3]
3. Cognitive behavioural therapy models highlighting the importance of helping relatives understand psychosis and build on existing strategies;
4. The research team's own expertise.

The REACT toolkit consisted of 13 sections, designed to be used flexibly depending on the individual needs of relatives. These were:

1. Introduction to REACT
2. What is psychosis?
3. Managing positive symptoms
4. Managing negative symptoms
5. Dealing with crises
6. Dealing with difficult behaviour
7. Managing stress – thinking differently
8. Managing stress – doing things differently
9. Understanding mental health services
10. Treatment options
11. The future
12. Resource directory
13. Jargon terms.

Through this combination of modules and the directory, the toolkit aimed both to support users directly with advice, information and case studies, and to connect them to other sources of advice and support. The toolkit was printed in A5 format and given to each participant. It could also be read online or downloaded from a website made available to participants, though this was very little used and relatives made clear in feedback they preferred a resource they could hold in their hands. Most sections were under 24 pages — the shortest was 11, the longest was the resource directory at 43 pages. The large quantity of links to other services and resources meant the toolkit required constant editing and updating to maintain its accuracy.

Support in using the toolkit came from EIP support workers, who conducted one-to-one introductory sessions with each participant, with ongoing support available for 6 months by telephone or email as preferred, limited to 60 minutes a week. Participants who did not contact their support worker or who missed appointments were called at least monthly to maintain engagement. The intention of this personalised support was to help relatives to identify their greatest challenges and to then navigate the toolkit to find information or useful strategies that could be used. The focus was on practical engagement rather than transmission of information, with relatives encouraged to adopt and adapt new strategies, acquire and use new skills and reflect on the results – an active rather than passive approach.

The feasibility and acceptability of the toolkit was tested in a randomised controlled trial (RCT), in which the toolkit was offered in addition to treatment as usual (TAU). Relatives' distress and wellbeing outcomes were compared at 6 months' follow-up against those receiving TAU. This study showed that relatives were very keen to engage with the intervention, that staff could integrate delivery of REACT into existing EIP services, and that relatives who received REACT were significantly less distressed compared to those receiving TAU at 6 months, as measured by the General Health Questionnaire (GHQ–28)[61] (regression coefficient -6.59, 95% confidence interval (CI) -12.55– -0.64). They also had higher levels of perceived support (measured by the Carer Wellbeing and Support measure (CWS);[62] regression coefficient 4.86, 95% CI 0.77–8.96) and perceived ability to cope (measured by the Family Questionnaire;[63] regression coefficient -4.89, 95%CI -9.34– -0.44).

As well as strongly preferring the printed toolkit over the online version, relatives showed a slight preference for accessing support by telephone rather than email. There were practical challenges in retaining trained NHS staff for the study and maintaining their allocated time to support the intervention.

Qualitative feedback from relatives who used REACT was extremely positive.[64] Relatives reported feeling less isolated and more supported as a result of REACT:

> *Say it were a Saturday night and they aren't available, I still know come Monday morning I could ring that number, and that could help me through that weekend.*

When asked what they felt REACT had changed for them they reported changes in their ways of thinking about the service user's behaviour ("[It] made me see things differently from a different point of view") and in their coping strategies:

> *I now know how to say things to David – rather than, I would have said, "Oh David, do you have to smoke? Your teeth are going to be yellow," I will say something now like, "Oh David, you know, you are so nice looking, you would be even nicer if you didn't smoke because smoking can actually make your teeth go yellow." So I know how to word things more to make him feel not guilty about the smoking.*

They also reported feeling more supported as a result of the intervention:

> *Oh, very reassuring. It [support] saved my life. I know that sounds melodramatic, but it saved my life; I feel as if it saved my sanity in a way.*

Subsequent development of REACT

Based on qualitative feedback from relatives using REACT in the feasibility trial, as well as input from our patient and public involvement (PPI) group and from clinical academic experts in our research team, we proposed the following goals for the next version of the intervention:

1. To adapt REACT for a broader range of relatives, including those outside EIP and those supporting people with BD;
2. To make a more interactive version of REACT, available to relatives online; and
3. To support REACT with expert relatives rather than NHS staff.

The reasons for these goals are explained in the following section.

Adapt REACT for a broader range of relatives

While targeted early interventions have been successful in improving outcomes, these improvements are not sustained when service users move from specialist EIP services into routine mental health services.[65, 66] There are also many relatives supporting people with

psychosis who are not accessing mental health services at all. There is an urgent need to develop interventions that can be extended beyond EIP services, and to include relatives outside of mental health services, and to support people with a broader range of diagnoses.

A more interactive, online REACT

In the feasibility trial, relatives preferred the paper version of REACT. However, the online version was restricted to static PDFs, with none of the advantages that interactive online interventions can offer. The paper version was also very difficult to update regularly, and had high production costs, which might limit dissemination.

Due to the general increase in use of the Internet to access healthcare interventions, the advantages of being able to update information quickly as required, and the opportunity to add more interactive components and multimedia formats, such as video clips, we proposed delivering REACT as an online intervention, despite the preferences stated in the feasibility study.

Online interventions are well established for many mental health conditions, including depression and anxiety,[67] and some have now been developed for psychosis[68] and BD.[69] Such interventions are particularly suited to delivering standardised information together with a platform for sharing ideas through online forums. Online support is also being developed for relatives of people with other chronic health conditions,[70] and may be particularly useful for these groups due to the flexibility of use, and empathy and support available from other carers.[71] There is some evidence that online interventions would be well received by carers,[72] though acceptability, along with clinical and cost-effectiveness, needs further testing.

Support REACT with expert relatives rather than NHS staff

Offering REACT to all relatives, including those not in contact with mental health services, and putting it online allowed us to develop a single dedicated team to support the intervention. This gave us greater control over the nature and design of the support. We chose to employ peer workers – relatives with lived experience of supporting someone with a mental health problem – for several reasons.

Our PPI group strongly favoured this approach. Our co-applicant (VM) had worked with Rethink Charity for many years, sharing her knowledge and experience to support other relatives. There was a shared perception that peer workers would be highly knowledgeable,

empathetic and motivated to support other relatives. This was reiterated in the design workshops that we conducted to develop the online version of REACT (see *Chapter 2*).

Qualitative and observational studies have identified a number of benefits of using peer workers, both for those receiving support, and for the peers themselves.[73] For service users, these benefits include reduced admission rates, greater empowerment, empathy, acceptance and hope, better social functioning, and less stigma. Benefits reported by peer workers include support for their own recovery and personal grown, acquisition of new skills, and the therapeutic effect of helping others. For paid peer workers, there are also financial benefits.[74, 75] Employing relatives as REACT supporters to support the REACT website was an opportunity to develop the strategic role of service users and carers in delivery of services and explore the benefits and challenges of this role. It also circumvented the difficulty of identifying existing staff who had the expertise, time and support to take on this role. Developing the peer worker role as part of the NHS workforce was also consistent with recommendations from NICE in 2016.[76]

Securing funding to evaluate REACT

In January 2013, we applied to the NIHR for health technology assessment (HTA) funding to deliver these adaptations and test the clinical and cost effectiveness of the new version of REACT in a large definitive trial. The application was rejected (13 December 2013) as the trial was seen as too expensive to deliver, at £2,032,667. Given the positive outcomes we had already demonstrated and the correspondence of the intervention to NICE guidance requirements to offer all carers psychoeducational and emotional support, the HTA funding committee suggested we consider how best to deliver REACT in the NHS.

We then responded to the HTA efficient design call for RCTs that tested efficient trial designs to address the problem of the escalating costs of large-scale definitive trials. This offered the opportunity to test the online REACT intervention in an entirely online trial. Advantages of online trial design include the potential to reach a greater number and range of participants; reach a population more representative of those likely to use an online intervention; to recruit more people over a shorter time frame; to simplify protocols for secure randomisation and data entry; and to deliver a trial much more cheaply because fewer staff were needed.[77] However, retention rates for such trials can be low,[77, 78] compromising internal validity of the trial.

This efficient design reduced the costs of the trial to £633,404. We were awarded funding for 36 months, to begin in October 2015.

In parallel, we applied to NIHR health services and delivery research (HS&DR) programme for funding for an implementation study to identify the factors affecting successful delivery of an online intervention within EIP services. This study was also funded for 30 months, starting in March 2016. The two studies were complementary. The HS&DR study explored factors affecting implementation of a clinician-supported intervention in EIP services in the NHS, in contrast to this study's peer worker-supported intervention. It also includes an evaluation of outcomes for the relatives, using the same measures and follow-up period as this study. We thus had the potential to compare both the reach and the outcomes achieved by providing REACT through two very different study designs. This allowed us to answer questions about which was likely to be the most effective service provision model, as well as to compare the effectiveness of peer worker and clinician-supported approaches. The HS&DR report was submitted for publication in December 2018.

Study design

The REACT trial is a single-blind, parallel online RCT to determine clinical and cost effectiveness of REACT, including an online resource directory (RD), compared to RD only, for relatives of people with psychosis or BD. No changes were made to any other support that relatives received outside the trial. See *Chapter 3* for the specific objectives of the trial.

Research team

Our team included relatives, clinicians, academics, and methodologists from a range of disciplines, with a common interest in developing and evaluating new ways to support people with mental health problems and their relatives. Team members were all UK-based, and though some had worked together previously, the team in its entirety came together specifically for this project. Although the team all differed in background, training, epistemological and ontological stance, some important factors underpinned the team in working together successfully:

- A commitment to improve the lives of people with mental health problems and their relatives in non-stigmatising, empowering, and recovery-focused ways
- A recognition of the huge role that relatives play in supporting people with health problems, and of the current lack of adequate support available to them

- A belief in the importance of evidence-based healthcare and the need to carry out high quality research to inform how NHS funding is spent
- An interest in testing the potential of digital technology to increase accessibility and reduce costs of clinical interventions, while also exploring the challenges and barriers to this approach
- A commitment to identify efficient ways to carry out publicly funded research to provide value for money to the UK taxpayer.

Trial monitoring

Trial management group

The trial management group (TMG) was involved in developing the study ideas and was responsible for delivering the project. This group included the study co-applicants: a relative with many years supporting a family member with a diagnosis of schizophrenia (VM); two clinical academic psychologists (FL and SJ) based in Lancaster; a clinical academic psychiatrist with a lead role nationally in EIP services (SJo) and a clinical academic GP who is an expert in development and evaluation of digital health interventions (EM); a trial statistician who is director of the Clinical Trials Research Centre (CTRC) in Liverpool which oversaw the data management and statistical analysis (PW); and a health economist based in Lancaster (CM).

The TMG met monthly and also included our trial managers (HR and BM), IT experts who built and maintained the REACT toolkit and data collection systems (DA and AW), and lead and support statisticians who managed the data collection and recruitment and retention reporting, as well as conducting the final analysis (SD and NB). To accommodate the geographical spread, and consistent with our efficient design, all meetings took place by teleconference.

The REACT toolkit was supported by a team of trained relatives (SF, AH, LC, NA) and supervised by two clinical psychologists (SJ, BS).

Trial steering committee and data monitoring and ethics committee

Finally, our study was overseen by an independent trial steering committee (TSC) and a separate data monitoring and ethics committee (DMEC). The TSC was chaired by an expert in clinical trials testing psychological interventions (SR) and included two academic clinical psychologists (GH and PL), a statistician (AM), a service user (TR) and a relative (FT). It

also included a representative of the sponsoring organisation Lancaster University (SD), and the NIHR Clinical Research Network (MW). The TSC met before the start of the study, at 10 months to review progress with recruitment, at 15 months to determine whether the findings from the internal pilot supported the continuation of the study, and then annually to the end of the study.

The DMEC was chaired by a statistician who directs a clinical trials unit (KH), and included another academic clinical psychologist with expertise in developing and evaluating digital health interventions (CC). The role of the DMEC was to monitor the data and specifically to assess whether or not we had met the stop/go criteria set for our internal pilot (see *Chapter 3*), and to monitor any ethical or safety concerns. The DMEC met before the start of the study, at 10, 12 and 15 months and then annually, timed to feed reports into meetings of the TSC. All meetings were by teleconference.

Patient and public involvement

Consistent with the *Framework for Mental Health Research* (Department of Health 2017),[79] this project was developed and conducted in partnership with service users and carers.

Co-investigator

One of the study investigators and co-author is a parent of someone living with psychosis and was extensively involved in the development of REACT, the resource directory and the data collection processes. She was part of the supervisory team for the REACT supporters. She was also invited to attend the TMG meetings.

Development of REACT

Relatives were involved in the development of the initial content for the toolkit,[80] and in subsequent iterations to develop an online toolkit:[1] see *Chapter 2*.

Relatives' advisory group

At the start of the project, we set up the relatives' advisory group (RAG) of 13 relatives or close friends of someone with BD and/or psychosis and one individual with lived experiences of BD. Their role was to provide consultative input to each stage of the research.

Consistent with the online nature of the trial, members of the group worked mainly remotely, providing detailed feedback on the REACT toolkit (reviewing its content and format) and the

online data collection process (including selection of questionnaires and items used for eligibility screening), and advising on strategies for maximising recruitment and retention.

In addition to independent review work, the group met three times during the study: before the start of the study, to familiarise themselves with the REACT toolkit and trial and data collection tools; at 12 months to review the recruitment strategy; and at 22 months to advise on the follow-up strategy. The first meeting was held face-to-face at Lancaster University; the other meetings were held online, which facilitated the involvement of people from a wider geographic area and a greater diversity of relatives' experiences. RAG members were also invited to write blogs for the website to stimulate discussions on the REACT forum. The results of the trial have been presented to the RAG members, and work continues with this group on interpretation and broader dissemination of the data.

RAG members received a high street shopping voucher for £10 to £50 (depending on the length of the task undertaken) as a thank-you for their time.

REACT supporter role

REACT supporters were relatives with lived experience of supporting someone with psychosis or BD. They were employed by the host NHS trust as NHS band 5 staff. See *Chapter 2* and *Stand Alone Documents 1 and 2* for more details on their role.

Trial steering committee

One relative and one service user were appointed to the TSC at the start of the study. They both had experience of using services, but also had research expertise. The service user was employed as a research associate on another NIHR funded study, and the relative was a retired academic.

Chapter 2 Intervention development

Introduction

In this chapter, we describe how the paper-based REACT intervention (see *Chapter 1*) was adapted into an online version, and the resulting content. The three key adaptations, based on learning from the feasibility trial, were to:

- Broaden REACT to make it suitable for relatives outside EIP services and for relatives supporting people with BD;
- Make REACT more interactive and directly available online to relatives; and
- Offer REACT with support from trained relatives.

In the feasibility trial of paper-based REACT, modules were posted online as PDFs to aid availability. Clearly, this is not the same as an online intervention, which would typically be more structured, self-guided, interactive, visually rich, and personally tailored. Considerable work was therefore needed.

Following guidance from CONSORT–EHEALTH v1.6.1,[81] we describe the history, development and initial formative evaluations of REACT, details of how the dynamic components worked and how the site was updated. We provide relevant screenshots and have archived the site (access available on request). We also present the development and content of the resource directory (RD) that was offered as our active control intervention. As CONSORT requires, we identify the sponsor and ownership of the site.

Our aim was to involve relatives, clinicians, and the clinical academic team in co-developing content and design to ensure both would be high quality, user-friendly, meet the needs of relatives, and engender confidence in potential referrers. The importance of understanding the needs of users and involving them in design has been well reported.[82] We carried out a series of workshops with users (relatives), and drew on the expertise within our clinical academic team to develop a list of design features, which guided our development of REACT.

Understanding user perspectives: method

We held two workshops (Workshops 1 and 2, with 13 and 11 participants respectively) to explore the needs of relatives outside EIP services, and their views about how REACT should be developed. We aimed to recruit participants from diverse backgrounds in terms of age, gender, relationship with the service user, length of experience as a caregiver, and computer literacy. Workshop participants were invited if they identified as supporting a relative or close friend with psychosis or BD. Our recruitment strategy was to advertise locally to obtain a convenience sample that could attend face-to-face workshops. Advertisements were circulated via Lancaster University's Spectrum Centre for Mental Health Research, using email, social media and post. The Spectrum Centre is a multidisciplinary research centre focusing on development and evaluation of psychosocial interventions for people with long-term mental health problems (http://www.lancaster.ac.uk/shm/research/spectrum/, last accessed 28 October 2019).

In accordance with our approval from Lancaster University Ethics Committee, those who indicated interest were sent an information sheet by email or post before the workshop, allowing them to raise any questions in advance. This information included the purpose of the workshop, its location and duration, that participation was voluntary, and what would happen to their audio-recorded data.

Participants were offered a £20 Amazon voucher in recognition of their time and input. Two researchers facilitated each workshop, using a semi-structured topic guide to lead discussion and ask open questions to elicit a range of views.

First, the participants were encouraged to reflect and share their lived experiences as caregivers of people with psychosis or BD. This included how their relative was first diagnosed, how they became involved as caregivers, the impact of mental health problems on their family and daily life, and their current sources of support, as well as the types of support or strategies they found most useful.

Second, they were asked their views on gaps in the support system for caregivers, how to fill these, and whether online support could play a role in this. Finally, they reviewed the REACT booklets together and discussed whether and how these could be redesigned as a web-based intervention, and what additional support might be needed to facilitate its use online. Each workshop was audio-recorded with participants' permissions, and transcribed verbatim for later analysis (see the data analysis section).

We conducted an additional workshop (Workshop 3) with two participants to scope the types of features that could be included in the web-based REACT intervention. Both participants were comfortable using computers, used social media frequently, and were interested in helping with the design of REACT. Before the workshop, participants were given access to the PDFs website. They were also asked to identify other websites they liked or disliked, both related and unrelated to mental health. We explored their aesthetics and functionalities together. This was followed by visual demonstration of a series of design prototypes for the web-based REACT intervention, based on our findings from Workshops 1 and 2. The prototypes were developed in conjunction with a web design company and mainly focused on aesthetic aspects of the web interface such as logo, font style and size, navigation menu, colour scheme and multi-media choices.

We wanted to know how to translate the values and needs that participants had highlighted in Workshops 1 and 2 into functionalities. In particular, we wanted to understand how best to give users a positive experience. We therefore asked participants in Workshop 3 to discuss how to design the web-based REACT to be more engaging; what features might motivate users to keep returning; and what types of support could be offered only online.

A full description of the findings of all three workshops is reported elsewhere,[83] but is summarised in the next section.

Understanding user perspectives: results

The majority of participants in Workshops 1 and 2 were female, over the age of 45, parents and infrequent computer users. Most had had many years' experience caring for relatives with severe mental illness (on average about 10 years). In Workshop 3, one participant had taken part in Workshop 1 and was typical of that group, while the second participant was aged 21 and new to the study. In total, 25 participants took part in this qualitative study across all three workshops (18 females; age range 21–75; n=20 parents). Participants comfortably shared their experiences and no prompting was required for conversation to flow. Key findings covered their caregiving experiences, the support they believed was needed, the potential role of online interventions and their design.

Caregiving experiences

Identity as a carer

Relatives talked about feeling a loss of sense of self in their journey to becoming a carer. They felt they had been pushed into a "carer" role and found it hard to maintain their identity as a father, wife, etc:

> ***Workshop 1, Participant 9:*** *I don't want to be a carer, I don't like the word. I'm a mother. I know somebody has me down as a carer even if they don't give me a decision. But in my head, I'm not.*

The role of carer was particularly unappealing as it came with no formal training or guidance, so as well as being imposed, it was also very challenging. Many relatives described it taking years for them to learn strategies to cope with the impact of psychosis or BD on the rest of the family.

Impact on the whole family

Participants described the very broad impact mental health problems had on the wider family, and the need for support for all family members:

> ***Workshop 1, Participant 1:*** *Our youngest son didn't understand what his brother was going through…It must have been terrible for him and in fact not long ago he actually left the family.*

In addition, caregivers discussed needing support not just as caregivers but as individuals in their own right, with other responsibilities in their lives:

> ***Workshop 2, Participant 3:*** *I might have had a right morning with my son; threatening suicide or wrestling for my own life. And I'd have to go in work…change into my uniform and drive to work and I've got a lump in my throat. And I'd phone my partner [saying] "I'm going to cry.".*

Social isolation

Caregivers of people with physical illness may have little opportunity for social interaction because of the need for constant caring. In mental health, social isolation can be further exacerbated by stigma and lack of public awareness about mental health. Participants talked about finding it difficult to open up to their friends and families:

> ***Workshop 2, Participant 10:*** *My children used to say to me what do we say to our friends about [relative]? And I told them to [deny relative has a mental health problem], which I don't know is right, because I thought they'll get bullied. Or otherwise they will say your relative's crazy or…*

Many had found it challenging initially to find others with similar lived experiences. Once they were in contact with other caregivers, they found this invaluable, not only for emotional support, but also for signposting to important information and guidance. Many were part of charity-run face-to-face peer support groups facilitated by an "expert caregiver".

> ***Workshop 1 participant 1:*** *The person who runs our small group is a godsend. What's worrying is if she couldn't do that job what would we do with it? That's what I always think about because there's got to be a system there that does what she does.*

Though valuable, these groups were considered scarce, and almost invisible to newly diagnosed caregivers.

Support needed

Information

Participants reflected on the knowledge and information they wished they had had as they first adapted to the caregiver role:

> ***Workshop 1, Participant 1:*** *We've been caring for so many years, I thought there's nothing I can learn now. I know it all. But actually a lot of what was in [the REACT booklet] was kind of new to me and if somebody had told me that at the beginning, you know, how to – how to break through the system, then I think things wouldn't have got so bad.*

They acknowledged that it could take years for relatives to learn about the mental health condition, and on reflection identified three types of educational sources that newly diagnosed caregivers would greatly benefit from:

- A comprehensive list of available sources of support such as local support groups and national charities:

> ***Workshop 1, Participant 6:*** *This exists. That exists. You can read this. You can read that. You can go here. You can go there. You've got a right to this – this is practical help, not the general pat you on the back and say everything's*

alright and happy clappy, and let's be friends, but actual hard practical, meaningful.

- Information about medication, including types, side effects and how to manage doses:

  Workshop 2, Participant 5: *We're never given sort of like a comparative – information about the various anti-psychotics. They had awful side effects.*

- Legal rights:

  Workshop 1, Participant 1: *I think actually what carers are entitled to under the law is very different from what they get in real life. And you've got to know.*

Overall, participants agreed that knowledge is power and that less experienced relatives would benefit from guidance on how to get help, and from being directed to trusted and up-to-date resources.

Emotional support

Participants talked about the emotional impact of supporting someone with psychosis, and the importance of emotional, as well as practical, support:

> ***Workshop 2, Participant 2:*** *I had some professional experience [in mental health] but it's completely different when you are emotionally involved…It's literally like somebody's just parachuted you into a foreign country. You've no idea of what should be happening, what is available. And you need to know that sometimes to be able to get it.*
>
> *But the peer support is about emotional support. And I think what health professionals sometimes don't understand is by the time you get to them you've been doing this for months, 24 hours a day, 7 days a week. And the emotional toll on you…*

They talked about the importance of hearing that their experiences were not unique, as well as the need for explicit reassurance that the development of mental health problems within the family was not their fault and that they were doing all they could to manage the situation:

> ***Workshop 2, Participant 7:*** *My mum never forgets this nurse who said to her, it could happen to anybody. This is not your fault. You're doing everything you can. And that just lifted that guilt off my parents. But sadly that was the only time.*

Opportunities to have social contact with similar caregivers, to share experiences and feel connected and supported were particularly valued:

> ***Workshop 3, Participant 1:*** *There's nothing better than seeing that somebody else has had the same fears and guilt to start with. Worries about the future and practical travel problems.*

A recovery-focused approach

While most of the discussion revolved around challenges relatives faced, the need to focus on positive outcomes was also evident. One participant explained how she desperately struggled to find positive role models for her son:

> ***Workshop 3, Participant 1:*** *Then I realised that the positive role models don't want to go back and look again. And there's got to be thousands of recovered or people who are managing their condition but they don't really want to join the club. And that would be priceless, to have more positive role models. People who have managed and are managing their conditions or have completely recovered.*

There was a general feeling that caregivers and service users would benefit from hearing positive stories to give them hope that recovery was possible.

The role of online interventions

For the majority of relatives in this group, online support was seen as part of a *"big scary virtual world"*. They described several practical challenges regarding using the Internet, including limited access and skills:

> ***Workshop 1, Participant 10:*** *I live in the country and my internet doesn't work half the time and my computer is probably my biggest source of stress.*

However, it was not only practical issues that made them concerned. There was a lot of fear associated with online activity, and many relatives felt reluctant to post personal information on any website. They feared that, once shared, it could never be removed and would always be "Googleable". There was also an ethical dilemma that, in sharing their experiences online, they could also be sharing their relatives' experiences, without their explicit consent. Participants felt it was often unclear "whose story" it was:

> ***Workshop 1, Participant 10:*** *I don't mind saying anything about my own medical symptoms or if I had a mental health problem, but…if my anxiety and stress and my needs are because my relative's issues aren't being addressed,*

> *then it is about me but it's still about her…But everybody's different so I think there needs to be a number of ways to access this information.*

This dilemma was exacerbated by fear of the impact their posts might have on their relative if they saw them:

> ***Workshop 1, Participant 8:*** *If my relative happened to get access to it, it could trigger a major episode.*

This led to limits in how open relatives felt they could be online:

> ***Workshop 1, Participant 5:*** *My relative has now got access to all my Facebook discussions. But I've always feared letting [my relative] know how I'm feeling about things…I'm not sure how far we can open up.*

Overall participants had mixed views about the value of online support but felt that people in the generation below them might be more positive, and might even be put off by paper-based support.

> ***Workshop 1, Participant 1:*** *We're all of a certain age. And what I'm finding is that, the people in the group who are a lot younger are actually perfectly happy to go all over Facebook.*

> ***Workshop 2, Participant 6:*** *It's often a generational thing and a lot of younger carers are siblings. Would never dream of getting something off paper, they would automatically go online.*

Online design for REACT

Most of the specific ideas for design features came from Workshop 3, whose two participants were more frequent and confident users of computers. The key design issues they identified are summarised here.

The paper-based REACT PDFs are too text-heavy for online

Initially participants were presented with the website containing the PDF versions of the REACT booklets. Unsurprisingly, they found these too text-heavy, and felt relatives would not have time to read them and would quickly lose interest. Their suggestion was for much more use of video to convey factual information and sharing of experiences.

Importance of vicarious learning in addition to didactic instruction

One challenge of a self-management toolkit for long-term health conditions is that it is difficult to make concrete recommendations when there is often no right or wrong answer. One participant felt that a limitation of many sites they had reviewed was that they tried to provide checklists: “A lot of websites will say, oh why don’t you try meditation [or] going for a walk” (Workshop 3, Participant 2). Instead it was suggested that online support needed to be thought-provoking, to facilitate “thinking and reflecting” exercises that enabled users to learn problem-solving strategies that could then be applied to their own particular context.

> ***Workshop 3, Participant 2:*** *Stuff that helps you ask questions and helps you think about what you’re feeling rather than like, try this, try [that], because there’s only like so much a hot bath can cure.*

Sometimes relatives had questions to which there Google – and online interventions – could provide no useful answer:

> ***Workshop 3, Participant 2:*** *How much am I supposed to do? What’s too much? What’s not enough? How strict am I supposed to be? When’s the point when I back off? And that’s not really a question that I felt I could ask Google ’cause I’m not going to get anything useful from that.*

Need for a personalised record of support

Supporting someone with a mental health problem is often a long episodic journey. Participants suggested offering a personal space in which relatives could save useful and interesting information to revisit easily, “like some kind of like scrapbook section…where like people just put different stuff in” (Workshop 3, Participant 2). The value of this would be not only in having a useful place to store things, but also to facilitate a process of reflection on progress over time:

> ***Workshop 3, Participant 1:*** *It’s very affirming to go back to some of the earlier learning content to realise that you have learnt, you know, I’ve acted correctly. You have been a good carer.*

Attractive, appealing and easy-to-navigate design

Participants were keen that we retain the colour-coded modular design of the toolkit, and suggested more emphasis be given to the invitation to dip in and out in an order and frequency of the user's choosing, without the need to complete modules in sequence.

> ***Workshop 3, Participant 1:*** *Instead of having to go through it in like a sequence, you can just like go onto the ones you choose…Like you can do it quite easily with the hard copy.*

They recommended including a "how to use the intervention" section to explain that REACT covered a wide range of topics and to encourage shorter sessions, selecting the modules that were most relevant to the challenges they faced at that time.

When asked about frequency and mode of delivery of prompts, participants felt this would vary and that users should be able to customise this. They both disliked receiving too many prompts and would feel "suffocated" or "pressured", especially if they were having a good day. They therefore recommended "reject" and "unsubscribe" buttons. They also preferred to receive person-centred prompts:

> ***Workshop 3, Participant 2:*** *What's your question this week? What are you worrying about this week? You never get any e-mails that just say, How are you doing? How are you?*

Participants recommended using colourful, positive images and artworks throughout the toolkit.

> ***Workshop 3, Participant 1:*** *I'm just thinking right the way back to 2000, I think probably what my family were given were, Here's these leaflets, which weren't even colour leaflets at that point, you know. You can imagine that it was like [to] read that info.*

Trustworthiness

The design of the toolkit was felt to be very important in engendering a sense of trust in participants. Simplicity, ease of navigation and a professional look were all seen as qualities that would attract users by assuring them that the intervention was legitimate:

> ***Workshop 3, Participant 2:*** *'Cause you look at it and you go, Oh wow, this looks legitimate, like I can trust this. And then you start building up that trust and start using it.*

Participants compared the look of a website to a building and suggested aiming not for a slick look, like a building with shiny floors that felt corporate, but instead for something simple and professional that provided information.

Creating the design brief

Based on these findings, we drew on the expertise of the TMG to create a design brief for building REACT. The TMG included a relative with extensive experience of supporting other relatives through a leading charity, and a consultant psychiatrist, two consultant clinical psychologists and a GP, all with expertise in supporting people with mental health problems and their families, and some with expertise in designing and delivering digital health interventions (SJo, EM). The brief was as follows:

The modules

The content of the paper versions of the modules was updated and rewritten for a broader range of relatives. Large sections of text were replaced by video material wherever possible. Videos included experts sharing their clinical expertise on each topic, and actors sharing the personal experiences of relatives and service users.

We were very keen to ensure these latter videos felt authentic to people using the site. We considered filming real relatives and service users, but were concerned that subjects might change their mind over time about sharing their story, and that removing a story already uploaded to the Internet might not be possible. Relatives' questions in workshops about the ownership of stories also made us wary. We therefore invited relatives and service users to talk on video, and then, supplemented by face-to-face discussions with relatives and service users at the Spectrum Centre in Lancaster University, worked with the actors to create hybrid characters who shared their "experiences" to camera.

Additional modules were added, including: "What is bipolar disorder?" and "Managing mood swings"., and new introductory sections created: a welcome page, "Meet the team", and a "how-to" module which outlined the aims and structure of REACT and how it could be used. All new and revised modules were shared with the RAG, which gave detailed feedback on the language and structure.

Signposting

We specified the need for a comprehensive signposting page, which could be updated regularly, and contained direct links to other useful organisations and websites providing information or support.

Peer-to-peer support

The strong desire to meet and learn from the lived experiences of other relatives led us to specify the need for an online function to allow this. We chose to allow people to be anonymous in this space due to their fears around confidentiality. We were also keen that this be moderated to ensure that any negative responses could be managed, and any risk issues quickly identified and responded to (see *Protocols and policies* below).

Confidential support

In addition to peer-to-peer support, we also specified the need for direct confidential support for those relatives who did not want to share their experiences with peers, but had specific questions they wanted answered.

A place to store the history

We really liked the idea of an online place where relatives could securely store any documents they found relevant to their supporting role and might want to revisit. We hoped this would also allow them to reflect on their caring journey by providing reminders of events over time and the challenges they had overcome.

Look and feel

The site should be simple, easy to use, create a positive tone, and include images relevant to the content. We reused many of the images from the paper-based toolkit. In addition, one of the relatives who took on a REACT supporter role was a professional artist and created additional images for the site.

Building and hosting the REACT intervention

REACT was initially built in WordPress by a web design and hosting company local to Lancaster. The plan was initially for them to host and maintain it during the trial. However, due to difficulties in establishing a sustainable plan to do this, the site was brought in-house and is now located on a dedicated virtual server at Lancaster University. It is maintained and updated bimonthly by a digital technology developer within the REACT team (AW).

To meet the design brief, the WordPress site required a number of plug-ins. These included standard ones such as BBPRESS to run the REACT Group forum, and some built bespoke for the REACT site.

REACT toolkit

The content of the toolkit was informed by family intervention models that underpin effective face-to-face treatments for people with psychosis.[84-88] The key components of the toolkit were: 12 information modules; a comprehensive resource directory; and peer support through a group forum, and a confidential direct messaging service. A "Meet the Team" page ensured that relatives were fully informed about who was delivering the content of the site. Logos for Lancaster University, Lancashire Care NHS Trust, University College London, Liverpool CTRC, and the McPin Foundation were prominently displayed on the login page. Mytoolbox offered users a confidential space to save links to any information they might want to access easily later, including specific toolkit content, their self-reflection tasks, and external web links. A blog page offered a flexible space for additional communication with site users which could be edited by the REACT supporters.

REACT information modules

Each of the 12 modules contained: evidence-based written information; videos of clinical experts and/or content from experts by experience to illustrate key points; and self-reflection tasks to ensure content was personalised to the user.

1. *What is psychosis?* Information about psychosis, what it feels like, possible causes and common misconceptions.
2. *What is bipolar disorder?* An overview of BD, its main features, different presentations and how it feels to experience it.
3. *Managing "positive" symptoms:* An explanation of the term "positive symptoms", how these might be experienced, how they might appear to relatives and friends and how they can be managed.
4. *Managing "negative" symptoms:* A detailed description of signs that make up "negative symptoms", how these can manifest and how relatives can spot them; how they might make relatives feel; and suggestions for helping the person experiencing these symptoms.
5. *Managing mood swings:* How to help people avoid extreme lows and highs, maintain a stable mood and support a relapse prevention or staying well plan; with suggestions for creating a low-stress environment in a friendly, non-judgemental way.

6. *Dealing with difficult situations:* Describes the difficult situations that relatives and friends can encounter, including risky, illegal, or embarrassing behaviour, and suggests ways to manage these.
7. *Managing stress – doing things differently:* Helps relatives consider what stresses they have in their own lives and how to adapt their behaviour to manage.
8. *Managing stress – thinking differently:* Helps relatives consider how they think about the stresses in their lives, and whether different perspectives might help reduce their distress; explores the many common thinking traps such as jumping to conclusions or mind-reading; and helps relatives to test their own thoughts.
9. *Understanding mental health services:* Supports relatives in navigating services, helping to ensure they talk to the right people to get the right information and the support they need.
10. *Treatment options:* Information on the medication, psychological interventions and other therapies that people with psychosis or BD and their relatives should be offered, according to the NICE guidelines; aims to empower relatives by outlining choices.
11. *Dealing with crisis:* Clear suggestions about what to do in a crisis, where to turn to for help and what to expect from services; creates a useful personalised "What to do in a Crisis" plan.
12. *The future and recovery:* Focuses on supporting recovery, with useful tips on how to help people with BD or psychosis to develop confidence and gain independence, including: finding a balance between support and enabling independence; looking for positive changes to celebrate; accepting new goals and challenges; and focusing on the bigger picture.

The resource directory

The resource directory (RD) provided to participants in the REACT trial and the control group contained a comprehensive list of national organisations supporting people with psychosis or BD and their relatives (such as Rethink, Mind, Carers UK and Bipolar UK), and those for related conditions (such as Anxiety UK and Samaritans), with website addresses and phone numbers. The RD also listed 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, Samaritans, and a link for finding contact details for the user's local NHS mental health services out-of-hours crisis team.

The RD given to those in the REACT arm of the trial also contained additional elements, including extensive information on topics such as advance directives, advocacy, benefits,

direct payments, carer's allowance, carer's breaks, confidentiality, and mental health law, and an interactive map of support groups in different geographical areas. This content was developed in consultation with REACT supporters and the RAG, and was added to over the period of the trial in response to information from users.

Support

Support was offered through confidential direct messaging with trained relatives (REACT supporters), and peer support through a moderated online forum. The REACT supporters were available on the site Monday to Friday, from 9am to 4.30pm, excluding bank holidays and university holiday closures. Their key role was to provide emotional support, and to guide relatives to relevant parts of toolkit or other resources as appropriate. They were also trained to moderate the forum and could hide posts or withdraw access in response to inappropriate use. They were trained to identify and report risk, and were supervised by two clinical psychologists and an expert relative. A REACT supervision manual (*Stand Alone Document 1*) and REACT supporter manual (*Stand Alone Document 2*) were provided.

Reminders

Participants allocated to REACT were emailed reminders to visit the website after a week of inactivity. Participants could change the frequency of these reminders or turn them off.

Appearance

Screenshots in *Figure 1* show the look and feel of the REACT intervention.

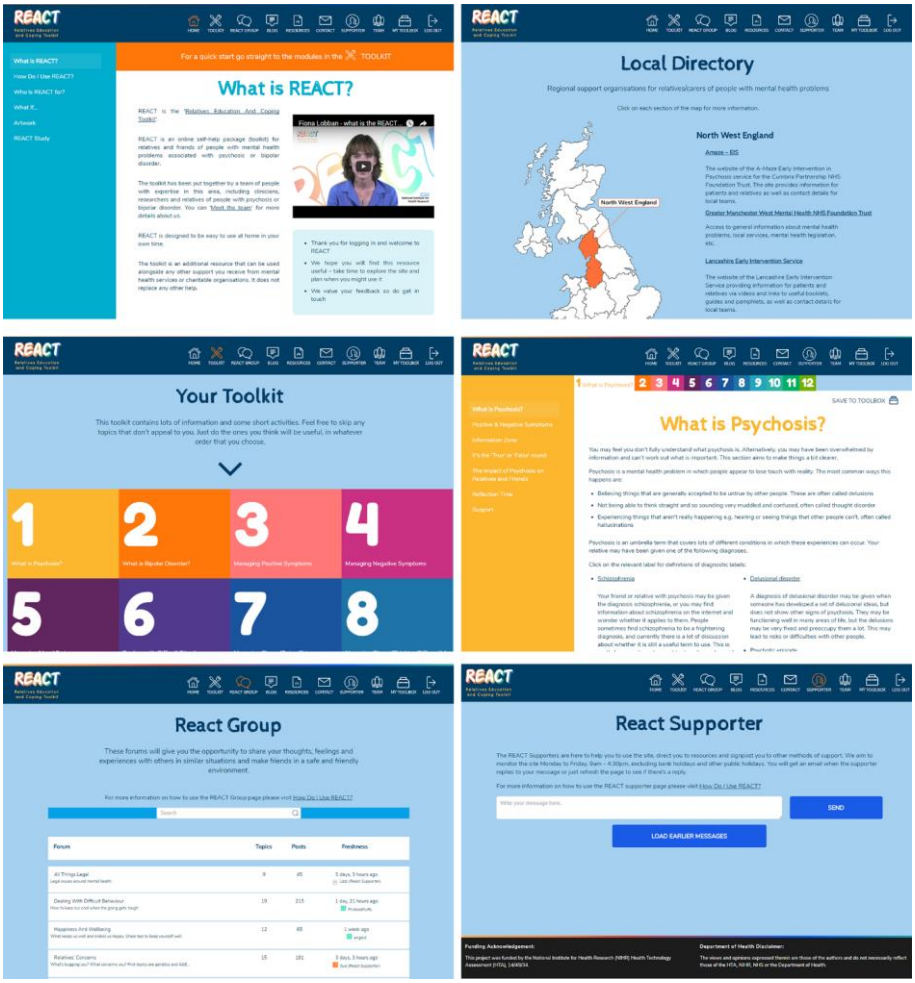

Figure 1: Screenshots of the REACT intervention website

REACT supporters

The role, training and supervision of REACT supporter are briefly summarised here. *Stand Alone Documents 1 and 2* provide the detailed manuals for REACT supervisors and REACT supporters respectively. The REACT risk protocol is found in *Stand Alone Document 3*.

Role

REACT supporters were carers with lived experience of supporting a relative with psychosis or BD. Their role was to offer support to REACT participants through forum posts, direct messages and blogs. REACT supporters did not give direct advice but provided empathetic support while helping participants access relevant information and resources. They also moderated forum activity to ensure there were no inappropriate posts and checked forums and direct messages for risk (see *Protocols and policies*, below). Carers rather than clinicians were selected to support the intervention so that supporters had personal experience of the issues raised by people using the site and so could readily empathise with these issues in a sensitive and appropriate manner.

Training

The primary focus of REACT supporter training was on familiarising supporters with the REACT toolkit's content and functions and giving them confidence to make timely forum posts and respond to personal messages from relatives while logging any risk issues. There were three intended domains for training: clinical, technical and co-worker sharing.

Clinical training was provided by the clinical supervisor (SJ) and chief investigator (FL) before REACT was launched, and supplemented with ongoing clinical supervision (see next section). As REACT supporters were able to draw on their personal experience of caring, clinical supervision helped train them in providing empathetic support and guiding relatives to the best use of the toolkit and associated resources to deal with their concerns.

Technical training was provided by the IT/digital support lead (AW) and clinical supervisor (SJ). This was intended to ensure that REACT supporters were very familiar with the REACT site and module content, the research directory, and how to access the automated emails informing them about posts.

Co-worker sharing was intended to offer a supportive environment in which supporters could share information and learning and develop ideas to increase site activity.

The REACT supporter role was relatively novel and there were therefore few training and supervision models to draw on at the beginning of the programme. REACT supporters indicated that they would have appreciated more in-depth structured training in how to moderate peer-to-peer interactions on the forum and offer support, more detail on site functionality and longer access to training around clinical issues in mental health. Although REACT supporters did successfully execute their roles with the training provided, the

REACT supporter and supervision manuals provide additional information on how such training could be improved in future.

Supervision

Supervision was led by an experienced clinician fortnightly for up to 1.5 hours to provide a space for REACT supporters to discuss relevant issues in a supportive environment. Issues typically covered in supervision included clinical issues, site cover and supporter wellbeing, with other issues as required. Supervisors and REACT supporters would review topics raised in direct messaging and the forum, including any risk issues. Urgent risk issues between sessions were dealt with in accordance with the risk protocol (see next section).

Site cover issues included planned site closures such as Christmas, as well as staff leave, training and sickness absence. It was important to ensure that adequate time was allocated to supporter wellbeing. This included consideration of how personal and work factors might affect different supporters at different times and reviewing approaches to address this. Other issues covered as required included reviews of planned blog posts, ideas for updates, refinement of site materials, technical issues and site promotion.

Protocols and policies

All forum posts and private messages were reviewed by REACT supporters for potential risk, in accordance with the risk protocol (*Stand Alone Document 3*). Risk was categorised as low or high. Low risk was defined as showing no indication of immediate or serious threat of severe harm or risk to life but either:

- Clear evidence of high levels of distress, or
- Concerns for risk of harm or abuse towards participants or others (safeguarding risks).

REACT supporters who detected low-risk posts where distress was the primary issue responded with a standardised email to the carer. For potential safeguarding issues, the supporter consulted their clinical supervisor and used their NHS trust safeguarding team to discuss potential risks if appropriate.

High risk was defined as the presence of clear evidence of immediate and serious risk to life or child welfare. If immediate risk of severe harm or death was detected, the protocol stipulated an emergency call should be made to police (risk to life) or social services (other risk to child). Any concerns that might constitute a risk issue but fall outside these definitions

were discussed as urgent with the clinical supervisor to decide on a course of action. All risks were logged by the REACT supporter on the REACT system to provide a record of the level of risk identified, where the risk was identified (forum post, direct message or other source), which supporter identified the risk, what action was undertaken and what follow-up actions were performed, including the name of the clinical supervisor consulted. SJ was the lead clinical supervisor. To allow for leave and other commitments a rota of alternative clinically qualified contacts was employed including BS, SJo, NF and FL. FL was the contact of last choice, to avoid unblinding, and was never required. SJ and BS dealt with the vast majority of risk queries, none of which met the high risk criterion.

As part of their role REACT supporters also monitored the site for inappropriate posts in line with an agreed posting policy (*Stand Alone Document 4*). If the supporter believed a post might cause significant distress to participants, they had authority to remove it temporarily. It was then discussed with the clinical supervisor at supervision or at an earlier ad hoc meeting if required. This discussion was used to reach a final decision as to whether the post would be removed permanently or reinstated.

Resource directory-only intervention

Participants allocated to the RD arm logged into the same website, but were able to see only the “Meet The Team” and RD pages. At the end of the study those in the RD only group were given access to the modules, without forum or direct messaging.

Logic model for REACT

For any intervention, it is important of making explicit the underlying theoretical basis. *Figure 2* outlines the process by which we hypothesised that REACT would benefit relatives.

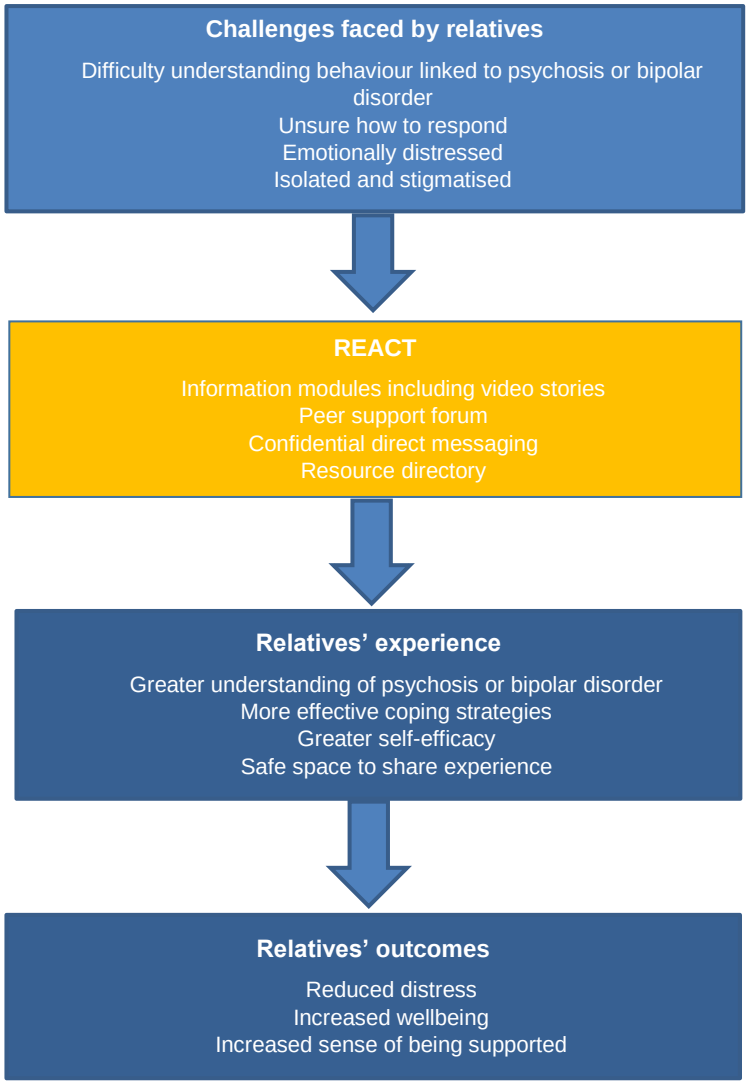

Figure 2: Hypothesised mechanism for REACT

Reflections on developing REACT

REACT drew on evidence-based cognitive and behavioural psychological theories and clinical practice. The content had been developed and refined over many years, with extensive input from relatives, clinicians, and service users in an early intervention context. Therefore, in building the online version, we already had a good idea of the problems faced by relatives, an understanding of the processes underlying these difficulties, and the strategies that could be successfully used to address them.

Even so, in broadening the reach of REACT to relatives of people outside EIP services and those with bipolar experiences, we felt it was important to explore further what challenges these groups experienced and what support they valued. We also wanted to investigate relatives' views about online interventions. This information was invaluable in helping us to build a design brief, and ultimately develop the online version of REACT in time to start our trial. However, there were many challenges along the way, and we learnt a lot in overcoming them.

The drive to translate REACT from a paper-based to digital intervention came primarily from the practical need to have something that was easy to update, cheap to deliver and consistent with the NHS's direction of travel towards Digital NHS.[89] However, the extent to which service users and relatives wanted to receive support online was not clear. Many studies showed support for digital health interventions (DHIs) in mental health, but none from representative samples of the service-using population, and most had recruited small convenience samples of people interested in digital health.[90, 91] The relatives in our workshops were also a convenience sample, but were invited into the study to talk more broadly about their experiences of supporting someone with a mental health problem and so may have been less biased in their views about online support. They had many reservations about the use of online interventions, but also suggested this might be a cohort effect, and that a younger population would perhaps be less concerned and more comfortable with this mode of delivery.

Although all the relatives in our sample could access online support, some were limited in their access to private spaces to use computers, and in their connectivity, skills and confidence. There is some concern that rather than broadening access, online interventions might in fact narrow access, dividing those with and without easy access to online computers, and also those with and without the skills, confidence and motivation to go online.[92] In many ways it was helpful to hear the concerns of these relatives as it made us

think about how to address these in our design. However, involving more regular users of online technology might have generated ideas for additional functionality. For example, live social media feeds are now a standard feature of many online interventions and with hindsight might have been of benefit by ensuring constant new material that brought people back to the site.

Drawing on the extensive work done to develop the paper-based REACT also gave us a text-heavy starting point, which required a lot of reverse engineering to produce content more relevant to an online intervention. Starting from scratch might in some ways been easier and led to a more digitally friendly product.

We wanted REACT to be built by experts who could work face-to-face with the relatives in our RAG. We did not have an existing relationship with any digital health companies, and Lancaster University did not at the time have a list of preferred providers. We therefore put the build of REACT out to tender among local companies. We had a limited budget which proved to be well below the costs quoted by many companies offering bespoke builds. We knew that REACT would need to evolve, with edits made over time, and that staff would need training in how to use the site, all of which would make us reliant on those who could write the code, further increasing ongoing costs. We also recognised that many web-development businesses do not survive, and so we were wary of stranding ourselves with a bespoke site built in a code we could not then edit.

We therefore employed a local digital technology company with some experience of building attractive websites using the open source WordPress programme and who quoted within our budget. However, during the build process, we became concerned about the company's ability to deliver secure storage and regular updates for the website and decided to bring the project in-house. The site was moved onto the university server, we ensured all identifiable user data was stored separately at the Liverpool CTRC, and all edits and updates were done by IT experts within the REACT team. This proved to be a wise decision as the company ceased to trade less than 12 months later.

While a genuine partnership with a digital technology company would have offered many advantages, including greater investment in the product design, and support for wider dissemination, there were also many challenges to this model. Digital technology companies are rarely run as not-for-profit social enterprises, and as such will look to maximise profit from the NHS. Given the NHS's increasing reliance on digital technology, costs to the NHS are likely to rise exponentially. This may cause serious financial problems in the future.

Finally, we know that having people to support digital interventions is crucial to their success,[93, 94] but how and by whom this is best done remains to be answered. The relatives in our workshops talked extensively about the power of peer-to-peer support. This is consistent with feedback from our feasibility trial, and with growing support for the development of peer-worker roles in mental health services around the world.[95-100] In developing the design brief for this role, we identified a range of new skills that need to be learnt (e.g. managing online forums and communicating effectively in text format) and existing protocols that need to be adapted, such as risk management. Not only were these new and challenging to REACT supporters, but also to supervisors. Considerable time and effort were therefore needed to provide training, support and development for all members of the team.

Chapter 3 Clinical effectiveness: methods

Introduction

This chapter outlines the methods used to assess the clinical effectiveness of REACT. The chapter follows the structure of the CONSORT statement,[101] including the extension for pragmatic trials,[102] and for eHealth interventions.[81] As our data was collected online, we have also reported data collection in line with the Checklist for Reporting Results of Internet E-Survey (CHERRIES).[103]

Study design

This was a primarily online two-arm pragmatic single-blind individually randomised controlled superiority trial. The trial is described as *primarily* online as all of the intervention and most of the data collection occurred online. However, some text, telephone and postal reminders were used to support the registration process and to maximise retention.

Setting

This study took place online in the UK. It was hosted by one NHS foundation trust, and other trusts and CCGs were eligible to take part as participant identification centres (PICs). Recruitment also took place through local and national mental health charities, media, social media, and Google Ads. REACT was built using WordPress open source software, and hosted and maintained at Lancaster University. Data was collected using a bespoke web-based system at Liverpool CTRC.

Participants

Eligibility criteria were designed to be as broad as possible. Inclusion criteria were (according to self-report):

- Aged 16 or over
- Living in the UK
- Relative or close friend of someone with psychosis or BD

- Currently experiencing distress due to their relative or close friend (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 floor effect on levels of distress at baseline, and was the item that correlated most highly with the GHQ total score in the REACT feasibility trial
- Currently seeking help (self-identified), and therefore likely to engage with support offered
- Access to an Internet-enabled computer
- Sufficient English fluency to comprehend intervention content.

Exclusion criteria included living in any of the six geographical areas by postcode taking part in the parallel IMPART implementation study[104] of the same intervention. In addition, only one relative per service user was allowed to participate, to avoid a clustering effect.

Recruitment strategy

Recruitment took place from 22 April 2016 to 30 September 2017. Before this, relatives who visited the website were invited to leave a contact email. A range of online and offline recruitment strategies was used, all directing potential participants to the study home page (www.reacttoolkit.co.uk) which provided information about the study and how to take part.

At registration. participants were asked how they had found out about REACT. The number of participants coming into the study through each avenue was monitored by the TMG at its monthly meeting, and our recruitment strategy adapted accordingly.

Social media

Twitter

Studies of Twitter as a recruitment tool for online studies have been mixed: some found it to unsuccessful,[105] others successful.[106] Given its large reach and free nature, we set up a REACT Twitter account. The research team posted several times a week about the trial and relevant mental health news, and encouraged colleagues with Twitter accounts to tweet or retweet. We posted or retweeted 325 times and gained 711 followers.

Facebook

Facebook had been used successfully for recruitment in previous studies.[107] We set up a REACT Facebook page to post relevant mental health and trial-related news. After an expensive and fruitless attempt at creating Facebook adverts ourselves, we enlisted an agent for this purpose, funded by one regional clinical research network for 13 months and by another five networks across the UK for the last 7 months.

In all, 70 carousel and standard-type adverts were used, targeting seven geographical areas. We split-test each variant, reallocating the spend to the best performing adverts. The standard advert type outperformed the carousel adverts, and the more obvious images, containing text that reiterated the messaging, outperformed other adverts. The best performing ads are shown in *Figure 3*.

Adverts were viewed on mobile devices over desktops by 40:1. Over 13 months, we reached 873,096 individuals; 53,216 people engaged with an advert (liking, commenting or sharing) and there were 71,026 clicks through to the REACT website.

Figure 3: Screenshots of Facebook adverts

Websites and forums

Recommendations from previous studies[77] led us to increase our online presence through promotion on websites, within online forums and through Google Ads. We encouraged PICs to display information on their NHS websites (outcome unknown as this was not specifically monitored). Promotion via forums proved difficult due to restrictions on joining as a researcher.

Google Ads were suggested by previous research into online recruitment to online intervention.[108] Google displayed a short advert whenever browsers searched for our keywords (e.g. bipolar disorder, relative, carer and information), depending on our budget and competition with other advertisers for our keywords. We set our budget at £10 per day for 12 months, reviewing our strategy and keywords regularly. Google Ads data showed that our advert was seen 1,323,900 times and received 11,448 clicks.

Charitable organisations

Promotion through trusted charity sites can ensure high numbers of visitors,[77] and endorsement by the charities can reassure participants, increasing the likelihood of sign-up.[77] REACT was promoted by Bipolar UK, Rethink Mental Illness, Mind, Sane, the McPin Foundation, National Survivor User Network, National Centre for Mental Health and Carers Link through a combination of websites, social media, blogs, e-newsletters, mail-outs, offline magazine adverts and dissemination of material at events and meetings. Charitable organisations were invited to be included in the RD listing of support services.

Universities

Promotion through universities was focused locally. An email was sent to all members of the Faculty of Health and Medicine at Lancaster University. Posters were displayed on plasma screens and stickers in the university building. REACT was also promoted in the monthly university e-newsletter and Lancaster University community day. REACT supporters also presented the trial at University of Central Lancashire PPI group.

Newspaper and radio

Local and national newspapers and radio stations were contacted but the trial was covered by only one local radio station and one local newspaper, so the strategy was not pursued.

NHS

As with charities, previous studies suggested that promotion through healthcare providers would reassure and encourage participants to sign up.[91] We therefore targeted the NHS strongly. However, NHS trusts and GP surgeries rarely have an accurate, up-to-date way of identifying relatives. Contact with relatives is often documented only in patient notes, not recorded against a separate code in the electronic record. Listed next of kin may not be the person offering day-to-day support (our target population). Therefore, recruitment is often through the patient, who may forget or not wish to pass information on.

We invited 54 NHS mental health trusts in England (out of 60, six trusts being participants in the parallel IMPART study), two trusts in Wales and two in Scotland to become PICs for REACT. We also invited 124 primary care trusts (which later became CCGs). Across the UK, 54 mental health trusts (50 in England, 2 in Wales and 2 in Scotland) and over 74 primary care trusts or CCGs gave approval. Lancashire Care NHS Foundation Trust was the host trust.

Given the challenge of persuading busy clinical services to engage in research, we offered PICs an incentive to recruit to REACT by allocating accruals to the PIC (based on participant postcode), rather than to the host trust (which is sometimes the case when sites are operating as PICs).

The research team gave presentations, put up posters and disseminated flyers and business cards at NHS trust sites, GP practices and support groups locally (in the North West of England). The trial manager (TM) hosted two webinars for NHS staff involved in recruitment (numbers not recorded but participants described them as helpful). The TM periodically sent e-newsletter updates to PIC staff and responded to any contact from clinical studies officers, including requests for recruitment material. REACT supporters presented the study at clinical team meetings and NHS support groups.

Across England, the clinical research networks supported recruitment through clinical studies officers and research nurses in secondary care mental health trusts, and promotion and database searches in GP practices. Practices were asked by clinical studies officers in their area to display posters, flyers and business cards in waiting areas; however, we did not keep a record of how many did this.

Across the UK, 35 GP practices searched their databases for patients with a diagnosis of “psychosis/schizophrenia/schizophreniform disorder/psychotic disorder/schizoaffective

disorder/bipolar disorder/manic depression/cyclothymia", and sent invitations and participant information sheets to these patients to pass on to a relative. The 35 practices sent 2,377 letters in total (range 5–451; median 34). At least two practices included REACT on their websites; we did not keep a record of this activity, so the number may be greater.

PICs also did their own online promotion via social media, intranets and websites. We did not monitor this activity in detail.

To maximise efficiency of resources within NHS services, our recruitment focused initially on England and then moved into Wales and Scotland. We reached our target before moving on to Northern Ireland.

Service user and carer support groups

REACT supporters presented the study at two local non-NHS service user and carer support groups. These groups were attended by both service users and carers, but not in large numbers.

Consent

We adhered to British Psychological Society guidelines for taking informed consent online.[109] These included: taking a record of valid consent; including check boxes relating to specific consent statements; limiting the number of consent items; and ensuring participants were fully informed of study procedures, risks, confidentiality and right to withdraw. Capacity to consent was assumed, as there is little scope to assess it in an online trial. All participants were emailed a Word copy of the completed consent form, with a version kept on a secure server and in the study database.

Participants were informed that they were free to withdraw at any time, but that online questionnaire data could only be removed within 2 weeks of data collection, and web usage data, online forum posts and direct messages could not be removed and would be used for research purposes. Participants were informed that data would be stored on secure servers at Liverpool CTRC and Lancaster University. Note: the study predated the EU General Data Protection Regulation (GDPR).

Interventions

The design and delivery of REACT were described in detail in *Chapter 2*. Participants were randomly allocated to either the REACT arm (TAU plus toolkit including RD) or to TAU plus RD. Those in the REACT arm could access the toolkit with a username and password, without charge, whenever they wished throughout the trial (minimum of 24 weeks to last follow-up for final participant). REACT supporters were available on weekdays from 9am to 4.30pm excluding public holidays and university closures (1.5 weeks at Christmas and 1 at Easter). Participants were advised to use the intervention as they needed. No changes were made to existing support and treatment.

Participants allocated to the RD only arm logged onto the same website, but could see only the “Meet the Team” and RD pages. At the end of the study they were given access to the modules, without the forum or direct messaging.

Objectives and hypotheses

The aim of this RCT was to determine the clinical and cost effectiveness of the REACT toolkit (including online RD) and TAU, compared to TAU and RD only. This comparator was chosen to test the effect of offering REACT as an additional intervention to the support that relatives could already access. Relatives were likely to be accessing support from a wide range of services. In this context, TAU was used to indicate that no attempts were made to make any changes to any of these other sources of support.

Objectives were to determine the REACT intervention’s:

- Impact on relatives’ distress
- Impact on relatives’ wellbeing and support
- Impact on hypothesised mediators of change including relatives’ beliefs, perceived coping, and amount of use of REACT
- Delivery and maintenance costs
- Incremental cost-effectiveness ratio (ICER)
- Key issues for which relatives seek support

The primary hypothesis was that there would be a significant difference ($p<0.05$) between the two arms of the trial in general health questionnaire (GHQ-28) scores at 24-week follow-up.

Outcomes

All outcomes were collected online using a closed system available only to participants with an account on the REACT site. Questionnaires were all validated self-reporting measures, though not originally designed for use online. These were presented in order of priority to the study (primary outcome first) and used drop-down options and tick boxes. Participants were required to respond to all items before moving to the next measure. At baseline, participants were required to complete all measures before being randomised. Following completion of each questionnaire, the data was submitted and participants were unable to edit it.

Primary outcome

The primary outcome was relatives' distress at 24 weeks, assessed using an online version of the GHQ-28 with Likert scoring (0–3).[61] GHQ-28 showed sensitivity to change[2, 110] and had shown significant associations with important functional outcomes in the general population, including GP visits,[111] absence from work,[112] incapacity benefits,[113] and severe adverse health outcomes, including death.[114] We chose 24 weeks to allow the content of the site to be processed and have an effect on cognition and behaviour, and for these to have an impact on distress.

The Likert scoring method assigns a value of 0 to 3 to each possible multiple-choice answer (with higher scores indicating more severe distress) and results in a total score between 0 and 84.

The total 28-item score can be divided into four subscales of seven items each. These were explored for secondary analyses:

A. Somatic symptoms (items 1–7)
B. Anxiety/insomnia (items 8–14)
C. Social dysfunction (items 15–21)
D. Severe depression (items 22–28)

The alternative "caseness" scoring method (assigning either 0 to the first two categories of response, and 1 to the last two categories) was presented as a secondary analysis.

Secondary outcomes

Secondary outcomes included the relatives' experience of caring, assessed online at 24-week follow-up using the CWS questionnaire;[115] and distress (GHQ-28) and carer experience (CWS) assessed online at 12-week follow-up. CWS covers all aspects of the carer's experience of caring for someone with a serious mental health problem, including relationships, roles, financial concerns, physical and emotional health, stigma, worries about safety, satisfaction with support offered and ease of obtaining information.

The CWS questionnaire consists of two separate scales. The wellbeing scale consists of 32 questions about the user's caring or support role, relationship with the person they care for or support, relationship with family and friends, financial situation, physical health, emotional wellbeing, experiences of stigma and discrimination, personal safety and the safety of the person they care for or support. Carers rate their level of concern in each area using a 5-point Likert scale (from "A lot" to "Not at all"). The overall wellbeing score is derived by assigning a score of 0 to the most negative answer ("A lot of concern") and a score of 4 to the most positive answer ("Not at all"), then summing scores from all 32 questions, creating an overall score between 0 and 128, where a higher score indicates greater wellbeing.

Similarly, the support scale consists of 17 questions relating to the carer's level of satisfaction with the information and advice they receive, their involvement in treatment and care planning, and support from medical and care staff, each measured on a 4-point Likert scale (from "Very dissatisfied" to "Very satisfied"). The overall support score is derived by summing scores from these 17 questions, with a score of 0 assigned to the most negative answer ("Very dissatisfied") and 3 to the most positive answer ("Very satisfied"), creating an overall score between 0 and 51, where a higher score indicates better support.

Mediators

To test the proposed mediators of change in relatives' outcomes, participants also completed online versions of the Brief Illness Perception Questionnaire (Brief IPQ),[116] a 15-item Likert scale assessment of beliefs about psychosis and BD, with an additional single item to assess perceived coping; and Brief COPE,[117] a 28-item measure widely used to assess coping styles.

REACT was designed using a cognitive behavioural framework, which proposes that the way in which relatives think about the challenges they face, and the things they do in response, will determine their levels of distress.[118] The Brief IPQ allowed us to assess the

way in which relatives made sense of the psychosis or BD, i.e. their cognitive models. Brief COPE allowed us to assess the specific strategies they were using to manage their distress.

Brief Illness Perception Questionnaire

The Brief IPQ consists of 16 questions (rated by the carer between 0 and 10) regarding perceptions of illness, some focusing on the service-user experience (e.g. How much control do you feel your relative/close friend has over their mental health problems?), others on the carer (e.g. How much control do you feel you have over your relative/close friend's mental health problems?). It can therefore be summarised into two total scores, one relating to the service user and the other to the carer. Answers to seven of the questions (items 4, 5, 6, 7, 10, 11 and 15) must be inverted according to the formula where x becomes $10–x$). Thus a higher total score indicates an overall perception of illness as more severe (e.g. more negative consequences, longer timeline, less control).

The service-user score was derived by summing the ratings (between 0 and 10) for questions 1, 3, 8, 12 and 13, resulting in a total score between 0 and 80 (with a higher score indicating more severe perception of illness). The carer score was derived by summing the ratings (between 0 and 10) for each of the questions 2, 9, 14 and 16, resulting in a total score between 0 and 70 (with a higher score indicating more severe perception of illness).

An additional item added to the Brief IPQ (question 6, How able do you feel to cope with your relative/close friend' mental health problem?).

Brief COPE

Brief COPE consists of 28 questions (rated by the carer from 1 to 4) about the methods used by the relative to cope with the stress of their caring role. Values are assigned to the answers to each question as follows:

- "I haven't been doing this at all" = 1
- "I've been doing this a little bit" = 2
- "I've been doing this a medium amount" = 3
- "I've been doing this a lot" = 4.

There is no overall score for the brief COPE; instead the following subscales are computed:

- Self-distraction: questions 1 and 19;

- Active coping: questions 2 and 7;
- Denial: questions 3 and 8;
- Substance use: questions 4 and 11;
- Use of emotional support: questions 5 and 15;
- Use of instrumental support: questions 10 and 23;
- Behavioural disengagement: questions 6 and 16;
- Venting: questions 9 and 21;
- Positive reframing: questions 12 and 17;
- Planning: questions 14 and 25 ;
- Humour: questions 18 and 28;
- Acceptance: questions 20 and 24;
- Religion: questions 22 and 27;
- Self-blame: questions 13 and 26.

Web usage

Website usage data for each participant was downloaded from the intervention site and summarised for participants in each intervention group. Data were available for the website as a whole, and for each of the 12 information modules, forum, direct messaging and RD, to investigate which components were used most.

These data were then condensed into a small number of summary covariates over the 24 weeks to determine causal effects of the intervention for each participant:

- Total number of webpage downloads
- Total number of logins to the REACT site
- Total time spent logged on to REACT site.

Inactivity (where the user was logged in but with no evidence of activity) on any given page was capped at 20 minutes. Given that these capped values were not likely to reflect the true time spent on a given page and were likely to skew the data, imputation of the mean total time spent per page for REACT participants was performed for those with capped values. The imputed mean values were considered to be more realistic than using capped values of 20 minutes; however, it is acknowledged that the use of imputed values inflates the precision

of summary estimates (as unknown values are assumed to be known) as would the assumption of 20 minutes for these capped values.

The time spent on the final webpage of any given session was not available and therefore had to be imputed. For pages with a video, video feedback data allowed calculation to within 5 seconds. If there was no video, it was assumed that the time spent on this page was equal to the mean time the participant had spent on all previous pages to date.

The number (%) of participants who did not log in to their assigned intervention was presented for each randomised group, as well as the number (%) of participants in each randomised group who did not log in again after their initial login.

To assess the hypothesis that DHIs provide a distinct advantage in allowing "out-of-hours" access, the timing of web access was summarised relative to the working week (defined as 9am to 5pm, Monday to Friday, excluding public holidays, UK time).

We explored whether reminders would increase intervention use by comparing participants' patterns of use (using measures of frequency and time spent on intervention) within 1 day, 3 days and 7 days of reminders being sent with their intervention use during the period prior to their first reminder.

Sample size

We aimed to recruit 666 relatives of people with psychosis or BD to accurately test the primary hypothesis that there would be a significant difference ($p<0.05$) between the trial arms in distress, measured by GHQ-28 scores at 24-week follow-up.

Our feasibility trial[2] had shown a mean difference between groups at 6 months (controlling for baseline) of 6.59 units (standard deviation (SD) 16.6 units) in favour of the REACT arm.

To build a degree of protection against pilot results proving optimistic, and to accommodate adaptations to the design of the study and the intervention, we reduced our estimate of the mean difference in this trial from 6.59 to 5.0 units. A detailed qualitative and quantitative analysis of our feasibility data suggests that a (within-relative) reduction of 3 units on the GHQ can indicate clinically meaningful change; however, the minimum difference required for the between-group comparison (of change in GHQ-28 from baseline) was set at 5 units, to justify the staff and resource costs associated with delivery of the intervention.

We retained our estimate of SD of 16.60 from the feasibility study, consistent with other studies using this measure with relatives in EIP services[13] and somewhat higher than those from other mental health or dementia services.[119, 120] A total of n=666 (333 per arm) participants provided 90% power to reject the null hypothesis ($p<0.05$) with effect size 5.0 units, assuming 30% dropout by 24 weeks. Although dropout was only 17% in our feasibility trial, it tends to be higher in online trials.[78]

Recruitment rate

Recruitment to face-to-face trials often starts slowly; recruitment online is often very fast. Given that we planned to recruit both via clinical providers and through online marketing, we hypothesised a steady rate of recruitment and set our criteria using an average monthly rate of more than 37 relatives per month over an 18-month recruitment period.

Internal pilot

Monthly recruitment rates were monitored under a 9-month internal pilot with the following criteria:

- GO: 100% or more of anticipated recruitment at 9 months (333+ participants)
- AMEND: 80–100% of anticipated recruitment (267–333 participants): review and amend recruitment strategies
- STOP: Less than 80% of target for 9 months (<267 relatives): inform funders who would determine whether to stop trial.

An assessment of the SD of GHQ-28 scores was also planned for the 24-week follow-up at the end of the internal pilot. We planned that a higher SD than the estimated 16.6 units would result in the sample size being increased; a lower SD would result in an unchanged recruitment target. If GHQ-28 retention at 24 weeks had been less than 70%, the recruitment target would have been increased.

Randomisation

Sequence generation

Eligible participants were randomised using a 1:1 ratio to “REACT (including RD) plus TAU” versus “RD plus TAU” by Liverpool CTRC. We used a web-based variable block randomisation, in which the unit of randomisation was the relative. Given the lack of

convincing evidence that the effectiveness of REACT would be associated with any baseline variables, we did not stratify randomisation.

Allocation concealment

Following randomisation, participants received an email telling them which arm of the trial they had been allocated to. The email included a link to the REACT toolkit, and their username and password. All participants were aware that the RD was one component of the intervention, and therefore were likely to perceive REACT as the "intervention of interest" and the RD as the "comparator".

Once participants had completed their baseline questionnaires, they were asked to click a button which enabled them to be randomly allocated to a group and their account on the intervention site was created. Access to the intervention site was dependent upon the randomisation having taken place.

Data collection

Registration

The REACT landing page included text about what the study involved and the eligibility criteria. Based on PPI feedback, text was kept short, and a video of the chief investigator included. To reduce attrition, the landing page also highlighted the need to commit to follow-ups at 12 and 24 weeks.

Participants who clicked "Register" moved to a second page outlining the next stages and a video of REACT supporters explaining what taking part would involve. The random allocation design of the trial was also described here, to reduce attrition from the control arm.

The online registration process included an eligibility check (by check boxes relating to essential criteria), consent form (by check boxes confirming they had read and agreed to a series of statements), recording of participants' email, phone and postal contact details, and an identity check via text message.

Applicants found to be not eligible for the trial were given an explanation and pointed to other potentially relevant studies. As in traditional trials, flows through the study were recorded and monitored.

Participants were informed that we needed their contact details to allow follow-up contact to increase retention, and in case a safety issue was identified; their encrypted details would be stored on the study database. Email addresses were verified by sending an email with a confirmation link, and at the activation stage a code was sent to each participant's mobile phone (by SMS) or landline (in a call by the TM to be entered to the system). This also allowed the research team to ensure that the registrant was not a robot.

To ensure each randomisation was a unique participant and prevent multiple registrations by individuals, we checked each new registration against existing data.

Baseline measures

Demographic information and baseline measures were completed before randomisation. To make the process less daunting, questionnaires were paginated rather than appearing as one long webpage. Validating algorithms ensured that all questions were completed and inappropriate answers minimised. These methods were reviewed by the RAG to ensure they were fit for purpose. Demographic data included age, gender, ethnicity, marital status, education, employment, living arrangements (including dependents), primary diagnosis of service user, length of time in caring role, number of people caring for, relationship to person(s) with mental health problem, whether or not they lived with the person(s), level and type of contact, whether or not they received support from NHS services, and internet access.

On completion of the baseline questionnaires participants were randomised to either the REACT arm or to the RD only arm, using a list generated by the statistical team.

At 12 and 24-week follow-up, up to three reminder emails were sent at five-day intervals. If data entry had still not started, the TM was prompted to send a personalised email; and finally to try to make contact by phone to ask if the participant would complete the GHQ (primary outcome) questionnaire over the phone (with the TM entering the data), or in writing in which case the researcher would download and post a personalised letter and questionnaire. Returned data would be entered manually by the researcher. Towards the end of the study, the researcher was also able manually to trigger an SMS with a unique URL for the GHQ questionnaire. To identify "stuck" participants, the TM's dashboard displayed how many questionnaires had completed at each stage.

The REACT participant information sheet, available on the website, explained the withdrawal process. A link to withdraw from the study featured in all reminder emails, and in the toolkit. Withdrawing participants were required to select from a drop-down menu of options:

- “I don’t want to complete the 12-week follow-up questionnaires but I am happy to be contacted for the 24 week follow-up”
- “I don’t want to complete ANY more follow-up questionnaires but I would like to continue to use the website. NB: any data inputted to the website will continue to be used for research purposes”
- “I don’t want to complete ANY more follow-up questionnaires and DO NOT want to use the website anymore. NB: your access to the website will cease”.

Participants were also invited to provide an optional reason for withdrawing:

- “I don’t have time due to other commitments”
- “I didn’t like the website I was given”
- “I don’t like filling in the questionnaires”;
- “I don’t feel well enough to take part”
- “Other (please specify)”.

Researchers would ask the same sets of questions of participant who withdrew over the phone or by email, and enter this information into the system. Withdrawal also blocked further automated reminders.

The data collection process is shown in *Figure 4*.

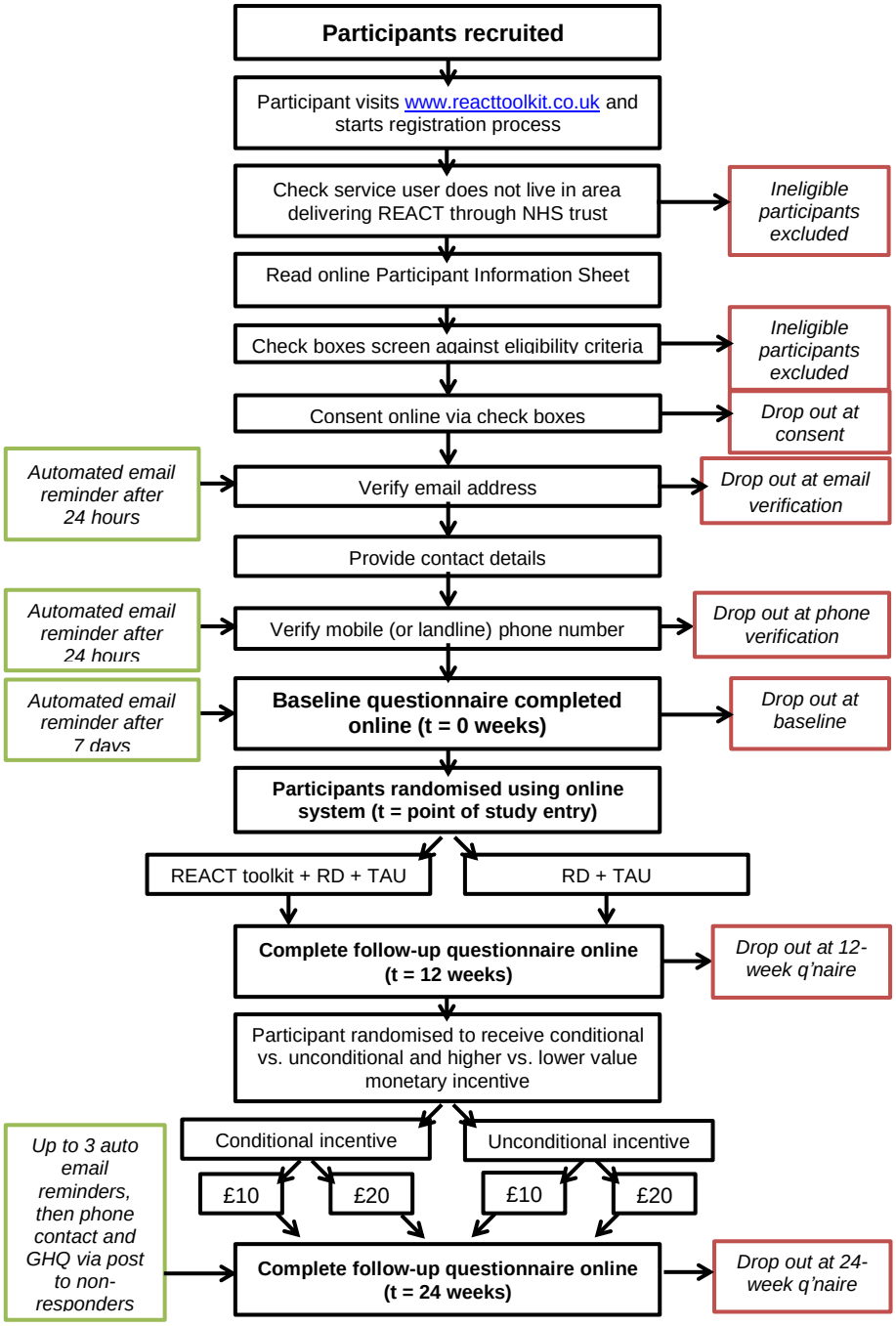

Figure 4: Data collection process

The REACT trial registration process incorporated a number of strategies to enhance engagement:

- Lay language speech bubbles;
- A progress bar appeared at the top of each registration page and an indication of how long each stage should take;
- An automated email reminder with detailed instructions if participants had not progressed within 24 hours of giving consent;
- The same process 24 hours after participants completed activation and 7 days after starting the baseline questionnaire;
- Email reminders were copied to the TM to check the registration process was working correctly;
- The option to email the TM throughout registration to get email or phone support through the process; and
- A dashboard allowing the TM to monitor progress and identify those that needed chasing.

Retention strategy

Dropout from follow-up is a particular problem in online trials.[78] Drawing on lessons from previous studies,[77, 107, 121-123] we used the following strategies to maximise follow-up:

1. We only randomised participants once baseline assessment measures were completed;
2. We included detailed explanations in our recruitment materials about why data completion at follow-up was so important;
3. We obtained multiple contact details at registration;
4. We sent multiple reminders by different methods and with different options for completing data, based on PPI feedback, striking a balance between cost, data and burden on participants;
5. We gave £10 or £20 vouchers as incentives to complete follow-up data (see *Appendix 2, Study Within a Trial*);

We informed RD only participants that they would be able to access toolkit modules after the final follow-up.

Blinding

All data was self-reported and predominantly entered online by participants. Outcome questionnaires submitted by post were recorded as such and inputted by the TM, who was blind to allocation. Data was uploaded directly to the CTRC database. The system allowed only valid values to be entered. To prevent any bias in the conduct of the study, the chief investigator, TM and statisticians were blinded to treatment assignment. The REACT supporters, clinical supervisors, qualitative interviewer, one CTRC analyst of web usage data and technical staff (AW) were unblinded. Participants were also unblinded.

To minimise 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. All instances of unblinding were recorded.

Statistical analysis

A full statistical analysis plan was published on 22 March 2017, before the start of data collection, and updated on 20 December 2017, before the end of data collection. Both versions are available at https://figshare.com/articles/REACT_Statistical_Analysis_Plan_v1_0_An_online_randomised_controlled_trial_to_evaluate_the_clinical_and_cost_effectiveness_of_a_peer_supported_self-management_intervention_for_relatives_of_people_with_psychosis_or_bipolar_disorder_Relatives_Education_And_/4775539, last accessed 28 October 2019.

Updates to the plan are listed in Appendix 1. All analyses were done using SAS statistical analysis software, version 9.4 or Stata version 14.

Primary outcome

Mean scores and SDs on the GHQ-28 at 24 weeks were calculated separately for each arm and compared between groups using analysis of covariance, adjusting for baseline score and including all participations according to the randomisation scheme.

The baseline characteristics of those who provided 12-week and 24-week follow-up data were compared, to investigate whether missingness could be assumed to be random for 12-week and 24-week follow-up data (at least with respect to baseline characteristics). A joint modelling approach was used to check for any difference in GHQ-28 (see *Report Supplementary Material File 1, Section 6.6.4*).

Of the four subscales, somatic symptoms and anxiety/insomnia were summarised for each randomised group by mean and SD, and were compared between randomised groups using ANCOVA, adjusting for the corresponding baseline subscale score. Severity of depression and social dysfunction were summarised for each randomised group using median and interquartile range (IQR) and compared between randomised groups using Mann–Whitney U tests, as the distributions of these subscales were non-normal. Multivariate ANCOVA ("MANOVA" in Stata) was used to assess the impact of intervention group on each of these subscales, while taking into account correlation between the subscales.

Secondary outcomes

Relatives' distress at 12 weeks was assessed using GHQ-28, and analysed as for GHQ at 24 weeks. Relatives' wellbeing at 12 and 24 weeks were assessed using the CWS measure on both the wellbeing and support scales and summarised for each arm using means and SDs. They were also analysed as for the primary outcome GHQ-28 scores, using ANCOVA and joint modelling.

Causal analysis

To investigate the relationship between website use and outcome, we recorded data on baseline covariates (correlated with website use and outcome) and relevant website use (from participants in both randomised arms). Instrumental variable (IV) regression was used to estimate the impact of intervention use on outcome using the IV regression (ivreg) command in Stata.

Intervention use (i.e. webpage downloads from the REACT intervention site excluding the RD) was summarised as a single continuous covariate derived from web usage data. Given the extensive password protection of the REACT site, it was assumed that participants in the control arm had null intervention use.

Exploratory analyses of total number of logins and total time spent logged on over 24 weeks as other measures of use were also conducted, and the suitability of randomisation as the instrument in this regression was assessed (see *Report Supplementary Material File 1*).

Testing mediators

The hypothesised mechanism of change for the REACT intervention was that participants' distress levels (the primary outcome) would be mediated by their understanding of the service user's disorder, their insight into the service user's experiences and their own perceived ability to cope.

These potential mediators were measured by the Brief IPQ and Brief COPE at 12 weeks and 24 weeks. Baseline characteristics of those who did not provide data were compared with those that did (as for primary outcome), to determine whether absent data could be assumed missing at random. Collected data sets collected were then summarised for each treatment group by mean and SD or by median and IQR depending on whether normally distributed. We then compared the groups and analysed the impact of intervention on subscales using ANCOVA and MANOVA as before.

To test whether these potential mediators actually predicted change in outcome, mediation analysis was carried out using ivreg in Stata, as for causal analysis above, adjusting for each baseline variable that was included in the final regression model (along with baseline GHQ-28 score) for the primary outcome. This analysis was not successful, as the "instrument" was not useful (very weak) in each case, so we instead performed post hoc mediation analysis along with sensitivity analyses to check robustness of the model results to the assumption of no unmeasured confounders.

Each potential mediator was assessed individually in this exploratory analysis:

- Overall Brief IPQ score
- Additional IPQ coping question
- Brief COPE summary scores (each individual score assessed individually).

Due to the number of variables being considered, this mediation analysis was entirely exploratory in order to generate hypotheses for confirmation in future studies.

Additional analyses

Exploratory analyses were conducted to determine the impact of the following baseline factors on the intervention effect on total GHQ-28 score at 24 weeks, by including the following baseline factors in the linear regression model along with baseline GHQ-28 score and randomised intervention:

- Age (older relatives are likely to have been caring for longer and have their own physical health needs)
- Gender (women tend in society to spend more time on the caring role and take greater responsibility for caregiving)
- Ethnicity (minority ethnic groups may experience barriers to receiving support)
- Marital status (a relationship may provide support for the carer or relative)
- Living arrangements (as above)
- Dependents (may add to the carer or relative's stress)
- Highest education (the intervention may be overly complex for those without sufficient reading or cognitive ability)
- Employment (work commitments may impede use of the intervention)
- Home internet access (aids ease of use of the intervention)
- Caring role (the intervention's impact is likely to relate to the burden of care).

Results from each individual model (i.e. the regression coefficient, 95% CI and p-value associated with each baseline factor when added to the model containing baseline GHQ-28 and randomised intervention) were presented for each of these baseline factors separately. A stepwise selection procedure (with entry/exit criterion based on p-values of 0.05/0.1 respectively) was used to determine which baseline variables to include in the final multivariable regression model (along with baseline GHQ-28 and randomised intervention).

This exploratory analysis included a formal test of treatment–covariate interaction to assess the effect of relationship with service user (i.e. according to whether or not the relationship was parental) by including the "intervention-service user (non/parental) relationship" interaction term in the linear regression model (along with baseline GHQ-28, randomised intervention and main effect of service user (non/parental) relationship).

The impact of "lurking" on social forums

We tested the hypothesis that reading but not posting ("lurking")[124] on social forums would lead to worse outcomes than posting on (or not logging on at all to) social forums. In the absence of a second instrument to facilitate this three-way comparison (lurking versus non-use versus use), ordinary least squares regression was used to assess the impact of lurking on GHQ-28 at 24 weeks.

The validity of this analysis was assessed by repeating this model for the binary comparison between users and non-users (with lurkers included as users), adjusting for the same baseline covariates, and comparing the group effect from this model with that obtained using ivreg for the users versus non-users comparison (with randomisation as the instrument).

Lurkers were defined as those who logged on to the forum at least once over the 24 weeks but posted no comments; users were defined as those who logged on and posted at least once on the forum over 24 weeks; and non-users were defined as those who never logged on to the forum over 24 weeks.

Participants' experiences of the intervention

Participants in the REACT intervention group were asked the following questions at 12 and 24 weeks post-randomisation (based on previously published studies):[125]

- "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".

Appropriate use of the site

The following data was collected automatically via the site and summarised for the REACT intervention group only:

- Number of times a relative flagged content as requiring attention
- Number of times the REACT supporter hid a comment from the site
- Number of participants' accounts suspended.

Missing data

Participants were asked to complete the primary outcome measure (GHQ-28) before being presented with any other measures, to maximise primary outcome data collection. In addition, participants were unable to submit any questionnaire with a missing field; therefore, by design, no data was missing from questionnaires completed online. (This was not true for some items assessing the relatives' caring role due to an error in design and testing; hence there are some missing values for these variables.)

The only instance of missing outcome data was in the case of GHQ-28 questionnaires returned by post. These were included in the analysis if more than half of the questions in each of the four subscales had been completed: missing answers were given the mean value of given answers within that subscale for that participant. This approach was chosen following discussions with the TSC, with guidance provided by http://www.datadictionary.nhs.uk/data_dictionary/nhs_business_definitions/p/patient_health_questionnaire-9_de.asp, last accessed 28 October 2019.

Commented [NB3]: Deleted unnecessary suffix of URL

This simple approach was chosen as there were very few missing data entries (four missing questions from three patients at 12 weeks, and one missing question at 24 weeks) on which to base multiple imputation.

Data entered up to 18 weeks post-randomisation was considered to be 12-week data; data entered beyond 18 weeks and up to 30 weeks post-randomisation was considered to be 24-week data. Any duplication of 24-week data entered by a given participant (i.e. if the participant provided "12-week" data beyond 18 weeks and later entered 24-week data) was addressed by choosing the data entered closest in time to 24 weeks post-randomisation.

Missing completion dates for postal GHQ-28 questionnaires were estimated using the midpoint between dates of sending out and receiving back. If not recorded, the date of receipt was imputed using the mean number of days between sending and receiving questionnaires for all accurately recorded postal GHQ-28 questionnaires.

Joint modelling of the longitudinal outcome data and the time to dropout was carried out using the stjm command in Stata, to demonstrate any association between these two processes. A longitudinal trajectory plot was produced using the subsidiary command "stjmgraph"; this graph shows dependence between the longitudinal profiles and dropout.

Monitoring of adverse events

Adverse events were assessed in terms of the number of participants for whom it was necessary to trigger the risk protocol, for both low-risk and high-risk events (see *Stand Alone Document 3*). Risks were identified in one of three ways:

- "Red flags" raised by the system in response to answers to GHQ-28 items D3, D4, D6 or D7 that indicated possible risk to self, or to CWS questions 29 or 30 indicating possible risk from the person cared for, with the TM notified via the dashboard;
- By REACT supporter through the forum or direct messaging; or
- By the TM when contacting non-responders for follow-up (in both arms, with strategies to ensure blinding was not broken).

Low-risk alerts triggered a standardised email to the participant, expressing concern, checking they were OK, and pointing them to appropriate support. High-risk alerts, defined as clear evidence of immediate and serious risk to life or to child welfare, and referred to as "serious adverse events" led to immediate contact with police or social services as appropriate, including sharing participant details. Safeguarding concerns were also covered by the protocol.

Add-on studies

We conducted a study within a trial (SWAT) into factors influencing the success of incentives to participants (see *Appendix 2*) and a qualitative study to understand participants' experiences of using REACT (see *Chapter 6*). We also plan to conduct a qualitative analysis of the posts on the REACT Group to identify the key issues that relatives raised in the online forum (see *Chapter 6* for initial themes).

Ethical approval and research governance

Ethical approval was given by Lancaster National Research Ethics Service committee (15/NW/0732) on 21 September 2015. The eight ethical amendments (current version 1.8 dated 6 December 2017) can be found at https://www.journalslibrary.nihr.ac.uk/programmes/hta/144934/#/, last accessed 28 October 2019.

Patient and public involvement strategy

One of the study investigators is a parent of someone living with psychosis and was extensively involved in the development of REACT, the RD and data collection processes. She was part of the supervisory team for REACT supporters.

We established an RAG working primarily online to give detailed feedback on the REACT toolkit, online data collection processes and recruitment strategy.

Our REACT supporters were people with lived experience of supporting someone with psychosis or BD; as well as supporting the REACT intervention, they were involved in promotion, recruitment, interpretation, and writing up the findings. They will also be involved in disseminating the findings subject to funding and availability following the end of the study. Our TSC included a relative and service user.

Data management storage and security

All participant trial data was collected through an online system at Liverpool CTRC and stored on secure servers physically located within access-controlled server rooms and backed up nightly to a separate physical location. All identifiable data was encrypted using a 256bit encryption algorithm. CTRC servers were subject to penetration-testing audits undertaken by University of Liverpool central IT staff. Website usage data, and qualitative data from the REACT Group forum and direct messages to REACT supporters were taken from the REACT toolkit and hosted on a dedicated virtual private server at Lancaster University. All communication with website users was limited to SSL-protected HTTPS protocol, to protect passwords and data in transit over internet.

REACT data is stored on a secure server at Lancaster University which complies with relevant statutory provisions including the Data Protection Act 2018 and the EU General Data Protection Regulation. Data held on Lancaster servers are stored in a resilient storage infrastructure which is dual-housed in the university's data centres (on site). There are multiple levels of redundancy built into these storage arrays – snapshots and backups are automated and taken regularly.

University SSO (single sign-on) credentials are required to access the shared network drive; the PI controls access to specific folders and ensures this is monitored regularly.

Data sharing

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 the 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 (10.17635/lancaster/researchdata/306). The study protocol[126] and statistical analysis plan (https://bit.ly/2YttbhQ, last accessed 28 October 2019) are already published and freely available.

Commented [NB4]: This is the long URL used earlier -- https://figshare.com/articles/REACT_Statistical_Analysis_Plan_v1_0_An_online_randomised_controlled_trial_to_evaluate_the_clinical_and_cost_effectiveness_of_a_peer_supported_self-management_intervention_for_relatives_of_people_with_psychosis_or_bipolar_disorder_Relatives_Education_And_/4775539 -- can we use the bit.ly address there? Or, conversely, should we print the full url here? Not sure about convention for these things.

Chapter 4 Clinical effectiveness: results

Introduction

This chapter reports the findings from analyses to test the clinical effectiveness of REACT. The structure follows the CONSORT guidelines and the methods section in *Chapter 3*. A full statistical analysis is available as *Report Supplementary Material File 1*.

First, we describe the flow of participants through the trial. We then list any deviations from our published protocol.[126] We describe the levels of intervention use in both arms of the trial. Next, we present our rate of recruitment, report the findings of our internal pilot, test the effectiveness of our online and offline strategies to maximise recruitment, and explore the impact of the reminders protocol on retention.

We then present the baseline data for each of the key outcomes: distress (GHQ-28), carer wellbeing (CWS) and carer support (CWS). We test the impact of the REACT intervention on each of the main outcomes (primary outcome GHQ-28 at 24 weeks; secondary outcomes GHQ-28 at 12 weeks and CWS at 12 and 24 weeks), and explore evidence for any causal impact. We test whether illness perceptions and coping strategies mediate any relationship between the intervention and GHQ-28 as hypothesised.

We present two additional analyses, testing the impact of participants' baseline characteristics on the primary outcome and the impact of "lurking" on the REACT Group forum. Finally, we report the adverse events that occurred during the trial.

Technical issues that arose with the trial are set out in *Report Supplementary Material File 1, Table 6.6*. Deviations from protocol that resulted are set out in *Appendix 1, Table 54*.

Participant flow

The total number of visits to the REACT study page from 22 April 2016 to 30 September 2017 was 451,832. The total number of visits to the study registration page was 4,348.

Figure 5 shows the flow of participants through each stage of the study.

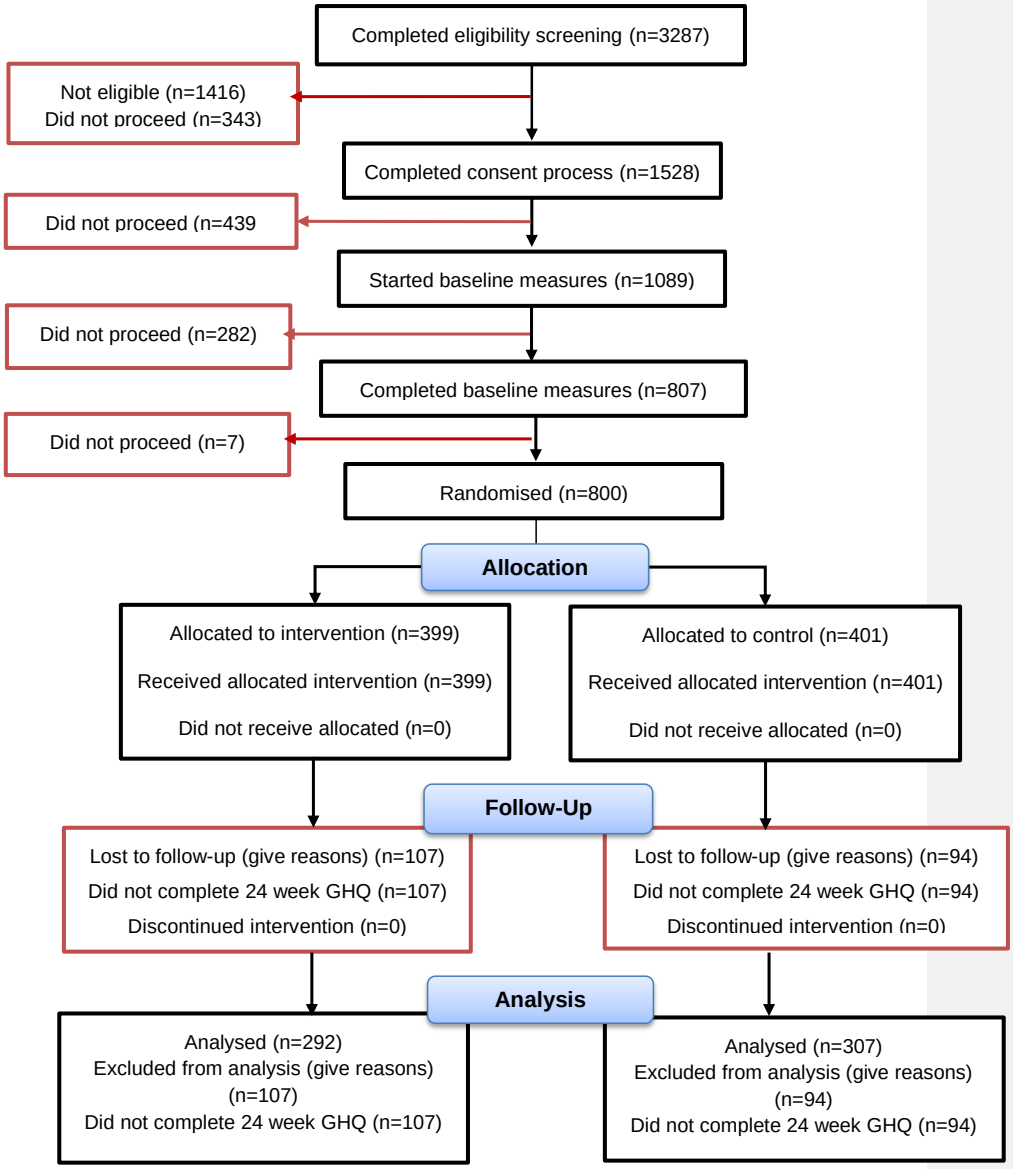

Figure 5: CONSORT diagram shell

Of the 3,287 who completed the eligibility screening, 1,528 (46%) went on to consent to the study. Of these, 343 failed to proceed through the registration process and 1,416 people

failed on at least one of the eligibility items. The number failing on each eligibility item is shown in *Table 1* (note, 55 people failed on more than one criterion).

Table 1: Numbers failing eligibility questionnaire, by criterion

Question	Number failing (% of total ineligible)
I am 16 years old or over	10 (0.7%)
I am a relative (or close friend providing regular support) of someone with psychosis or bipolar disorder	88 (6.2%)
Have you recently been feeling nervous and strung-up all the time?	1146 (80.9%)
I would like to receive help for my distress through an online toolkit	118 (8.3%)
I have regular access to a computer which is connected to the Internet	28 (2.0%)
I have a good working knowledge of written and spoken English language	13 (0.9%)
I live in the UK	13 (0.9%)
To the best of my knowledge, I am the only relative/close friend of the person I support taking part in the REACT study	67 (4.7%)

The most frequently failed item was the requirement for participants to score a 2 (“Rather more than usual”) or 3 (“Much more than usual”) on the GHQ item “Have you recently been feeling nervous and strung-up all the time?”

Of the 1,528 who consented, 1,089 started the baseline measures but 282 did not proceed; 807 completed the measures. Seven did not proceed at this point, and 800 (52% of those consenting) went through to randomisation.

Use of the intervention (compliance with treatment)

Table 2 shows the level of intervention use in each arm of the trial. These data were available for only 700 of the 800 people as page view numbers only began to be recorded

part-way into the trial. The number of participants who logged into the site at least once was similar in both arms of the trial, but the total number of logins after this was much higher in the REACT arm. The median time spent on REACT in the REACT arm was 50.8 minutes (296.8), with a large amount of variation between individuals (range 0.1–4505.5 minutes). The median time spent on the RD in the RD only arm was 0.5 minutes, again with large variation, ranging from 0 to 42.9 minutes.

Detailed statistics on use of the intervention split by module are shown in *Report Supplementary Material File 1, Table 6-9*.

The most popular module (most people visited at least once) was the REACT Group, the online forum. More than half of the people allocated to REACT visited this module (n=207, 52%). The least popular were “Recovery: looking to the future” (n=108, 27%), and “Managing stress; thinking differently” (n=108, 27%).

Table 2: Use of the intervention

	REACT (n=348)	RD (n=352)	Overall (n=700)
REACT site			
Total number of web page downloads from intervention site[a]			
n	51416	4276	55692
Mean (SD)	149.9 (266)	12.7 (39.1)	82 (202.9)
Median (IQR)	69 (18–179)	6 (3–13)	14 (5–76)
Min–max	1–3501	1–651	1–3501
Total number of times participants logged on to intervention site[a]			
Number of participants who logged in	343	336	679
Total number of logins	2724	681	3405
Mean (SD)	7.9 (13.3)	2 (1.7)	5 (10)

Median (IQR)	4 (2–9)	1 (1–2)	2 (1–5)
Min–max	1–159	1–12	1–159
Total time spent on REACT intervention page per person (mins)[b]			
Number of people who accessed page	343	N/A	N/A
Total time (across all participants)	46531.5	N/A	N/A
Mean time on page per person (SD)	135.7 (296.8)	N/A	N/A
Median time on page per person (IQR)	50.8 (12.4–172.1)	N/A	N/A
Min–max time spent on page	0.1–4505.5	N/A	N/A
Number of participants who did not log on to intervention site	5	16	21
Number of participants who did not log on to intervention site after initial login	75	184	259
Resource directory			
Page hits			
Total number of page hits	971	645	1616
Mean page hits per person (SD)	5.1 (5.6)	2.5 (3.9)	3.7 (4.9)
Median page hits per person (IQR)	3 (2–7)	2 (1–3)	2 (1–4)
Min–max page hits per person	1–37	1–58	1–58
Total time spent on page (mins)			
Number of people who accessed page	189	253	442
Total time (across all participants)	159.7	189.0	348.7

Mean time on page per person (SD)	4.7 (7.9)	2.2 (5.2)	3.3 (6.6)
Median time on page per person (IQR)	1.4 (0.5–5.5)	0.5 (0–1.6)	0.9 (0–3)
Min–max time spent on page	0–55.8	0–42.9	0–55.8

[a] Not including randomisation.

[b] Including time immediately after randomisation.

Timing of intervention access

Table 3 shows how site use varied by time of week. Both online interventions (REACT and RD) were accessed considerably more outside of the working week (9am to 5pm Monday to Friday, excluding public holidays, UK time) than during these hours. This provides evidence for the need for online interventions to be available 24 hours.

Table 3: Out-of-hours access

	Working week access[a]			Out of hours access[a]		
	REACT n=343	RD n=336	Overall n=679[b]	REACT n=343	RD n=336	Overall n=679[b]
Total number of web page downloads from intervention site						
Mean (SD)	49.3 (99.0)	4.9 (12.2)	27.3 (74.2)	100.6 (193.3)	7.9 (30.3)	54.7 (146.4)
Median (IQR)	14 (0–57)	0 (0–5)	3 (0–19)	44 (9–124)	3 (1–8)	8 (2–48)
Min–max	0–890	0–128	0–890	0–2611	0–523	0–2611
Total number of times participants logged on to allocated intervention						
Mean (SD)	2.8 (5.7)	0.8 (1.1)	1.8 (4.2)	5.1 (8.8)	1.3 (1.3)	3.2 (6.6)
Median (IQR)	1 (0–3)	0 (0–1)	1 (0–2)	3 (1–6)	1 (1–2)	1 (1–3)

Min–max	0–54	0–6	0–54	0–105	0–9	0–105
Total time spent on allocated intervention per person (mins)						
Mean time on page per person (SD)	58.9 (109.6)	6.6 (11.7)	37.4 (88.2)	97.3 (231.6)	6.2 (8.9)	56.3 (177.5)
Median time on page per person (IQR)	24.5 (4.8–64.9)	3 (0.9–6.7)	7.1 (2.2–35.6)	33.6 (7.2–110.2)	2.7 (1.1–7.0)	8 (1.8–45.4)
Min–max time spent on page	0.1–1054.3	0–97.3	0–1054.3	0–3445.8	0–61	0–3445.8

[a] Working week defined 9am–5pm, Monday to Friday (excluding public holidays) UK time; out-of-hours is any other time

[b] Total sample excludes those for whom web usage data was unavailable (100) and those who never logged on

Impact of email reminders to visit the REACT site

This analysis explores whether reminders led to an increase in intervention use, by comparing participants' patterns of intervention use within 1 day, 3 days and 7 days of the first reminder being sent (standardised to a daily rate) compared to their intervention use during the period before the first reminder. Data prior to first reminder is standardised by the number of days from randomisation to the first reminder where appropriate. Data summarised in *Table 4* are based on 246 participants in the REACT group who had available web usage data and received a reminder.

Table 4: Intervention use (REACT group only) within 1 day, 3 days and 7 days of first reminder to access intervention compared to period prior to first reminder

	Daily rate within 1 day of first reminder	Daily rate within 3 days of first reminder[a]	Daily rate within 7 days of first reminder[b]	Daily rate prior to first reminder[c]
Page hits (average per person per day)				
Mean (SD)	2.9 (10.2)	2.0 (5.3)	1.3 (2.8)	3.0 (4.4)

Median (IQR)	0 (0–0)	0 (0–0.7)	0 (0–1.6)	1.6 (0.5–4.0)
Min–max	0–94	0–38.7	0–24.6	0–49.4
Total time spent on intervention (average per person per day in minutes)				
Mean (SD)	0.1 (0.4)	0.1 (0.3)	0.04 (0.1)	2.6 (3.6)
Median (IQR)	0 (0–0)	0 (0–0.02)	0 (0–0. 1)	1.0 (0.2–4.1)
Min–max	0–4.8	0–4.5	0–0.7	0–30.3

[a] Based on each participant's daily average over the 3 days following the first reminder

[b] Based on each participant's daily average over the 7 days following the first reminder

[c] Based on each participant's daily average over the period prior to the first reminder

Participants' experience of the intervention

Participants' experiences of the REACT intervention were assessed at 12 and 24 weeks. Results are shown in *Table 5*. At the end of the intervention period, 88% of participants reported having always felt supported by the REACT supporters; 89% always felt supported by the REACT Group (forum); and an even greater proportion (96%) always felt that the REACT site was a safe and confidential environment.

Table 5: Participants' experience of the REACT intervention

	REACT: n (%)			
	Strongly agree	Agree	Disagree	Strongly disagree
Always feel supported by REACT supporters				
12 weeks (n=226)	65 (28.76%)	132 (58.41%)	24 (10.62%)	5 (2.21%)
24 weeks (n=239)	69 (28.87%)	141 (59.00%)	24 (10.04%)	5 (2.09%)
Always feel supported by REACT group				
12 weeks (n=226)	58 (25.66%)	138 (61.06%)	27 (11.95%)	3 (1.33%)

24 weeks (n=239)	67 (28.03%)	145 (60.67%)	24 (10.04%)	3 (1.26%)
Always feel the REACT site was a safe and confidential environment				
12 weeks (n=226)	118 (52.21%)	95 (42.04%)	10 (4.42%)	3 (1.33%)
24 weeks (n=239)	125 (52.30%)	105 (43.93%)	6 (2.51%)	3 (1.26%)

Appropriate use of the site

Users had the option to flag content on the forum as “requiring attention” if they felt it was inappropriate or hostile. REACT supporter were able to hide posts. Only two posts were hidden during the trial. These were posted by the same participant, and were felt to have the potential to put unreasonable burden on other participants in the forum. No user accounts were suspended during the trial.

Recruitment

Rate

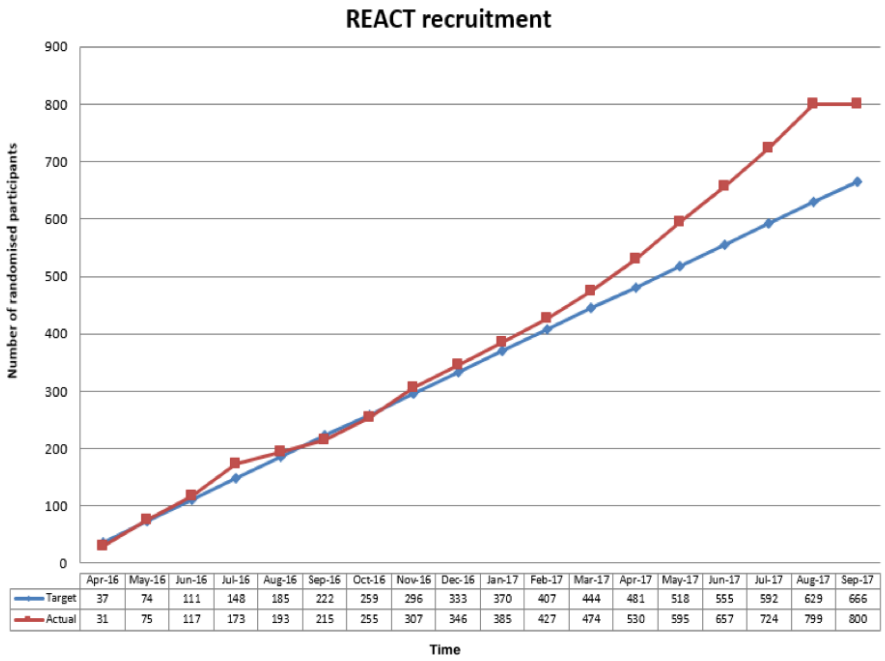

Figure 6: Recruitment rate

Recruitment took place from 22 April 2016 to 30 September 2017. The rate of recruitment is shown in *Figure 6*. Recruitment was steady and close to target for the first eight months, and then rose above target. Ethical approval was granted to continue recruitment throughout the recruitment phase despite the target having been reached, to ensure we had an adequate sample size to test our primary and secondary hypotheses. The increase in recruitment in July 2016 may have been due to circulation of a Bipolar UK e-newsletter at this time, and the accelerating rate from December 2016 may have been a result of increasing Facebook activity.

Effectiveness of recruitment strategies

The success of each recruitment strategy used is indicated by the number of randomised participants who were recruited via each strategy (*Table 6*). Each strategy has been categorised as primarily online or offline. Of the randomised participants, 421 (53%)

were recruited through five primarily online strategies and 379 (47%) were recruited through ten primarily offline strategies. Thus, combining online and offline recruitment was important in meeting our recruitment target.

Table 6: Recruitment strategies for randomised participants

Recruitment strategies for randomised participants		Online/offline	n (%)
1	Facebook	Online	206 (25.8%)
2	Mental health teams/professionals	Offline	151 (18.9%)
3	Internet search	Online	121 (15.1%)
4	Mental health charities	Online	77 (9.6%)
5	Recommended by a friend/family	Offline	74 (9.3%)
6	GP	Offline	59 (7.4%)
7	Carer or service-user support group	Offline	42 (5.3%)
8	NHS contacts	Offline	25 (3.1%)
9	Twitter	Online	15 (1.9%)
10	Employer	Offline	8 (1.0%)
11	Other third sector organisation	Offline	8 (1.0%)
12	Not classifiable	Offline	6 (0.8%)
13	Other public adverts (excluding NHS adverts)	Offline	4 (0.5%)
14	Local newspaper	Online	2 (0.3%)
15	Research team	Offline	2 (0.3%)

Internal pilot

At 9 months into recruitment we had recruited 368 participants. The pooled SD of the GHQ-28 at 24 week follow-up (based on 134 participants who had completed by this point) was 11.91. This result was reviewed by the independent data and safety monitoring committee and it was agreed that we had met our Go criteria and no changes were needed to the sample size. The study continued.

Effect of reminders on retention

With ethics committee approval, participants received the following series of reminders to complete follow-ups (until follow-up was completed):

Up to three automated email reminders at 5-day intervals.

A manual text message from the TM three days after the final automated email, with participant's login details and instructions on how to complete the follow-up.

A phone call from the TM three days after the text message, asking the participant to complete the questionnaires online, but offering to complete the primary questionnaire over the phone. If the participant did not answer, a second attempt was made and answer machine message left if this too was unsuccessful.

A postal pack containing a letter, primary questionnaire and reply-paid envelope, and an automated text message triggered by the TM through the trial dashboard. The message contained pre-specified text and a link to complete the primary questionnaire on their mobile phone.

Participants who indicated any reluctance to remain in the sample were withdrawn from the trial immediately. *Table 7* shows the number of participants completing the primary outcome measure after each reminder for each time-point. Most participants who completed follow-ups did so after the first automated email reminder (n=399). However, all reminders (online and offline) increased completion, suggesting that multiple reminders and different options for completion (online and offline) have a positive, cumulative effect on follow-up rate. There was no obvious difference in the impact of reminders at 12 and 24-week follow-ups.

Table 7: Participant completion of the primary questionnaire after each reminder

Reminder	Online or offline retention strategy	12 weeks: number completed (%) n=594	24 weeks number completed (%) n=599
Completed online after first reminder email	Online	177[a] (30)	162 (27)
Completed online after second reminder email	Online	114 (19)	71 (12)
Completed online after third reminder email	Online	61 (10)	93 (16)
Completed online after manual text message	Offline	80 (13)	94 (16)
Completed GHQ over the phone or online after phone call	Offline	68 (11)	81 (14)
Completed GHQ via post or online after receiving a postal pack	Offline	84 (14)	76 (13)
Completed GHQ via autotext	Online	10 (2)	22 (4)

[a] Five patients were not sent a 12-week reminder email: 2 of these were due to issues with the reminder system; 3 patients completed the 12 week follow-up at 11 weeks post randomisation, i.e. before the first reminder was sent.

Baseline data

The demographic and situational characteristics of the participants are presented in *Table 8* (a fuller version can be found in *Report Supplementary Material File 1*).

Participants were typically middle aged (53% aged 40–60), white British (91%), female (81%), mothers (48%), highly educated (55% to university level), and supporting a young adult aged 35 or less (61%). More than half (58%) were supporting someone with BD. 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 8.5% reported being unable to work specifically due to their caring responsibilities. All bar four participants had home internet access.

Table 8: Demographic 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)
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 (3.48)
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 education (university)	226 (56.64)	211 (52.62)	437 (54.63)
Employment status			
Employed full-time (35 hrs+ 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)	12.4 (8.0)
Min–max	2–48	1–30	1–48

Baseline scores on the main outcomes are presented in *Table 9*. These showed very high levels of distress. Using Likert scoring, a mean total score of 40 on the GHQ, with SD 14, suggested that the majority of the sample scored above the 23/24 cut off for psychiatric caseness.[127, 128] Highest scores were on the anxiety/insomnia subscale.

Wellbeing and support scores measured using the CSW questionnaire were also very low compared to other studies using this measure with groups of relatives of people with psychosis, although there are no clinical thresholds or established norms for this scale. Mean wellbeing scores 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). Other studies of relatives of people with mental health problems report CWS means in the 70s for wellbeing and 30s for support.[2, 62, 129] This pattern is likely to be a result of the stringent eligibility criteria used to prevent a floor effect on distress scores.

There are no clinical thresholds or published norms for scores on the Brief IPQ or the Brief COPE. These measures are used to assess change over time, and the relationship between illness perceptions and coping styles, and relevant outcomes.

Table 9: Baseline assessments

	REACT **n=399**	**RD** **n=401**	**Overall** **n=800**
General Health Questionnaire (GHQ-28)			
Mean (SD)	40.3 (14.6)	40.0 (14.0)	40.2 (14.3)
Min–max	5–83	11–81	5–83
Somatic symptoms subscale			
Mean (SD)	10.3 (4.4)	10.4 (4.0)	10.3 (4.2)
Min–max	1–21	1–21	1–21
Anxiety/insomnia subscale			
Mean (SD)	13.0 (4.1)	12.9 (4.0)	13.0 (4.1)
Min–max	0–21	1–21	0–21
Social dysfunction subscale			
Median (IQR)	11 (8–13)	11 (8–14)	11 (8–13.5)
Min–max	1–21	3–21	1–21
Severe depression subscale			
Median (IQR)	4 (1–9)	4 (1–9)	4 (1–9)
Min–max	0–21	0–21	0–21
Carer wellbeing and support (CWS)			

Wellbeing			
Mean (SD)	55.9 (25.9)	55.8 (26.4)	55.9 (26.1)
Min–max	0–125	0–114	0–125
Support			
Mean (SD)	19.5 (11.6)	18.8 (11.7)	19.1 (11.7)
Min–max	0–51	0–51	0–51
Brief Illness Perception Questionnaire			
Carer			
Mean (SD)	41.0 (7.4)	41.4 (6.9)	41.2 (7.2)
Min–max	21–65	19–63	19–65
Service user			
Mean (SD)	44.4 (8.5)	44.2 (8.6)	44.3 (8.6)
Min–max	19–70	18–75	18–75
Additional item on coping			
Mean (SD)	5.6 (2.2)	5.6 (2.3)	5.6 (2.2)
Min–max	0–10	0–10	0–10
Brief COPE			
Self-distraction			
Median (IQR)	5 (4–6)	5 (4–7)	5 (4–6)
Min–max	2–8	2–8	2–8
Active coping			

Median (IQR)	5 (4–7)	6 (4–7)	5 (4–7)
Min–max	2–8	2–8	2–8
Denial			
Median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)
Min–max	2–8	2–8	2–8
Substance use			
Median (IQR)	2 (2–4)	2 (2–4)	2 (2–4)
Min–max	2–8	2–8	2–8
Use of emotional support			
Median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)
Min–max	2–8	2–8	2–8
Use of instrumental support			
Median (IQR)	4 (3–6)	4 (3–6)	4 (3–6)
Min–max	2–8	2–8	2–8
Behavioural disengagement			
Median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)
Min–max	2–8	2–8	2–8
Venting			
Median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)
Min–max	2–8	2–8	2–8
Positive reframing			

Median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)
Min–max	2–8	2–8	2–8
Planning			
Median (IQR)	6 (4–8)	6 (4–7)	6 (4–7)
Min–max	2–8	2–8	2–8
Humour			
Median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)
Min–max	2–8	2–8	2–8
Acceptance			
Median (IQR)	6 (5–7)	6 (5–7)	6 (5–7)
Min–max	2–8	2–8	2–8
Religion			
Median (IQR)	2 (2–4)	2 (2–4)	2 (2–4)
Min–max	2–8	2–8	2–8
Self-blame			
Median (IQR)	4 (3–6)	4 (3–6)	4 (3–6)
Min–max	2–8	2–8	2–8

Outcomes and estimated effect sizes

Table 10 sets out summary scores for total GHQ-28 and for each of the four subscales at baseline, 12 weeks and 24-week follow-up (primary end point).

Table 10: GHQ-28 scores at baseline, 12-week and 24-week follow-up

	REACT Baseline n=399	REACT 12 weeks n=287	REACT 24 weeks n=292	RD Baseline n=401	RD 12 weeks n=307	RD 24 weeks n=307	Overall Baseline n=800	Overall 12 weeks n=594	Overall 24 weeks n=599
General Health Questionnaire (GHQ-28)									
Mean (SD)	40.3 (14.6)	30.6 (15.2)	29.6 (15.9)	40.0 (14.0)	32.9 (15.4)	31.3 (15.2)	40.2 (14.3)	31.8 (15.3)	30.5 (15.6)
Min–max	5–83	3–80	2–79	11–81	1–77	3–81	5–83	1–80	2–81
Somatic symptoms subscale									
Mean (SD)	10.3 (4.4)	8.1 (4.3)	7.9 (4.7)	10.4 (4.0)	8.7 (4.4)	8.3 (4.5)	10.3 (4.2)	8.4 (4.4)	8.1 (4.6)
Min–max	1–21	0–21	0–21	1–21	0–21	0–21	1–21	0–21	0–21
Anxiety/insomnia subscale									
Mean (SD)	13.0 (4.1)	9.5 (4.7)	9.2 (4.9)	12.9 (4.0)	10.1 (4.8)	9.9 (4.9)	13.0 (4.1)	9.8 (4.7)	9.6 (4.9)

Min–max	0–21	0–21	0–21	1–21	0–21	0–21	0–21	0–21	0–21
Social dysfunction subscale									
Median (IQR)	11 (8–13)	8 (7–11)	8 (7–11)	11 (8–14)	9 (7–13)	8 (7–11)	11 (8–13.5)	9 (7–12)	8 (7–11)
Min–max	1–21	0–21	0–21	3–21	0–21	0–20	1–21	0–21	0–21
Severe depression subscale									
Median (IQR)	4 (1–9)	2 (0–7)	2 (0–6)	4 (1–9)	3 (0–7)	2 (0–7)	4 (1–9)	2 (0–7)	2 (0–7)
Min–max	0–21	0–21	0–21	0–21	0–21	0–21	0–21	0–21	0–21

Primary efficacy assessment: General Health Questionnaire at 24 weeks

Table 11 shows the analysis of covariance was used to compare GHQ-28 scores between the two groups at 24-week follow-up, adjusting for baseline scores. The estimated mean difference between the two groups favoured REACT but was small (-1.39, 95% CI -3.60–0.83), not statistically significant (p=0.2189) and unlikely to be of clinical significance. The same pattern was observed in the individual subscales (see *Report Supplementary Material File 1, Section 6.6.1*).

Table 11: Analysis of covariance, adjusting for baseline GHQ-28 (24 weeks)

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline GHQ-28	0.53 (0.45–0.61)	165.27	<0.0001
Treatment (REACT versus control)	-1.39 (-3.60–0.83)	1.51	0.2189

Secondary efficacy endpoint: General Health Questionnaire at 12 weeks

Table 12 shows that the estimated mean difference between the two groups at 12-week follow-up favoured REACT, but was small and, although statistically significant, was likely to be of limited clinical significance. The same pattern was observed in all of the individual subscales, but without significant differences between the two groups (see *Report Supplementary Material File 1, section 6.6.3*).

Table 12: Analysis of covariance, adjusting for baseline GHQ-28 (12 weeks)

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline GHQ-28	0.61 (0.53–0.68)	265.18	<0.0001
Treatment (REACT versus control)	-2.08 (-4.14– -0.03)	4.91	0.0271

Joint modelling analysis: GHQ-28 score

Details of the joint modelling analysis for the GHQ-28 scores can be found in *Report Supplementary Material File 1, Section 6.6.4*.

In summary, baseline GHQ scores were very high with a mean of 40.2 (SD 14.3). The highest subscale was anxiety. GHQ-28 fell over time in both arms of the trial. Most of this occurred during the first 12 weeks. At the 12-week follow-up, GHQ-28 scores were statistically significantly lower in REACT than in RD, but this difference was small and likely to be of limited clinical significance. There was no statistically significant difference between the groups by 24 weeks.

Retention at 12 weeks was 74 per cent and at 24 weeks was 75 per cent. Although similar numbers of participants dropped out in each arm, those who dropped out of the REACT arm were more distressed than those that 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 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 in both groups. When missing data were taken into account, using joint modelling methods (jointly accounting for time to drop out and longitudinal GHQ-28 measurements), there was no statistically significant difference between the REACT and RD arms over the 24-week follow up period.

Despite the significant (statistical and clinical) reduction in GHQ scores over time in both groups, mean scores at 12 and 24-week follow-up remained higher than the 23/24 threshold score suggestive of clinical caseness.

Secondary efficacy endpoint: carer wellbeing and support

The number of respondents and summary scores for the CWS wellbeing and support scales at baseline, 12 weeks and 24-week follow-up are presented in *Table 13*.

Table 13: Carer wellbeing and support questionnaire responses at baseline, 12 and 24 weeks

	REACT baseline n=399	REACT 12 weeks n=233	REACT 24 weeks n=249	RD baseline n=401	RD 12 weeks n=271	RD 24 weeks n=275	Overall Baseline n=800	Overall 12 weeks n=504	Overall 24 weeks n=524
Wellbeing									
Mean (SD)	55.9 (25.9)	72.0 (27.0)	77.0 (26.6)	55.8 (26.4)	68.9 (27.7)	72.6 (30.5)	55.9 (26.1)	70.3 (27.4)	74.7 (28.8)
Min–max	0–125	15–127	8–124	0–114	0–128	0–127	0–125	0–128	0–127
Support									
Mean (SD)	19.5 (11.6)	26.0 (12.0)	25.7 (11.7)	18.8 (11.7)	22.6 (12.0)	23.2 (12.2)	19.1 (11.7)	24.2 (12.1)	24.4 (12.0)
Min–max	0–51	0–51	0–51	0–51	0–50	0–51	0–51	0–51	0–51

Wellbeing and support at 12 weeks

Analysis of covariance at 12-week follow-up is presented in *Table 14*. The estimated mean difference in wellbeing between the two arms of the trial favoured REACT, but was small, not statistically significant (p=0.4225) and was unlikely to be clinically significant.

The estimated mean difference in support at 12 weeks also favoured REACT and was statistically significant (p<0.0001).

Table 14: Analysis of covariance, adjusting for baseline, wellbeing and support (12 weeks)

Covariate	Coefficient (95% CI)	F statistic	p-value
Wellbeing			
Baseline	0.66 (0.59, 0.74)	326.79	<0.0001
Treatment (REACT versus control)	1.53 (-2.21, 5.27)	0.64	0.4225
Support			
Baseline	0.68 (0.61, 0.76)	351.15	<0.0001
Treatment (REACT versus control)	2.50 (0.87, 4.12)	16.83	<0.0001

Number included in analysis: REACT n=233; RD n=271.

Wellbeing and support at 24 weeks

Analysis of covariance at 24-week follow-up is presented in *Table 15*. The estimated mean difference in wellness between the two groups favoured REACT at 24 week follow up, but was not statistically significant (p=0.2582) and was unlikely to be of clinical significance.

The estimated mean difference in support between the groups at 24 week follow up also favoured REACT and this was statically significant (p=0.0451).

Table 15: Analysis of covariance, adjusting for baseline, wellbeing and support (24 weeks)

Covariate	Coefficient (95% CI)	F statistic	p-value
Wellbeing			
Baseline	0.61 (0.53–0.69)	219.13	<0.0001
Treatment (REACT versus control)	2.39 (-1.76–6.54)	1.28	0.2582
Support			
Baseline	0.64 (0.57–0.71)	321.52	<0.0001

Treatment (REACT versus control)	1.65 (0.04–3.27)	4.03	0.0451

Number included in analysis: REACT n=249; RD n=275.

Joint modelling analysis: CWS wellbeing and support

Details of the joint modelling analysis for the CWS wellbeing and support scores can be found in *Report Supplementary Material File 1, Section 6.6.7*.

In summary, CWS wellbeing and support scores were very low at baseline, with a wellbeing mean of 55.9 and support mean of 19.1. but both improved significantly over time in both arms with most of this occurring during the first 12 weeks.

There was no statistically significant difference in wellbeing scores between the two groups at 12 or 24 weeks' follow-up. However, support scores were significantly higher in the REACT arm than in the RD arm at both 12 and 24 week.

Retention at 12 weeks was 63% and at 24 weeks was 66%. More people dropped out in the REACT arm than in the RD arm, and those who dropped out were more likely to have lower wellbeing scores. This meant that data could not be assumed to be missing at random in both groups.

When missing data was taken into account, there was no statistically significant difference between the REACT and RD arms for wellbeing or support over the 24-week follow-up period. However, the mean difference between the two arms on the support scale was 1.51 points, and the clinical significance of this remains unknown.

Causal analysis

Instrumental variable regression

IV regression was used to estimate the association between intervention use and GHQ-28 score at 24 weeks, using a number of measures of website use, principally the number of web page downloads during the 24 weeks of follow-up but also participants' total number of logins over the same period and their total time logged onto the REACT site. Scores for those in the control arm were taken to be 0 since they were not granted access to the intervention.

For web page downloads, randomised group was chosen as the IV as it was assumed to satisfy the following criteria:

- Association with web page downloads
- An indirect effect on GHQ-28 (via web page downloads)
- No common causes of randomisation and GHQ-28.

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.

Table 16 shows the outcome of IV regression of GHQ-28 scores at 24 weeks, based on web page downloads in the 24 weeks of follow-up, adjusted for baseline GHQ-28 score.

Table 16: IV regression of GHQ-28 at 24 weeks on web page downloads in 24 weeks of follow-up, adjusted for baseline GHQ-28 score

Covariate	Coefficient (95% CI)	Z statistic	p-value
Baseline GHQ-28	0.53 (0.44–0.62)	12.0	<0.001
Web page downloads	-0.01 (-0.02–0.01)	-1.1	0.295

Number included in analysis: REACT: n=252; RD: n=268.

The mean number of web page downloads in the REACT group was 149.9. For each additional download there was a mean reduction in GHQ-28 at 24 weeks of 0.01; however, this effect was not statistically significant (p=0.295).

Similarly, the mean number of logins to the REACT site was 7.9, with each additional login seeing a mean reduction in GHQ-28 at 24 weeks of 0.17, again not a statistically significant effect (p=0.296).

Finally, the median number of minutes spent on REACT was 50.8 with a mean reduction in GHQ-28 at 24 weeks of 0.01 for each additional minute on the site there – again, not statistically significant (p=0.296).

Details of the analysis of all three measures of website use, including the suitability of using randomisation as the instrument in this regression, can also be found in *Report Supplementary Material File 1, Section 6.6.8.1*.

Mediation analysis

Brief illness perception questionnaire

Table 17 shows scores on the Brief IPQ subscales at baseline, 12 and 24 weeks. Scores on the carer and service-user subscales show a pattern of decrease over time in both arms. Lower scores on this measure indicate a more benign perception of illness and its impact on both service user and carer. The additional item on coping also shows a pattern of decrease over time, suggesting carers feel more able to cope over time.

Multivariate ANCOVA was used to assess the impact of the intervention group on each of subscales, at 12 weeks and at 24 weeks, while taking into account correlation between the subscales. The results of the MANOVA and ANCOVA tables for individual subscales at each time point are shown in *Report Supplementary Material File 1*. The p-values for all tests are non-significant, indicating no evidence of a difference between randomised groups for one or more of the outcomes at either time point.

Table 17: Brief illness perception questionnaire at baseline, 12 and 24 weeks

	REACT baseline n=399	**REACT 12 weeks n=228**	**REACT 24 weeks n=244**	**RD baseline n=401**	**RD 12 weeks n=263**	**RD 24 weeks n=268**	**Overall baseline n=800**	**Overall 12 weeks n=491**	**Overall 24 weeks n=512**
Carer									
Mean (SD)	41.0 (7.4)	38.7 (7.5)	37.5 (7.7)	41.4 (6.9)	39.2 (7.0)	68.0 (7.7)	41.2 (7.2)	39.0 (7.2)	37.8 (7.7)
Min–max	21–65	16–59	10–61	19–63	16–55	10–62	19–65	16–59	10–62
Service user								42.6 (8.3)	
Mean (SD)	44.4 (8.5)	42.6 (8.5)	41.5 (8.7)	44.2 (8.6)	42.6 (8.1)	41.8 (8.4)	44.3 (8.6)	18–69	41.6 (8.5)
Min–max	19–70	18–66	15–65	18–75	20–69	13–66	18–75		13–66
Additional item on coping								0–10	
Mean (SD)	5.6 (2.2)	5.0 (2.3)	4.5 (2.1)	5.6 (2.3)	5.0 (2.2)	4.9 (2.2)	5.6 (2.2)		4.7 (2.2)
Min–max	0–10	0–10	0–10	0–10	0–10	0–10	0–10		0–10

IV regression, with the interaction between randomised group and baseline score of the mediator as the instrument, was performed to assess whether the 24-week mediator score was a predictor of the 24-week GHQ-28 score. These were found to be weak instruments and therefore causal mediation analysis was instead performed to estimate the average causal mediated effect (ACME) of GHQ-28 score at 24 weeks. None of the putative mediators had a significant mediation effect on outcome. Details of the analysis are in *Report Supplementary Material File 1, Section 6.6.9*.

Brief COPE

Table 18 shows scores on the subscales of the Brief COPE at 12 and 24 weeks. There was very little change in COPE scores in either group at any time point throughout the study. Active coping, planning, and acceptance remained the most commonly used strategies. Denial, substance use, and religion, were the least common strategies in both groups.

Multivariate ANCOVA was used to assess the impact of intervention group on each of these subscales, at 12 weeks and 24 weeks, while taking into account correlation between the subscales. The results of the MANOVA and ANCOVA tables for each subscale at each timepoint are shown in *Report Supplementary Material File 1*. The p-values for all the tests are non-significant. indicating no evidence of a difference that is significant at the p=0.05 level between randomised groups for one or more of the outcomes at either time point.

IV regression, with the interaction between randomised group and baseline score of the mediator as the instrument, was performed to assess whether the 24-week mediator score was a predictor of the 24-week GHQ-28 score. These were found to be weak instruments and therefore causal mediation analysis was instead performed to estimate the ACME of GHQ-28 score at 24 weeks. None of the putative mediators had a significant mediation effect on outcome. Details of the analysis are in *Report Supplementary Material File 1, Section 6.6.9*.

Table 18: Brief COPE at baseline, 12 and 24 weeks

	REACT Baseline n=399	REACT 12 weeks n=228	REACT 24 weeks n=243	RD Baseline n=401	RD 12 weeks n=263	RD 24 weeks n=265	Overall Baseline n=800	Total 12 weeks n=491	Total 24 weeks n=508
Self-distraction									
Median (IQR)	5 (4–6)	5 (4–6)	5 (4–6)	5 (4–7)	5 (4–6)	5 (4–6)	5 (4–6)	5 (4–6)	5 (4–6)
Min–max	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8
Mann Whitney U p-value		0.3654	0.9350						
Active coping									
Median (IQR)	5 (4–7)	6 (4–7)	5 (4–6)	6 (4–7)	5 (4–7)	5 (4–6)	5 (4–7)	5 (4–7)	5 (4–6)
Min–max	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8
Mann Whitney U p-value		0.6969	0.8700						
Denial									
Median (IQR)	2 (2–3)	2 (2–3)	2 (2–2)	2 (2–3)	2 (2 -2)	2 (2–2)	2 (2–3)	2 (2–3)	2 (2–2)

Min–max	2–8	2–8	2–8	2–8	2–8	2–7	2–8	2–8	2–8
Mann Whitney U p-value		0.2837	0.7378						
Substance use									
Median (IQR)	2 (2–4)	2 (2–4)	2 (2–4)	2 (2–4)	2 (2–4)	2 (2–4)	2 (2–4)	2 (2–4)	2 (2–4)
Min–max	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8
Mann Whitney U p-value		0.8157	0.4303						
Use of emotional support									
Median (IQR)	4 (3–5)	4 (3–6)	4 (3–6)	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)
Min–max	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8
Mann Whitney U p-value		0.0028	0.3877						
Use of instrumental support									
Median (IQR)	4 (3–6)	4 (3.5–6)	4 (3–5)	4 (3–6)	4 (3–5)	4 (3–5)	4 (3–6)	4 (3–6)	4 (3–5)
Min–max	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8

Mann Whitney U p-value		0.0559	0.9637						
Behavioural disengagement									
Median (IQR)	3 (2–4)	2 (2–4)	2 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	2 (2–4)
Min–max	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8
Mann Whitney U p-value		0.3561	0.2335						
Venting									
Median (IQR)	4 (3–5)	3.5 (3–4)	4 (3–5)	4 (3–5)	3 (3–5)	3 (3–4)	4 (3–5)	3 (3–4)	3 (3–4)
Min–max	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8
Mann Whitney U p-value		0.5816	0.3243						
Positive reframing									
Median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)
Min–max	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8
Mann Whitney U p-value		0.5805	0.3890						

Planning									
Median (IQR)	6 (4–8)	6 (4–7)	5 (4–7)	6 (4–7)	6 (4–7)	5 (4–7)	6 (4–7)	6 (4–7)	5 (4–7)
Min–max	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8
Mann Whitney U p-value		0.6936	0.9400						
Humour									
Median (IQR)	3 (2–4)	2 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	2 (2–4)	3 (2–4)	3 (2–4)	2 (2–4)
Min–max	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8
Mann Whitney U p-value		0.1743	0.9358						
Acceptance									
Median (IQR)	6 (5–7)	6 (5–7)	6 (5–7)	6 (5–7)	6 (5–8)	6 (5–7)	6 (5–7)	6 (5–7)	6 (5–7)
Min–max	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8
Mann Whitney U p-value		0.4409	0.4331						
Religion									

Median (IQR)	2 (2–4)	2 (2–4)	2 (2–4)	2 (2–4)	2 (2–4)	2 (2–4)	2 (2–4)	2 (2–4)	2 (2–4)
Min–max	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8
Mann Whitney U p-value		0.4568	0.2450						
Self-blame									
Median (IQR)	4 (3–6)	4 (3–5)	4 (3–5)	4 (3–6)	4 (3–5)	4 (2–5)	4 (3–6)	4 (3–5)	4 (3–5)
Min–max	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8	2–8
Mann Whitney U p-value		0.3386	0.6988						

NB: These results should be viewed as exploratory in nature in light of the multiple hypothesis tests that have been performed. In particular, it is likely that at least one p-value will reach 0.05 purely by chance rather than because of a true difference between treatment groups.

Additional analyses

The following analyses were conducted in addition to the testing of our main trial hypotheses which were pre-specified in the published statistical analysis plan.

Impact of baseline factors on intervention effect

When each baseline variable was added to the model separately (see *Report Supplementary Material File 1, **Error! Reference source not found.**~~Error! Reference source not found.~~ to **Error! Reference source not found.**~~Error! Reference source not found.~~*), the variables of gender, marital status, education level, and employment status each had a statistically significant effect on the 24-week GHQ-28 score (adjusting for baseline GHQ-28 and treatment). For the multivariable analysis, a stepwise selection process was performed to determine the significant predictors of outcome which should be included in the final model (using p-value criteria of 0.05 for entry and 0.1 for removal). When controlling for baseline GHQ-28 scores, gender, marital status and employment were all significant predictors of GHQ-28 scores, but treatment arm was not. Being male, single, and unemployed (or in unpaid work) were all associated with greater levels of distress. There was no significant impact of a treatment–mother interaction. Full details of the analysis are set out in *Report Supplementary Material File 1, Section 6.6.10*.

Impact of "lurking" on the REACT forum

Users were defined as participants who left at least one comment on the forum in the 24 weeks of follow-up. "Lurkers" accessed the forum but left no comments. Non-users did not access the forum. Those in the RD arm were all classed as non-users. *Table 19* gives the proportion of participants in each category.

Table 19: Proportion of people reading but not posting ("lurkers")

Status	**REACT** **n=348**	**RD** **n=352**	**Overall** **n=700**
Non-users	141 (41%)	352 (100%)	493 (70.4%)
"Lurkers"	140 (40%)	0 (0%)	140 (20.0%)
Users	67 (19%)	0 (0%)	67 (9.6%)

Total	348 (100%)	352 (100%)	700 (100%)

In the absence of an additional instrument (other than randomisation), it was not possible to employ IV regression to assess the impact of “lurking” versus non-use versus use of the forum. Therefore, a three-way (non-users versus “lurkers” versus users) ordinary least squares regression model was employed, adjusting for baseline covariates. Users were estimated to have lower GHQ-28 scores at 24 weeks compared to non-users (-2.0, 95% CI -5.9–1.9) and lurkers to have a similar effect size to non-users (-0.1, 95% CI -3.2–2.9) but with no evidence of a significant difference for this covariate (p=0.5949). However, an assessment of this model using binary comparisons suggested that the effect size estimated in the three-way ordinary least squares model might be conservative and the true effect larger than estimated (see *Report Supplementary Material File 1, Section 6.6.8.1.3*).

Adverse events

During the trial, 363 participants received a low-risk response (automated email sent in response to report of distress but with no threat to self or others) and 185 participants had more than one. No high-risk events (serious adverse events) were reported. The TM identified three low-risk events, all of which were in the RD arm. REACT supporters reported 16 low-risk events (eight forum posts, five direct messages, and three in email correspondence from people outside the intervention). *Table 20* shows the number of participants scoring a low risk item in each arm, and across each time-point.

Table 20: Number of participants with low-risk questionnaire items

	Baseline			12 weeks			24 weeks		
	REACT n=399	RD n=401	Overall n=800	REACT n=399	RD n=401	Overall n=800	REACT n=399	RD n=401	Overall n=800
Participants with at least one red flag	156 (39.1%)	139 (34.7%)	295 (36.9%)	51 (12.8%)	52 (13.0%)	103 (12.9%)	49 (12.3%)	57 (14.2%)	106 (13.3%)
GHQ-28 (D3)	22 (5.5%)	24 (6.0%)	46 (5.8%)	10 (2.5%)	12 (3.0%)	22 (2.8%)	11 (2.8%)	11 (2.7%)	22 (2.8%)
GHQ-28 (D4)	14 (3.5%)	19 (4.7%)	33 (4.1%)	4 (1.0%)	9 (2.2%)	13 (1.6%)	6 (1.5%)	7 (1.7%)	13 (1.6%)
GHQ-28 (D6)	27 (6.8%)	25 (6.2%)	52 (6.5%)	11 (2.8%)	11 (2.7%)	22 (2.8%)	12 (3.0%)	9 (2.2%)	21 (2.6%)
GHQ-28 (D7)	19 (4.8%)	18 (4.5%)	37 (4.6%)	5 (1.3%)	7 (1.7%)	12 (1.5%)	11 (2.8%)	8 (2.0%)	19 (2.4%)
CWS Q29	58 (14.5%)	54 (13.5%)	112 (14.0%)	14 (3.5%)	12 (3.0%)	26 (3.3%)	6 (1.5%)	19 (4.7%)	25 (3.1%)
CWS Q30	111 (27.8%)	100 (24.9%)	211 (26.4%)	26 (6.5%)	35 (8.7%)	61 (7.6%)	30 (7.5%)	41 (10.2%)	71 (8.9%)

Chapter 5 Health economic analysis

Introduction

This chapter presents the health economic analysis of REACT: a within-trial incremental cost-effectiveness analysis of using REACT and RD compared to access only to the RD. Both interventions were offered in addition to TAU.

In accordance with NICE guidance, our analysis adopted an NHS and personal social services perspective. Costs for REACT and the RD were considered as well as costs related to healthcare provided in a hospital setting, primary care, community health, emergency services, personal social services, and community mental health services. For health outcomes, relatives' distress was assessed using the GHQ, and quality of life was assessed using a generic measure of health-related quality of life, EQ-5D-5L Intervention costs were measured with a micro-costing approach. Results were also presented for the societal perspective including relatives' time off work due to their caring role.

Additionally, we also reported the burden to carers as time spent in caring role, using data about participants' unpaid hours spent looking after their relatives and time off work due to their caring role.

Information about the use of medicines was also collected, but due to errors in the data collection process which resulted in data about the length of time each medicine was used for, this data could not be included in the analyses.

All costs are presented in pounds sterling using 2018 available costs.

Aims and objectives

The aim of the health economic analysis was to determine the cost effectiveness of treatment as usual plus REACT and RD in reducing distress for relatives, compared to TAU and access to only the RD. Specific objectives were to determine:

1. Costs of delivering TAU plus REACT plus RD versus NHS and productivity cost savings in use of health services, and paid work adapted from the client service receipt inventory (CSRI).

2. Cost-effectiveness: cost of significant unit changes (defined as 3-point reduction) in the primary outcome (GHQ-28);
3. Cost-utility: marginal cost of any marginal change in quality-adjusted life years (QALYs), measured by the EQ-5D-5L.

Method: costs

Information about the trial design, setting, participants, recruitment, randomisation, data collection, and effectiveness outcomes are reported in *Chapter 3*. Following NICE guidance,[130] the economic analysis was undertaken from an NHS and personal social services perspective. Costs of real-world delivery within the trial were used. A micro-costing approach[131] was undertaken to value REACT and RD.

Costs of the REACT toolkit and the RD were calculated separately. Health care and personal social services use, and health outcomes, including a generic measure of health and wellbeing (GHQ 28) and a generic health-related quality of life outcome (EQ-5D-5L), were assessed online.

REACT intervention cost

The REACT intervention cost included several components:

- Cost of developing the intervention
- Cost of delivering the intervention
- Cost of participant recruitment.

Development costs

REACT was developed over many years, first in a paper version and subsequently adapted for the online version used in this trial. We assessed all costs relevant to content development, including the initial paper version. 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.

The most significant cost was the research and academic staff time incurred throughout the conception and design of the toolkit. Time spent by each person in each development activity was estimated. Detailed records and a retrospective analysis of invoices allowed us to assess the various activities and costs incurred.

The second substantive cost lay in employing an external web-design company to build the REACT website. Others included costs related to domain name registration, SSL (secure sockets layer) certification fees, web hosting and exclusive internet protocol (IP) address during development. All these were obtained from invoices and receipts.

Costs associated with the development of the intervention could be considered as "sunk costs", as they had already been incurred but were impossible to recover, and previous researchers have taken this approach.[132] However, we decided to follow a more conservative approach and include them in the analysis.

REACT delivery costs

Delivery of the REACT toolkit was described in *Chapter 2*. Related costs included general infrastructure for hosting the REACT website and the costs of training, supervision, and employment of REACT supporters for 6 months.

The most significant costs related to the REACT supporters' time spent on each clinical task (forum posts, direct messages, supervision and other activities), which we derived from staff time sheets. The second most significant cost was associated with supporter training.

Hourly rates for staff were obtained from national pay scales, with additional costs calculated for superannuation and national insurance, or from invoices when the staff involved were not directly employed by Lancaster University. Costs of relatives' contributions to toolkit delivery were obtained from invoices. Reimbursement was based on organisational policy at the time of activity.

Other costs in this phase related to web hosting, IP address, software used to send automated emails to participants, and technical maintenance to keep the website working

properly, obtained from invoices and receipts. These activities are required for regular maintenance and delivery of REACT.

Costs related to training, supervision, and employment of REACT supporters are for 6 months and 400 participants, based on the maximum number of people who were supported at any one time; this was considered to be at or near capacity for the number of REACT supporters employed. Costs of the infrastructure are also for 6 months, divided equally between the two arms of the trial (intervention and comparator), as both arms used equal amounts of infrastructure.

Recruitment costs

Recruitment of participants was necessary to deliver the intervention. As participants were relatives or carers of people with psychosis or bipolar disorder – not the service users themselves – social media and the internet were used to disseminate information. Online adverts on Facebook, Google and Bipolar UK were most successful in recruiting participants but there were also costs related to offline recruitment, such as printing flyers and leaflets. These recruitment methods would be unnecessary were the intervention to be delivered through the NHS in routine practice, but some method of referring relatives to the intervention would still be needed. We decided to use available data on costs incurred, in line with our in-trial analytical approach, rather than hypothetical data on costs of an NHS model of referral to the intervention. Total recruitment costs were divided by the number of people who completed eligibility screening for the trial (n=3,287).

Resource directory (comparator arm) cost

Participants in the control group were given access only to the online RD. Costs associated with development and delivery of the directory included time spent in developing materials, infrastructure costs of domain registration and web hosting. There were also costs to supporters editing and updating RD content during the trial. As for the REACT toolkit, staff and relative costs were calculated from the product of time spent on development and delivery by cost per unit of time.

Time spent on developing the RD was considerably less than time spent on developing REACT, as was the time spent by REACT supporters. Some of their time was allocated to updating the RD in both arms of the trial.

Costs of healthcare and personal social services

Participants were asked about their use of a wide range of healthcare and social services; this information was collected at baseline and at 12-week and 24-week follow-up. Data collected at baseline referred to the 12 weeks before entering the trial; data collected at each of the follow-up points covered the previous 12 weeks of the trial.

Participants self-reported their use of healthcare services, personal social services and medicines, using a client service receipt inventory developed for this study. Data collected covered the use of hospital services such as accident and emergency, general hospital, community hospital, day hospital, outpatient visits and clinics based at hospital sites. For primary and community services, participants were asked about their use of ambulance services, community matrons, community or district nurses, GPs, practice nurses and specialist nurses. Questions focused on the type of contact (home, clinic/office or phone), number of contacts and duration.

Personal social services use was identified through questions about the number and duration of home, clinic/office or phone contacts with social workers or care managers, home care or home help workers, private home helps or cleaners, or respite care.

Another set of questions covered community mental health services: psychiatrist/psycho-geriatrician, community psychiatric nurse or community mental health nurse and other mental health professionals. Once again, people were asked the number and duration of home, clinic/office or phone contact.

Participants were also asked about the number and duration of face-to-face and telephone contact with other community-based services they might have used in the previous 12 weeks.

Use of activities such as day care, lunch clubs and social clubs was collected. Participants were asked about use, number of contacts per week, total number of contacts over the past 12 weeks and how the service was paid for (i.e. by the participant, NHS trust, charity, social services, or other).

Participants were asked about their use of any voluntary or third sector support services and given the opportunity to select from a list over 40 organisations including Anxiety UK, Bipolar UK, Big White Wall and Samaritans. Questions were about the number and duration of contacts in the last 12 weeks and if those had been face-to-face, by telephone or online.

The last group of questions was about use of medications. Participants were asked whether they had taken any medication in the previous 12 weeks and, if so, the name, dose, frequency and duration of use.

Service use was costed by applying national average unit costs, obtained from Unit Costs of Health and Social Care 2017,[133] Reference Cost Collection[134] or other sources as appropriate (*Table 21*). Unit costs used include overheads, capital and infrastructure costs, allocated according to staff time. Average distance or time for home visits was not available; it was decided to use 10 minutes per visit based on the estimates made in Unit Costs of Health and Social Care 2017.[133] Travel expenses were not accounted for.

The unit cost of inpatient episodes covered only elective inpatient admissions. Unit costs of A&E visits included admitted and non-admitted patients. Information about clinical tests was not collected and therefore is not considered in the analysis.

Table 21: National average unit cost used in REACT health economic analysis

Resource	Cost (£)	Unit	Source
Accident & Emergency	160.00	Attendance	Reference Cost Collection: National Schedule of Reference Costs 2017/18, NHS trusts and NHS foundation trusts, table 2 (p5)
General hospital inpatient	3,894.00	Admission	Reference Cost Collection: National Schedule of Reference Costs 2017/18, NHS trusts and NHS foundation trusts, table 2 (p5)
Community hospital inpatient	3,894.00	Admission	Reference Cost Collection: National Schedule of Reference Costs 2017/18, NHS trusts and NHS foundation trusts, table 2 (p5)
Day hospital	742.00	Admission	Reference Cost Collection: National Schedule of Reference Costs 2017/18, NHS trusts and NHS foundation trusts, table 2 (p5)
Outpatient services	125.00	Appointment	Reference Cost Collection: National Schedule of Reference Costs 2017/18, NHS trusts and NHS foundation trusts, table 2 (p5)
Paramedic (ambulance service)	98.00	Service	Reference Cost Collection: National Schedule of Reference Costs 2017/18, NHS trusts and NHS foundation trusts, AMB

Ambulance calls	7.00	Calls	Reference Cost Collection: National Schedule of Reference Costs 2017/18, NHS trusts and NHS foundation trusts, table 6 (p9)
Specialist nursing, active case management (community matrons), adult, face-to-face	99.00	Contact	Reference Cost Collection: National Schedule of Reference Costs 2017/18, NHS trusts and NHS foundation trusts, N06AF
Specialist nursing, active case management (community matrons), adult, non-face-to-face	45.00	Contact	Reference Cost Collection: National Schedule of Reference Costs 2017/18, NHS trusts and NHS foundation trusts, N06AN
District Nurse, adult, face-to-face	38.00	Contact	Reference Cost Collection: National Schedule of Reference Costs 2017/18, NHS trusts and NHS foundation trusts, N02AF
District Nurse, adult, non-face-to-face	19.00	Contact	Reference Cost Collection: National Schedule of Reference Costs 2017/18, NHS trusts and NHS foundation trusts, N02AN
Practice nurse	36.00	Hour	Unit Costs of Health and Social Care 2017, table 2 (p117)
Specialist nurse (respiratory, diabetes, cardiac or other)	62.00	Hour	Unit Costs of Health and Social Care 2017 (cost per working hour)
Occupational Therapist, adult, one-to-one	81.31	Contact	Reference Cost Collection: National Schedule of Reference Costs 2017/18, NHS trusts and NHS foundation trusts, A06A1
Physiotherapist, adult, one-to-one	57.26	Contact	Reference Cost Collection: National Schedule of Reference Costs 2017/18, NHS trusts and NHS foundation trusts, A08AG

General practitioner	183.00	Hour	Unit Costs of Health and Social Care 2017, 10.3b GP (p162)
Social worker or care manager	43.00	Hour	Unit Costs of Health and Social Care 2017, 11.2 social worker (adult services) (p174)
Home care/home help worker	21.00	Hour	Unit Costs of Health and Social Care 2017, 11.6 home care worker, (p178)
Private home help/cleaner	12.50	Hour	Market price
Psychiatrist/psycho-geriatrician	108.00	Hour	Unit Costs of Health and Social Care 2017, consultant psychiatric
Community psychiatric nurse/community mental health nurse	62.00	Hour	Unit Costs of Health and Social Care 2017, 10.1 nurses, (p159)
Other mental health professional, please specify:	39.00	Hour	Unit Costs of Health and Social Care 2017, 12.2 community mental health team for adults with mental health problems (p186)
Day care – voluntary organisation	34.00	Per client attendance	Unit Costs of Health and Social Care 2017, 2.4 private and voluntary sector day care, (p46)
Day care – NHS (community-based)	104.00	Contact	Reference Cost Collection: National Schedule of Reference Costs 2017/18, NHS trusts and NHS foundation trusts, DCF30

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Dentist	127.00	Hour	Unit Costs of Health and Social Care 2017, 10.5 NHS dentist – performer-only (p165)
Optician	25.00	Appointment	Boots
Mental Health Care Clusters initial assessments	307.00	Assessment	Reference Cost Collection: National Schedule of Reference Costs 2017/18, NHS trusts and NHS foundation trusts, table 3 (p6)
IAPT	353.00	Episode	Reference Cost Collection: National Schedule of Reference Costs 2017/18, NHS trusts and NHS foundation trusts, IAPTMHCC

Health outcomes

Two health outcomes were used in the analysis: GHQ and QALYs derived from the EQ-5D-5L. Both measures were collected at baseline, 12 weeks and 24 weeks.

The EQ-5D-5L sets out five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) each with five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The tariff for the UK population[135] was used to compute the index score, with a range of -0.285 (worst health) to 1 (perfect health).

From EQ-5D-5L collected at baseline, 12 weeks and 24 weeks, the respective index scores were computed based on the results of Devlin *et al*.[135] To calculate the QALYs gained by the intervention index, scores for baseline and week 24 were divided by number of weeks in a year (365.25 divided by 7) and multiplied by 12 to match our time horizon of 24 weeks (the interpolation method).

GHQ is described in *Chapter 3* of this report.

Carers' productivity losses

Carers were asked at baseline, week 12 and week 24 to report any additional time off work due to their caring role, with a recall period of 12 weeks.

Burden of disease on carers: time spent in caring role

Carers were asked at baseline, week 12 and week 24 about the number of unpaid hours spent looking after their relative each week, with a recall period of 12 weeks. For the same recall period, they were asked to report any additional time off work due to their caring role.

Methods: analysis

A health economics analysis plan was developed and approved by the TMG before the analysis began (see *Report Supplementary Material File 2*).

Analysis of intervention costs

Costs of developing and delivering the REACT toolkit and RD were calculated separately. Half the costs of developing and delivering the RD were allocated to the intervention arm, and half to the comparator arm, reflecting the trial design of TAU plus REACT plus RD

versus TAU plus RD only. This meant that the total cost for development and delivery of REACT without the RD was divided by 400 (number of participants in the intervention arm) while total cost of the RD was divided by 800 to obtain an average per participant cost for each. Infrastructure costs were divided by 800 to reflect the total number of trial participants, and divided between the intervention and comparator arms.

Recruitment costs were calculated over the total trial period and divided by 3,287, the number of people that completed eligibility screening for the trial. Cost included an average per participant in both arms of the trial as both required recruitment.

All costs were computed for a 6-month period, the length of time that each individual participant took part in the trial.

Missing data

EQ-5D-5L data sets obtained at baseline, week 12 and week 24 were used in the primary analysis. The imputation of missing values was based on age, gender and values of EQ-5D-5L at baseline. We implemented a multiple imputation with chained equations system.[136] This involves first imputing each variable and then deleting the imputed values for the first variable and replacing them with values imputed from a regression using as independent variables all remaining imputed ones. Subsequently we then deleted the imputed values for the second variable and replaced them with the values imputed from a regression controlling for the remaining variables. This process is repeated iteratively. The estimation process used predictive mean matching with five “nearest neighbours” over 50 imputations by treatment group. Since the percentage of missing data was at worst 50%, we calculated 50 imputed values for each observation. Multiple imputation for missing data was undertaken for the total cost of the use of hospital services at baseline, week 12 and week 24, and for the EQ-5D-5L at week 12 and at week 24. Further to this, we undertook an analysis using the chained equation imputation combined with a seemingly unrelated regression model method.[136] This method takes into account the possible correlation between the error terms in the two equations (the QALYs and the costs) and can bring efficiency gains compared to ordinary least squares when estimating QALYs and costs adjusting for a different set of variables.

Cost utility analysis

Each EQ-5D-5L index score was converted to QALYs to perform a cost–utility analysis. QALYs were calculated over the duration of the trial.

The ICER was calculated by determining the difference in mean cost per participant in the two arms of the trial, and dividing this difference by the mean difference in QALYs (*Equation 1)*. The total cost per participant in the REACT toolkit arm comprised the costs of developing and delivering REACT with RD plus recruitment costs plus the cost of health and personal social services use. Total cost per participant in the RD arm comprised the cost of developing and delivering RD plus the cost of health and personal social services use.

Equation 1: Incremental cost-effectiveness ratio

$$ICER = \frac{\Delta(cost_{intervention\ arm} + \text{intervention cost}) - (cost_{comparator\ arm} + resource\ directory\ cost)}{\Delta QALY}$$

We performed both unadjusted and adjusted estimations. A linear model was fitted with the 24 weeks outcome as the dependent variable, adjusting for the baseline outcome. The difference in mean 24 weeks costs and outcomes were estimated based on the model. In the adjusted model we controlled for age, gender and utility at baseline in the QALY equation, and only for age and gender in the costs model. This is because the utility is likely to be influenced by age, gender and its baseline value. Healthcare use is influenced by age and gender.

To address the uncertainty present in the results obtained for the difference in mean costs and outcomes at 24 weeks, the non-parametric bootstrapping technique was employed. 1,000 bootstrapped samples were created and the total costs and outcomes estimated from each. The results from bootstrap resampling were used to construct 95% CIs for incremental costs and incremental QALYs. Those results were also used to plot the cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) to show the uncertainty surrounding conclusions.

Sensitivity analyses

The use of modelling can introduce uncertainty around the assumptions used, such as the health states described and data sources selected. We tested the robustness of the ICER by also undertaking a complete case analysis as a secondary analysis, as this uses alternative assumptions from those informing the multiple imputation.

Valuing carers' productivity losses

A value was ascribed to the mean time taken off work by carers using the average (median) hourly pay in 2017.

Valuing burden of disease on carers: time spent in caring role

The mean number of hours lost by carers at baseline, week 12 and week 24 in the REACT toolkit and in the RD were valued according to the latest average hourly pay published data.[137] The *t*-test for independent samples was used to assess differences reported at each time by participants in the REACT toolkit and RD groups. The *t*-test for paired samples was used to assess differences between baseline and week 24 in each arm.

Results

Costs

Development costs of REACT toolkit

The largest development cost for the REACT toolkit was £22,599 for staffing (*Table 22*), covering time spent by three professors of clinical psychology, one professor of psychiatry, two experienced clinical psychologists, two research assistants and one research fellow.

Costs for the information officer, communications and information manager and web-developer were £8,091, including time spent designing the website, filming, editing and post-processing videos and managing the content. The actors hired for the website videos cost £2,112. These actors worked closely with relatives whose own involvement in the design cost £3,693.

Costs associated with website infrastructure during development, including domain name, SSL certificate fees, web hosting and exclusive IP address, and costs related to the private website developer were slightly over £28,000. Total development costs were £64,535.99.

Table 12: Development costs for REACT toolkit

Type of cost	Total no. of hours or units	Cost per hour or unit	Total
Content generation			**£5,574.40**
Staff			£3,699.40
Professor of clinical psychology	*54 hours*	*£55.81*	*£3,013.74*
Clinical psychologist	*17 hours*	*£29.66*	*£504.22*
Research assistant	*18 hours*	*£10.08*	*£181.44*
Relatives			£1,875
Relative co-applicant	*29 hours*	*£20*	*£580*
Relatives in focus groups and advisory role	*118 hours*	*£10*	*£1,180*
Relatives' travelling	*23 persons*	*£5*	*£115*
Producing videos and images			**£18,422.78**
Staff			£14,326.13
Research fellow	*450 hours*	*£23.76*	*£10,692*
Research assistant	*157.5 hours*	*£15.83*	*£2,493*
Information officer	*37.5 hours*	*£30.43*	*£1,141.13*
Communications and information manager	56.25 hours	£31.36	£1,764
Actors			£2,112.65
Relatives	11 persons	£20/person	£220

Developing and designing the website			**£12,499.59**
Staff			£10,901.11
Professor of clinical psychology	*36 hours*	*£55.81*	*£2,009.16*
Professor of clinical psychology	*26 hours*	*£69.80*	*£1,814.80*
Professor of psychiatry	*26 hours*	*£68.00*	*£1,768.00*
Research assistant	*10 hours*	*£12.29*	*£122.90*
Digital technologist/web developer	*225 hours*	*£23.05*	*£5,186.25*
Relatives			£1,598.48
Relatives' focus groups	*56 hours*	*£20*	*£1,120.00*
Other relatives	*8 hours*	*£59.81*	*£478.48*
Website infrastructure during development (until going live)			**£28,039**
Domain name			*£9*
SSL certificate fees			*£30*
Web hosting and exclusive IP address			*£100*
Website development			*£27,900*
Total			**£64,535.99**

Delivery costs of REACT toolkit

We calculated the delivery costs for the 6 months the intervention lasted per individual (*Table ~~Table~~ 23*). Costs associated with website infrastructure totalled £5,119. The cost of employing REACT supporters (based on the 400 participants recruited to the trial) was

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£14,178; training was close to £4,500, and supervision amounted to £2,135. Recruitment costs totalled £12,635, the costliest component relating to the adverts.

Table 23: Delivery costs of REACT toolkit for 6 months

Type of costs	Total no. of hours or units	Cost per hour or unit	Total
General infrastructure for hosting REACT			**£5,119**
Digital technology/web developer	*180 hours*	*£23.05*	*£4,149*
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 hours*	*£15.83*	*£11,967.48*
Back-up REACT supporter	*94 hours*	*£13.52*	*£1,270.88*
Expert relative REACT supporter	*47 hours*	*£20*	*£940*
Supervision	*33 hours*	*£64.71*	*£2,135.52*
In-house training	*224.75 hours*	*£18.33*	*£4,119.17*
External training			*£380*
Recruitment			**£12,635.56**
Adverts (Facebook, Google and Bipolar UK)			*£11,059.56*
Printing			*£1,526.00*
Flyers and postage			*£50.00*
Total			**£38,567.61**

Total development and operating costs for REACT to the end of the trial period came to £103,103.60.

Average costs were calculated as follows:

- Total development costs: 800 users (total trial participants)
- General website infrastructure costs: 800 users (total trial participants)
- REACT supporter costs: 400 users (participants in REACT trial arm)
- Recruitment costs: 3,287 users (number that initiated a registration in the REACT website).

This gives an average cost of £142.95 per participant in the REACT toolkit arm. (NB If we cost only delivery, this cost is £62.27 per relative)

Resource directory costs

Participants in the comparator group were given access to the RD. Development and delivery costs were therefore divided by the 800 participants in both arms of the trial, calculated for the six months of each participant's involvement (*Table 24*). The most significant component related to staff (£530). Average participant cost was £0.84. (NB delivery only would require the infrastructure and REACT supporter time and cost £0.43)

Table 24: Resource directory development and delivery costs

Type of costs	Total no. of hours or units	Cost per hour or unit	Total
Development costs			**£463.50**
Staff			£324.50
Research assistant	*20 hours*	*£10.08*	*£201.60*
Research assistant	*10 hours*	*£12.29*	*£122.90*
Infrastructure			£139.00
Domain name	*1*	*£9.00*	*£9.00*

SSL certificate fees	*1*	*£30.00*	*£30.00*
Web hosting and exclusive IP address	*1*	*£100.00*	*£100.00*
Delivery costs			**£205.79**
REACT supporter	*13 hours*	*£15.83*	*£205.79*
Total			**£669.29**

Use of hospital and personal social services

Our starting point was a crude analysis of the number of visits to and users of hospital services, primary care, community health and emergency services, community mental health services and other community-based services at baseline, 12 weeks and 24 weeks (*Tables 25–8*). This showed, as expected, that hospital admissions were the type of service least used by carers, with a significant decrease from week 12 onwards, and outpatient visits at hospital sites were the most used in both arms. As for primary care, community health and emergency services, there was a decrease in the quantity of services used over time; however at 24 weeks the participants in the REACT arm were using more services than the participants in the control group. As perhaps could be expected, the most used service by participants in the REACT arm at baseline was GP services. This was followed by ambulance services (both face-to-face and phone contacts). The control group had a different usage pattern at baseline. GP visits were still the most used service followed by specialist nurse services, face-to-face ambulance services and occupational therapists. At 24 weeks, GP services were clearly the most used by both groups.

Community mental health services were used at baseline by more participants in the REACT arm than in the control group. However, there was a reduction throughout the duration of the trial and by week 24, participants in the control arm were using more services provided by community psychiatric or mental health nurses or other mental healthcare professionals. Dental services were used more than opticians and there was a shift in the pattern of use. More participants in the REACT arm were using these services at baseline; however at week 24 there were more participants in the control arm using these services.

We then calculated the mean frequency of use of hospital services, primary care, community health and emergency services, community mental health services and other community-based services at each time point (*Tables 29–32*). At baseline, all but one participant had complete data. Around 40% of data were missing at 12 and 24 weeks.

Overall use of health services was very low and highly skewed, with a very small number of participants reporting very high levels of service use. At least one participant in each arm reported at least one visit per week to an outpatient clinic. At baseline the mean use was slightly higher in the control group.

For the intervention group, mean use increased slightly for all hospital services except A&E from baseline to week 24. However, in the control group we observed a decrease in use of all types of hospital service except day hospital services over the same period. For all other services, mean values were very small at all time points, the exception being the mean value of GP visits. Participants in the intervention group used more GP services than participants in the control arm.

There was no information to report about the use of personal social services or the use of other community-based services, with the exception of dentist and optician services. For all other services, too few participants reported any usage, and when use was reported the information about the number of times the service was accessed was often missing. Further, it proved almost impossible to identify which services provided by the voluntary or third sector were paid for by the NHS and which by personal social services. Many of these services were registered charities and so were likely to be funded by a whole range of government grants, donations and other sources of income, with funding changing over time. Furthermore, the levels of use were not accurately recorded. Therefore these data were not included in the analysis.

Table 25: Quantity and number of users of hospital services at baseline, week 12 and week 24, by trial arm

	Baseline				12 weeks				24 weeks			
	REACT toolkit		RD		REACT toolkit		RD		REACT toolkit		RD	
	Quantity	n	Quantity	n	Quantity	n	Quantity	n	Quantity	n	Quantity	n
Accident & Emergency visits	63	44	87	51	18	14	22	16	23	16	25	20
General hospital inpatient days	55	20	162	26	4	3	9	5	80	12	9	7
Community hospital inpatient days	42	2	40	4	30	3	0		33	3	1	1
Day hospital	25	18	44	24	19	9	15	11	17	10	34	17
Outpatient visits at hospital site	266	115	298	110	128	57	159	68	170	67	159	58
Other	118	37	180	57	78	28	80	29	65	19	51	22

Table 26: Quantity and number of users of primary care, community health and emergency services at baseline, week 12 and week 24, by trial arm

	Baseline				12 weeks				24 weeks			
	REACT toolkit		RD		REACT toolkit		RD		REACT toolkit		RD	
	Quantity	n	Quantity	n	Quantity	n	Quantity	n	Quantity	n	Quantity	n
Paramedic (ambulance service – face-to-face)	47	10	92	11	10	4	2	1	0		12	4
Paramedic (ambulance service – phone)	39	4	4	2	0			0	0		0	
Community matron (phone)	1	1	0		0			0	0		0	
Community/district/practice nurse (face-to-face)	15	4	59	6	0		66	3	7	1	3	1
Community/district/practice nurse (phone)	0		10	3	0		3	2	5	2	0	
Specialist nurse (face-to-face)	27	4	96	9	10	3	8	2	24	2	7	1

Specialist nurse (phone)	0		0		0		1	1	1	1	0	
Occupational therapist	0		83	3	0		6	2	0	1	2	1
Physiotherapist	10	5	22	5	13	3	29	4	29	4	19	3
General practitioner	309	67	267	47	213	52	154	42	151	38	89	26

Table 27: Quantity and number of users of community mental health services at baseline, week 12 and week 24, by trial arm

	Baseline				**12 weeks**				**24 weeks**			
	REACT toolkit		**RD**		**REACT toolkit**		**RD**		**REACT toolkit**		**RD**	
	Quantity	**n**	**Quantity**	**n**	**Quantity**	**N**	**Quantity**	**n**	**Quantity**	**n**	**Quantity**	**n**
Psychiatrist/psycho-geriatrician	21	21	16	16	11	11	5	5	7	7	6	6
Community psychiatric nurse or community mental health nurse	32	31	19	18	12	12	23	23	14	14	16	16
Other mental health professional	28	24	29	29	15	14	10	10	12	12	18	18

Table 28: Quantity and number of users of other community based services at baseline, week 12 and week 24, by trial arm

	Baseline				12 weeks				24 weeks			
	REACT toolkit		RD		REACT toolkit		RD		REACT toolkit		RD	
	Quantity	n	Quantity	n	Quantity	n	Quantity	n	Quantity	n	Quantity	n
Dentist	19	19	9	9	10	10	14	14	6	6	14	14
Optician	2	2	5	5	1	1	1	1	3	3	2	2

Table 29: Mean use (SD) of hospital services at baseline, week 12 and week 24, by trial arm

	Baseline				12 weeks				24 weeks			
	REACT toolkit (n=398)		RD (n=401)		REACT toolkit (n=233)		RD (n=267)		REACT toolkit (n=245)		RD (n=268)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Accident & Emergency	0.16	0.534	0.22	0.735	0.08	0.326	0.08	0.348	0.09	0.389	0.09	0.390

General hospital inpatient days	0.14	1.237	0.40	4.886	0.02	0.160	0.03	0.292	0.33	3.197	0.03	0.218
Community hospital inpatient days	0.11	1.788	0.10	1.707	0.13	1.836	0.00	-	0.13	1.438	0.00	0.061
Day hospital	0.06	0.307	0.11	0.581	0.08	0.593	0.06	0.301	0.07	0.394	0.13	0.749
Outpatient visits at hospital site	0.67	1.487	0.74	1.994	0.55	1.447	0.60	1.304	0.69	0.112	0.59	1.650
Other	0.30	1.433	0.45	1.64	0.33	1.306	0.30	1.095	0.27	1.581	0.19	0.782

Table 30: Mean use (SD) of primary care, community health and emergency services at baseline, week 12 and week 24, by trial arm

	Baseline				12 weeks				24 weeks			
	REACT toolkit		RD		REACT toolkit		RD		REACT toolkit		RD	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Paramedic (ambulance service – face-to-face)	0.12	0.89	0.24	2.10	0.04	0.34	0.01	0.12			0.05	0.43
Paramedic (ambulance service – phone)	0.13	1.9	0.01	0.18								
Community matron (phone)												
Community, district or practice nurse (face-to-face)	0.04	0.49	0.15	1.43			0.26	3.76	0.03	0.46	0.01	0.18
Community, district or practice nurse (phone)			0.03	0.33			0.01	0.15	0.02	0.25		
Specialist nurse (face-to-face)	0.07	0.76	0.25	2.37	0.04	0.44	0.03	0.36	0.10	1.44	0.03	0.43
Specialist nurse (phone)							0.005	0.07	0.005	0.07		
Occupational therapist			0.21	3.64			0.02	0.27	0.004	0.06	0.01	0.12
Physiotherapist	0.03	0.22	0.06	0.52	0.06	0.65	0.11	0.98	0.12	1.21	0.07	0.75
General practitioner	0.78	2.81	0.67	3.53	0.93	2.98	0.58	2.05	0.62	2.75	0.33	1.17

Table 31: Mean use (SD) of community mental health services at baseline, week 12 and week 24, by trial arm

	Baseline				12 weeks				24 weeks			
	REACT toolkit		RD		REACT toolkit		RD		REACT toolkit		RD	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Psychiatrist or psycho-geriatrician	0.06	0.23	0.04	0.20	0.05	0.21	0.02	0.14	0.03	0.17	0.02	0.15
Community psychiatric nurse or community mental health nurse	0.09	0.29	0.05	0.23	0.05	0.22	0.09	0.28	0.06	0.23	0.06	0.24
Other mental health professional	0.07	0.31	0.08	0.27	0.07	0.27	0.04	0.19	0.05	0.22	0.07	0.25

Table 32:Mean use (SD) of other community-based services at baseline, week 12 and week 24, by trial arm

	Baseline				12 weeks				24 weeks			
	REACT toolkit		RD		REACT toolkit		RD		REACT toolkit		RD	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Dentist	0.06	0.23	0.03	0.16	0.05	0.22	0.06	0.23	0.03	0.17	0.06	0.24
Optician	0.01	0.08	0.01	0.12	0.01	0.07	0.004	0.06	0.01	0.12	0.01	0.09

Table 33: Mean cost (SD) of observed cases of hospital services at baseline, week 12 and week 24, by trial arm

	Baseline				12 weeks				24 weeks			
	REACT toolkit (n=398)		RD (n=401)		REACT toolkit (n=233)		RD (n=267)		REACT toolkit (n=245)		RD (n=268)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Accident & Emergency	£25.33	85.37	£34.71	117.61	£12.36	52.11	£13.18	55.66	£15.02	62.17	£14.93	62.44
General hospital inpatient days	£207.15	1,854.16	£605.58	7324.68	£25.73	239.68	£50.52	437.87	£489.47	4,792.33	£50.34	326.90
Community hospital inpatient days	£158.19	2,680.63	£149.53	2,559.33	£193.01	2752.34	N/A		£201.91	2,155.58	£5.59	91.57
Day hospital	£46.61	227.83	£81.42	431.34	£60.51	439.65	£41.69	223.61	£51.49	292.13	£94.13	555.57
Outpatient visits at hospital site	£83.54	185.92	£92.89	249.26	£68.67	180.86	£74.44	163.00	£86.84	220.06	£74.16	206.22

Table 34: Mean cost (SD) of observed cases of primary care, community health and emergency services at baseline, week 12 and week 24, by trial arm

	Baseline				12 weeks				24 weeks			
	REACT toolkit		RD		REACT toolkit		RD		REACT toolkit		RD	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Paramedic (ambulance service – face-to-face)	£12.03	87.31	£23.12	205.73	£4.32	32.96	£0.77	12.25			£4.47	41.71
Paramedic (ambulance service – phone)	£0.90	13.33	£0.09	1.25								
Community matron (phone)	£0.13	2.41										
Community, district or practice nurse (face-to-face)	£1.49	18.69	£5.73	54.50			£9.80	142.84	£1,13	17.32	£0.43	7.03
Community, district or practice nurse (phone)			£0.61	6.25			£0.26	2.85	£0.45	4.73		
Specialist nurse (face-to-face)	£6.98	75.66	£24.37	234.17	£4.38	43.56	£3.09	36.02	£142.31	10.07	£2.63	42.73
Specialist nurse (phone)							£0.20	3.02	£0.22	3.11		

Occupational therapist			£17.00	296.10			£1.83	22.26	£0.33	5.22	£0.61	9.97
Physiotherapist	£1.45	12.84	£3.17	29.73	£3.24	37.13	£6.24	56.04	£6.83	69.01	£4.09	42.74
General practitioner	£29.98	119.26	£34.02	284.29	£47.77	276.44	£32.82	283.00	£21.78	129.00	£10.69	41.00

Table 35: Mean cost (SD) of observed cases of community mental health services at baseline, week 12 and week 24, by trial arm

	Baseline				**12 weeks**				**24 weeks**			
	REACT toolkit		**RD**		**REACT toolkit**		**RD**		**REACT toolkit**		**RD**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Psychiatrist or psychogeriatrician	£3.04	12.46	£2.34	11.00	£2.59	11.57	£1.02	7.35	£1.57	9.09	£1.23	8.06
Community psychiatric nurse or community mental health nurse	£2.66	8.99	£1.59	7.22	£1.62	6.92	£2.68	8.73	£1.80	7.26	£1.88	7.41
Other mental health professional	£1.46	6.05	£1.52	5.24	£1.28	5.17	£0.73	3.72	£0.97	4.25	£1.32	4.92

Table 36: Mean cost (SD) of observed cases of other community-based services at baseline, week 12 and week 24, by trial arm

	Baseline				12 weeks				24 weeks			
	REACT toolkit		RD		REACT toolkit		RD		REACT toolkit		RD	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Dentist	£2.46	9.92	£1.13	6.85	£2.23	9.48	£2.48	9.96	£1.23	7.14	£2.52	10.04
Optician	£0.15	1.95	£0.37	3.03	£0.13	1.81	£0.10	1.62	£0.36	3.00	£0.21	2.30

Costs of health and personal social services used

We applied the unit costs in *Table 21* to the service use reported in *Table 25* to calculate the cost of hospital and social services presented in *Tables 33–6*. Given the diversity of services reported in the "other" category, these were not included. For some items we observed very large SDs, consistent with the reported usage patterns: many participants with no use of healthcare services and some participants with very high use.

Costs related to general hospital admissions were the largest component, as is usual in this type of analysis, followed by the cost of admissions into community hospitals. Total average costs decreased for the participants in the control group and increased for participants in the intervention group.

The other category with meaningful costs covers primary care, community health and emergency services. At baseline, the most relevant costs for the participants in the REACT arm were the ones associated with GP services and face-to-face ambulance services. For the participants in the control arm, the costs incurred with GP services were closely followed by those with specialist nurses, face-to-face paramedic services and occupational therapists. At 12 weeks, for both arms the most significant costs were associated with GP services. However, at 24 weeks, only specialist nurse costs were relevant for the participants in the REACT arm.

Mean costs of observed cases for community mental health services and other community based services can be considered negligible for both arms. All data is provided in *Report Supplementary Material File 3*.

Health-related quality of life

EQ-5D-5L

At baseline, the mean EQ-5D-5L index score was lower for the REACT intervention group than for the control group (*Table 37*). However, by the end of the 24 weeks, patients in the REACT toolkit arm presented higher EQ-5D-5L index scores (indicating better health). However, none of the differences was statistically significant.

Table 37: EQ-5D-5L index score at baseline, 12 weeks and 24 weeks follow-up by group

	REACT toolkit		RD	
	Mean (SD)	**n**	**Mean (SD)**	**n**
Baseline	0.757 (0.211)	399	0.764 (0.191)	401
12 weeks	0.795 (0.185)	235	0.788 (0.180)	273
24 weeks	0.799 (0.187)	247	0.792 (0.184)	270

Primary outcome

Results for outcomes and incremental costs and effectiveness based on imputed datasets are presented in the *Tables 38–40* as means with standard error (SE). Except at baseline, mean costs were always higher for the intervention group (*Table 38*). Overall, participants in the intervention arm had higher costs than participants in the control group, but the difference was not statistically significant. Incremental costs, adjusted for participants' baseline age and gender, came to £286.77 (95% CI -£858.81–£1432.36, p=0.624).

Table 38: Cost estimates for health and personal social services analysis per participant from imputed data, by group (mean, SE)

	REACT toolkit		RD	
	Mean	**SE or 95% CI**	**Mean**	**SE**
Intervention cost	£142.95		£0.84	
Baseline	£651.29	116.37	£1,263.70	402.50
12 weeks	£681.61	110.48	£505.41	27.55
24 weeks	£998.72	209.77	£450.14	41.13
Total	**£2,474.57**		**£2,220.09**	

Unadjusted incremental cost	**£254.47**		
Incremental cost adjusted for age and gender	**£286.77**	(-£858.81–£1432.36)	

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At baseline, estimated GHQ scores were similar in the control group and in the intervention arm. At 12 and 24 weeks GHQ scores were always lower in the intervention arm.

Table 39: GHQ estimates per participant from imputed data, by group (mean, SE)

GHQ	**REACT toolkit**		**RD**	
	Mean	**SE or 95% CI**	**Mean**	**SE**
GHQ Baseline	40.25	0.5145	40.05	0.4942
GHQ 12 weeks	31.27	0.4882	32.80	0.4882
GHQ 24 weeks	30.36	0.5123	31.43	0.4844
Unadjusted incremental GHQ	-1.067			
Incremental GHQ adjusted for baseline GHQ score	-1.160	1.127		
Incremental GHQ adjusted for baseline GHQ score and age and gender	-1.152	(-3.370-1.065)		

Incremental GHQ over the 24 weeks of the trial, unadjusted, was -1.067. Adjusted for baseline GHQ, it was -1.160 (CI 95% -3.371–1.051), indicating that participants in the intervention group were more likely to have a lower GHQ score than participants in the control group; however the difference was very small and not statistically significant (p=0.304). Further adjusting GHQ scores for age and gender, the difference between groups decreased slightly to -1.152 (CI 95% -3.370–1.065) but was still small and not significant (p=0.308).

For GHQ, the intervention was costlier and more effective (*Table 39*), suggesting that REACT users had a marginally better outcome compared to RD users. However, the 95% CI for costs and GHQ scores include zero, making this conclusion uncertain. For a reduction of 3 points in the GHQ score, an additional £746.8 per relative had to be spent, (calculated as cost per -1.152 is £286.77 then 3 is £746.8).

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Estimated EQ-5D-5L scores (*Table 40*) were always higher in the control group than in the intervention arm.

Table 40: EQ-5D-5L index scores and QALYs estimates per participant from imputed data at baseline, 12 and 24 weeks, by trial arm group (mean, SE)

	REACT toolkit		RD	
	Mean	SD or 95% CI	Mean	SD
EQ-5D-5L index score				
Baseline	0.7570	0.2113	0.7637	0.1908
12 weeks	0.7743	0.1886	0.7849	0.1676
24 weeks	0.7812	0.1890	0.7925	0.1666
QALYs				
QALYs 12 weeks	0.176		0.178	
QALYs 24 weeks	0.179		0.181	
Total QALYs	0.355		0.359	
Incremental QALYs				
Unadjusted	-0.0045			
Adjusted for baseline EQ-5D-5L index score	-0.0021			

Adjusted for baseline EQ-5D-5L index score, age and gender	-0.0024	(-0.0088-0.0039)	

Incremental QALYs over the 24 weeks of the trial, unadjusted, was -0.0045. Adjusted for baseline EQ-5D-5L, it was -0.0021 (CI 95% -0.0084–0.0042), indicating that participants in the intervention group were more likely to have a lower QALYs than participants in the control group; however the difference was very small and not statistically significant (p=0.517). Further adjusting QALYs for age and gender, the difference between groups increased slightly to -0.0024 (CI 95% -0.0088–0.0039) but was still small and not significant (p=0.448).

For EQ-5D-5L, the intervention was costlier and less effective (*Table 41*), suggesting that REACT users had health-related quality of life losses at extra cost compared to RD users. However, the 95% CI for costs and QALYs include zero, making this conclusion uncertain.

Table 41: Incremental cost-effectiveness estimated from imputed data (mean (95% CI))

Incremental cost adjusted for baseline age and gender	£286.77 (-£858.81–£1432.36)
Incremental QALYs adjusted for baseline EQ-5D-5L, age and gender	-0.0024 (-0.0088–0.0039)
ΔCost/ΔQALY	Intervention dominated by control as being costlier and less effective

The cost-effectiveness plane (*Figure 7*) illustrated this point. The uncertainty surrounding the point estimates of the incremental costs and incremental QALYs from the primary analysis was important, with the majority of the distribution scattered in the top quadrants of the plane, supporting the conclusion that the intervention was costlier. The magnitude of the incremental QALYs was rather small.

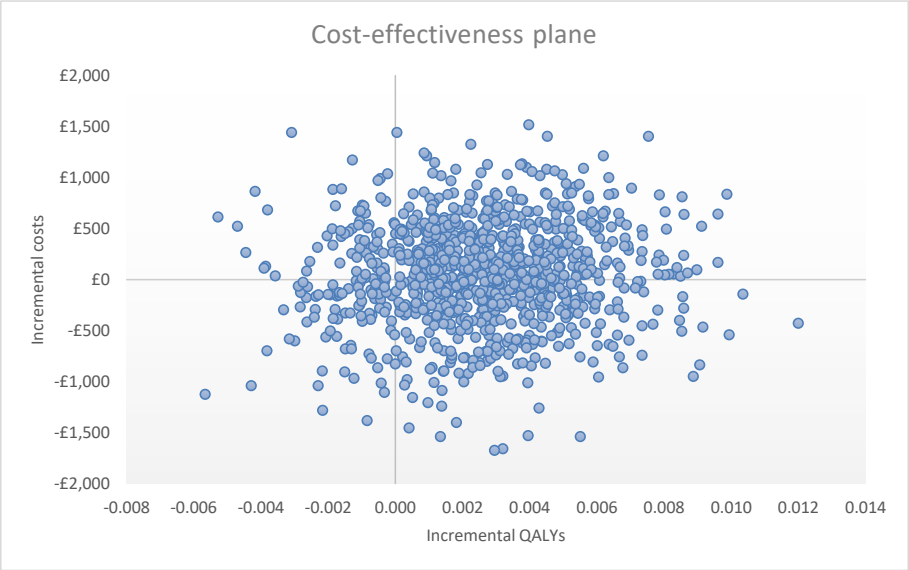

Figure 7: Cost-effectiveness plane, intervention group versus control group

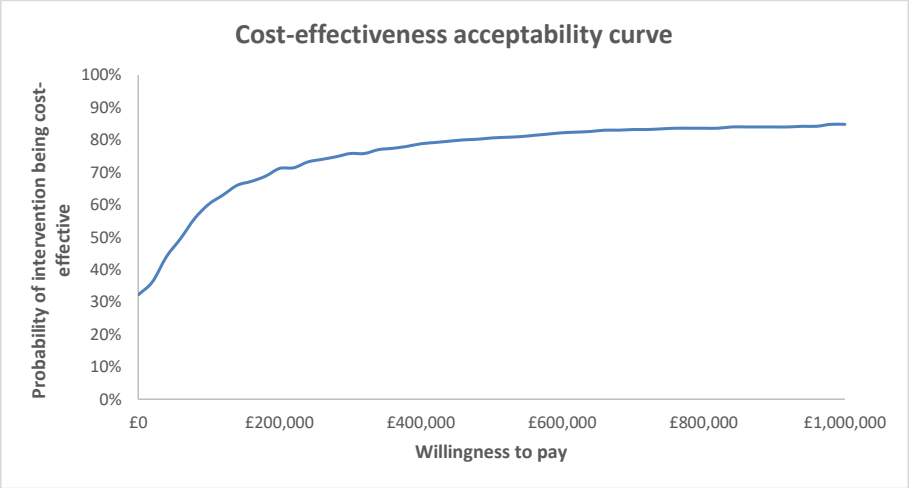

Figure 8: Cost-effectiveness acceptability curve for the intervention

The CEAC (*Figure 8*) was constructed using the bootstrapped data and showed the probability of the REACT toolkit being cost effective within the existing WTP threshold of £20,000 to £30,000 as around 50% when compared to RD.

Societal perspective

The societal perspective was added to the health and social services analysis to assess productivity losses associated with the caring role of the relatives. In order to account for those losses, we considered the number of hours people currently working had to take off work due to caring role.

EQ-5D-5L scores were the same as those estimated for the NHS and personal social perspective. In this section we added to the costs estimated for the health and personal social perspective, the costs associated to productivity losses of those at work.

The pattern observed for costs in the societal perspective (*Tables 42–3*) was similar to that observed for complete cases in the REACT arm: increasing costs from baseline to week 24. In the control arm, the opposite behaviour was observed: costs decreased from baseline to week 24. Costs reported by participants in the REACT toolkit arm were higher than the costs reported by participants in the RD group, as expected; however the adjusted incremental costs were similar to the ones observed in the NHS and personal social care perspective at £309.93 (95% CI -£861.04–£1,480.90) but not statistically significant.

Table 42: Imputed cases mean (SD) costs for societal perspective data at baseline, 12 weeks and 24 weeks follow-up by group

	REACT toolkit		RD	
	Mean	**SE**	**Mean**	**SE**
Costs				
Intervention cost	£142.95		£0.84	
Baseline	£891.52	167.60	£1,507.46	403.24
12 weeks	£909.81	110.76	£734.61	28.01
24 weeks	£1,243.32	211.15	£662.96	40.94

Total	**£3,187.60**	**£2,905.86**
Incremental costs		
Unadjusted incremental costs	£281.73	
Adjusted incremental costs for age and gender	£309.93	(-£861.04-£1,480.90)

Table 43: Societal perspective incremental cost-effectiveness (mean (95% CI))

Incremental cost adjusted for age and gender	£309.93 (-£861.04–£1,480.90)
Incremental QALYs adjusted for baseline EQ-5D-5L index score, age and gender	-0.0026 (-0.0089–0.0037)
ΔCost/ΔQALY	Intervention dominated by control as being costlier and less effective

Figures 9 and 10 present the cost-effectiveness plane and CEAC for societal perspective using imputed cases. It is clear from the distribution of the dots in the cost-effectiveness plane that the intervention can be costlier and less effective than the control.

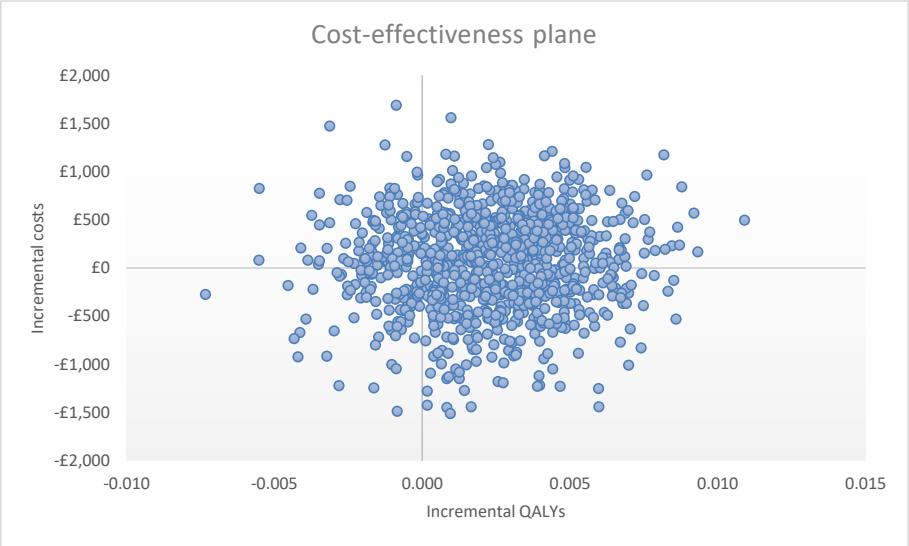

Figure 9: Cost-effectiveness plane, intervention group versus control group (imputed cases, societal perspective)

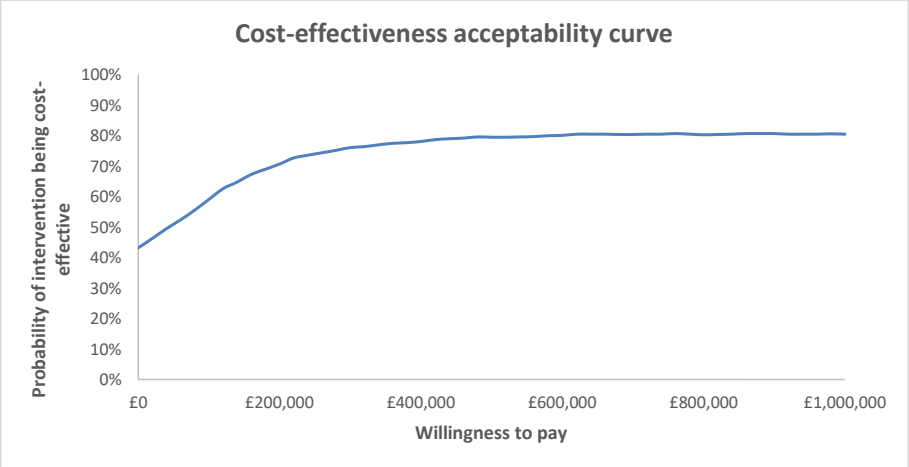

Figure 10: Cost-effectiveness acceptability curve for the intervention (imputed cases, societal perspective)

The probability of the intervention being cost-effective (*Figure 10*) was similar to what had been estimated from imputed data in the NHS and personal social services perspective. The probability of the intervention being cost-effective at £20,000 was 46%.

Sensitivity analysis

Commented [NB9]: This heading had been added. Is it meant to overarch the complete case analysis? I assumed so, and have demoted complete case analysis to level 3. But it's a bit odd. Shouyld it also take in the burden of disease to carers? Or did it belong further up?

Complete case analysis

Extent of completeness varied for the outcomes used in the primary analysis (*Table 44*). We considered complete cases to be participants who had information for all three data points.

Table 44: Number of complete cases for costs and EQ-5D-5L

	REACT toolkit	RD
Total costs (n)	196	236
EQ-5D-5L (n)	197	238

The EQ-5D-5L was completed at all the three time points by 193 participants in the REACT group and 233 participants in the control group (*Table 45*). Of these, REACT participants had higher mean scores at all three points than those who provided only partial data. This difference was not seen in the RD arm, where index score values were similar.

Unadjusted incremental QALYs was 0.0057 (95% CI -0.0091–0.02067, p=0.447) when we compare the REACT toolkit participants with the RD participants. When we adjust for baseline EQ-5D-5L index score, age and gender, there is no difference between the groups.

Table 45: Complete cases EQ-5D-5L index scores and QALYs at baseline, 12 and 24 weeks, by trial arm

	REACT toolkit n=193		RD n=233	
	Mean	SD or 95% CI	Mean	SD
EQ-5D-5L index score				

Baseline	0.781	0.186	0.764	0.196
12 weeks	0.797	0.181	0.788	0.185
24 weeks	0.806	0.182	0.793	0.183
QALYs				
QALYs 12 weeks	0.182	0.040	0.178	0.040
QALYs 24 weeks	0.184	0.040	0.182	0.040
Total QALYs	0.366	0.078	0.361	0.079
Incremental QALYs				
Unadjusted	0.0057			
Adjusted for baseline EQ-5D-5L index score	-0.0011			
Adjusted for baseline EQ-5D-5L index score, age and gender	-0.0013	(-0.0079-0.0053)		

The pattern observed for costs in complete cases (*Tables 46–7*) was different from that obtained with imputed cases. Costs reported by participants in the REACT toolkit arm were higher than the costs reported by participants in the RD group, as expected; and the adjusted incremental costs were only somewhat higher than the costs observed for imputed cases at £715.83 (95% CI -£328.48–£1,760.14).

Table 46: Complete cases mean (SD) costs at baseline, 12 weeks and 24 weeks follow-up by group

	REACT toolkit		**RD**	
	Mean	**SD**	**Mean**	**SD**
Costs				

Intervention cost	£142.95		£0.84	
Baseline	£252.00	587.92	£613.52	3675.92
12 weeks	£507.15	3026.46	£263.44	681.02
24 weeks	£935.07	5851.86	£225.10	553.60
Total	**£1,837.17**		**£1,102.90**	
Incremental costs				
Unadjusted incremental costs	£734.27			
Adjusted incremental costs for age and gender	£715.83			

Table 47: Complete cases incremental cost-effectiveness (mean (95% CI))

Incremental cost adjusted for age and gender	£715.83 (-£328.48–£1,760.14)
Incremental QALYs adjusted for baseline EQ-5D-5L index score, age and gender	-0.0013 (-0.0079-0.0053)
ΔCost/ΔQALY	Intervention dominated by control as being costlier and less effective

Figures 11 and 12 present the cost-effectiveness plane and CEAC as for the primary analysis but using only data from the 426 complete cases. It is clear from the distribution of the dots in the cost-effectiveness plane that the intervention can be costlier and less effective than the control.

Figure 11: Cost-effectiveness plane, intervention group versus control group (complete cases)

Taking this into account it is not surprising that the probability of the intervention being cost-effective (*Figure 12*) was much lower than estimated from imputed data. The probability of the intervention being cost-effective at £20,000 was only 8%.

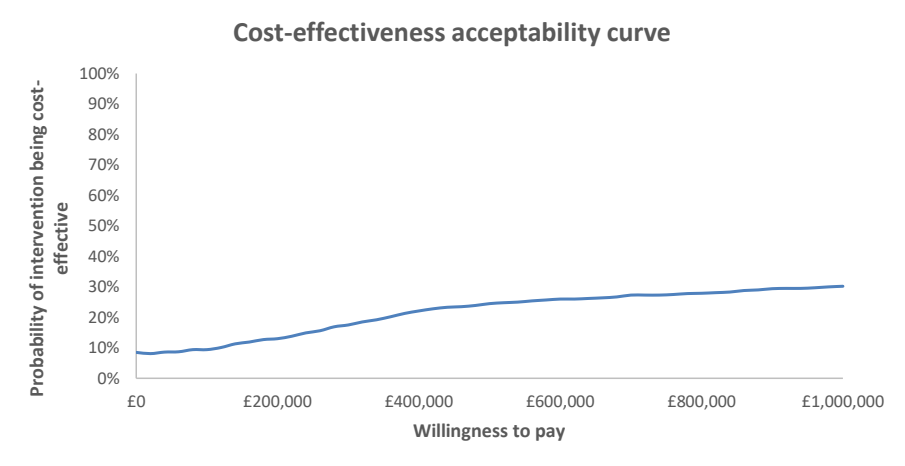

Figure 12: Cost-effectiveness acceptability curve for the intervention (complete cases)

Burden of disease on carers: time spent in caring role

In addition to the societal perspective we considered it relevant to report on the burden of the disease to carers based on the time spent in caring role. It is widely accepted that carers income and work life are affected by their role. Participants in the trial were asked about the number of unpaid hours spent each week looking after their relative(s). The number of hours spent caring was higher than the typical 40-hour week of a full-time job. The number decreased in both groups during the trial (*Table 48*).

Table 48: Mean (SD) unpaid hours looking after relative per week at baseline, 12 weeks and 24 weeks, by trial arm

	REACT toolkit			RD only		
	n	Hours	SD	n	Hours	SD
Baseline	399	43.92	46.40	401	44.58	45.77
12 weeks	231	42.87	47.63	266	45.17	44.18
24 weeks	243	41.00	45.29	265	39.03	41.59

Using a paired samples *t*-test, we observed that for carers in the REACT toolkit arm (n=243) the differences between the number of hours reported at baseline and at week 24 had no statistical significance (3.40 hours, 95% CI -1.272–8.063, p=0.153). However, for participants in the RD arm (n=265), the decrease was greater and had statistical significance (5.14 hours, 95% CI 0.703–9.576, p=0.023).

Participants were also asked about time taken off work due to their caring role in the previous 12 weeks. The number of hours off work decreased in both groups from baseline to week 24 (*Table 49*).

Table 49: Mean (SD) number of hours off work due to caring role in past 12 weeks at baseline, 12 and 24 weeks, by trial arm

	REACT toolkit			RD only		
	n	Hours	SD	n	Hours	SD
Baseline	118	21.28	15.81	117	21.49	15.80
12 weeks	63	19.71	15.10	61	21.15	17.93
24 weeks	51	20.06	14.72	46	19.17	18.27

Differences between the groups were not statistically significant. Mean difference at baseline was 0.208 hours (95% CI -3.855–4.270, p=0.920) in favour of the REACT toolkit arm. At week 24 it was -0.88 hours (95% CI -7.543–5.773, p=0.792) in favour of the group using only the RD.

Using a paired samples *t*-test for the 29 participants reporting in the REACT toolkit arm, the mean change in the number of hours off work from baseline to week 24 was 0.448 hours (SD 13.45) with a 95% CI (-4.668–5.564) and p=0.859, showing no statistical significance. For the 34 participants reporting in the RD arm, the mean change over the same period was 0.706 hours (SD 20.84) with a 95% CI (-6.567–7.979) and p=0.845, again not statistically significant.

The number of hours was fairly constant over time, showing the impact on family life. By multiplying the average number of hours at each time point by the respective number completing data for each arm, we reached a total of 9,462.13 hours off work for caring duties by the participants reporting in the trial. If we consider the average (median) hourly pay in 2017 was £11.31[137] we can estimate productivity losses potentially above £100,000 in the 36-week period under analysis for those providing data.

Across the whole trial sample from baseline to week 24, there was a reduction in the mean number of unpaid hours spent per week looking after a relative, and this difference was statistically significant (*Table 50*). A reduction was also observed in the number of hours off work for caring in the previous 12 weeks, but without statistical significance.

Table 50: Mean (SE) time spent in caring role at baseline and week 24 and paired samples t-test, 95% CI

	Time spent in caring role mean (SE)			Paired samples t-test for the difference			
	n	Baseline	Week 24	Mean	SE	95% CI	p
Number of unpaid hours spent per week looking after relative	508	44.28 (2.02)	39.97 (1.92)	4.30	1.63	1.10–7.51	0.009
Number of hours off work due to caring role in the past 12 weeks	63	21.02 (1.63)	20.43 (2.14)	0.59	2.23	-3.87–5.04	0.793

Discussion

Main results

As set out under *Aims and Objectives* above, the health economic analysis sought to determine the costs and cost-effectiveness of the intervention using three measures:

1. Cost of delivery versus NHS and productivity cost savings in use of health services and paid work
2. Cost of significant unit changes (defined as a 3-point reduction) in the primary outcome (GHQ-28)
3. Marginal cost of any marginal change in quality-adjusted life years (QALYs), measured by the EQ-5D-5L.

Cost of delivery versus NHS and productivity cost savings

REACT and the RD were inexpensive interventions in comparison with face-to-face family support or pharmacological interventions attempting to address the same type of problems. REACT cost £142.95 per participant to design and deliver (£62.27 delivery only). The RD only cost £0.84 to develop and deliver (£0.43 delivery only).

Overall use of health and personal social services was very low and highly skewed, with a very small number of participants reporting very high levels of service use. Participants in the intervention arm had higher costs than participants in the control group.

This within-trial health economic analysis of NHS, health and personal social services outcomes found the REACT toolkit to have higher costs of £286.77 (95% CI -£858.81–£1432.36, p=0.624), slightly better GHQ scores (incremental GHQ adjusted for baseline GHQ score and age and gender = -1.152 (95% CI -3.370–1.065), and slightly lower QALYs (incremental QALYs adjusted for baseline EQ-5D-5L index score, age and gender = -0.0024 (95%CI -0.0088–0.0039), but none of these differences was statistically significant.

Cost of significant change in primary outcome (GHQ-28)

REACT (including RD) added to TAU resulted in a decrease in GHQ score of -1.152 compared to RD only added to TAU. This was at an additional cost of £286.77. Therefore the cost of a reduction of 3 points in the GHQ score would be £746.80 per relative.

Marginal cost of any marginal change in quality-adjusted life years

REACT cost more money for poorer outcomes on the EQ-5D-5L. The probability of the REACT toolkit being cost effective within the existing WTP threshold of £20,000–£30,000 as around 50% when compared to RD.

Results of the additional analysis of societal perspective (including time off paid work) were based on imputed data. Incremental total costs were in line with the ones observed for the NHS and Social Care perspective £309.93 (95% CI -£861.04–£1,480.90) and the difference in health outcomes slightly lower (-0.0026 QALYs, -0.0089–0.0073). The probability of the intervention being cost-effective for a threshold of £20,000 fell from 50 per cent in the primary analysis to 46 per cent in the societal perspective analysis. Once again, these analyses suggest that participants in the intervention arm incurred higher costs and experienced no better health outcomes, making it very unlikely that the intervention was cost-effective at a standard willingness-to-pay threshold of £20,000.

Results of the analysis of complete cases were more uncertain than those obtained in primary analysis, which were based on imputed data. Incremental total costs were much higher but still not statistically significant £715.83 (95% CI -£328.48–£1,760.14) and the difference in health outcomes slightly lower but not statistically significant (-0.0013 QALYs, -0.0079–0.0053). The probability of the intervention being cost-effective for a

threshold of £20,000 fell from 50 per cent in the primary analysis to 8 per cent in the complete cases analysis. Taken together, these analyses suggest that participants in the intervention arm incurred higher costs and experienced no better health outcomes, making it very unlikely that the intervention was cost-effective at a standard willingness-to-pay threshold of £20,000.

Burden of disease to carers based on time spent in caring role is significant for carers. This burden is not taken into account in NICE guidance but should perhaps be considered in a broader assessment of the burden of psychosis and BD on families. The data showed that on average, for those participants reporting the information, carers spent 6 hours per day looking after their relative(s) and had taken 1.75 hours off work per week due to their caring role in the previous 12 weeks.

Strengths and limitations.

The analysis was undertaken following NICE guidance, and used actual data on costs incurred in development and delivery of the intervention and comparator and in recruitment of participants. We adopted a very conservative approach to the costs of developing the intervention, and included this real data in the analysis, even though they might be considered “sunk costs”. We opted to do this as otherwise we would have needed to include maintenance and updating costs, which would have been hypothetical. However, this does mean that the estimates of costs associated with the intervention are at the upper end of plausibility. We collected and presented the costs of the individual, as recommended.[138] Using the NHS and personal social care perspective, complete cases or the societal perspective, the results obtained were always in the same direction, that the intervention was more expensive than the alternative and with negligible effects in terms of health-related quality of life.

The analysis has some weaknesses. As is common practice, we relied on self-reported data on health service use.[139, 140] This may have been subject to recall bias. Due to problems in the data collection process, information about the use of medicines could not be used. However, given the consistent pattern across all the previous analyses, it is unlikely that adding the costs of medicines would materially alter the overall conclusion.

Fit with existing literature

This makes a significant addition to the literature on health economic analyses of DHIs, which, overall, remains scarce. A recent systematic review[138] identified 39 health economic analyses of mHealth applications, but found that many did not report all the factors

recommended by the CHEERS checklist,[141] and none of the reported interventions was in the field of mental health. We found one other study, reporting results of a DHI for carers of people with dementia,[142] whose impact in terms of QALYs was similar to that obtained here. Our study is particularly important as it shows that a more complex DHI was no more effective in reducing distress (GHQ) or improving quality of life, and probably less cost-effective, than a simple online resource directory which signposted users to existing sources of help.

Chapter 6 Relatives' experiences of using REACT

Introduction

The main aim of the trial was to assess the clinical and cost effectiveness of REACT. However, we also wanted to understand participants' experience of the REACT toolkit, how they interacted with the website and how it could be improved. Therefore, we conducted a qualitative study to understand relatives' experiences of using REACT. The qualitative interviews explored how people experienced REACT, the factors that influenced their levels of use, which areas of the toolkit were most used and how people experienced the support offered via the forum and personal messaging.

Method

We conducted a qualitative study using thematic framework analysis to understand participants' experience of the REACT toolkit, how they interacted with the website and how it could be improved. In addition to the formal qualitative interviews with participants described in this chapter, we also explored how people used the REACT forum and the types of topic covered. The latter was a preliminary analysis conducted during the trial; as per protocol, we are seeking additional funding to conduct further analysis on this data.

Sampling participants

Participants were drawn from a pool of 76 people who had:

- Been randomised to the intervention arm;
- Already completed 24-week follow-up; and
- Consented to be contacted about further research.

The aim was to recruit 20–25 participants and to ensure variation across levels of REACT website use (high, low and mid). For the 76 potential participants, median web use was 207.98 minutes (range 1.43–12,476.3 minutes; IQR 55.54–564.78 minutes). Using the interquartile range, users were classed thus:

- Low use ≤55.54 minutes
- Mid use >55.54 minutes and <564.78 minutes
- High use ≥564.78 minutes.

Development of topic guide

A topic guide for the interviews was developed by the REACT team with input from relatives on the relevance and appropriateness of the questions (*Stand Alone Document 16*). Open questions explored relatives' general experiences of REACT, factors influencing levels of use, which parts of REACT were used, experience of support from REACT supporters and any suggestions for improvements. Draft questions and prompts were shared with a REACT supporter who offered feedback from a carer's perspective. The interview schedule provided a flexible structure for each interview around the key domains of interest.

Procedure

Participants who had consented to being contacted for further research as part of the REACT trial were emailed an invitation with PIS (*Stand Alone Document 14*), and consent form (*Stand Alone Document 15*). Participants were also given the option of receiving material as hard copies by post. If there was no response to the email, the interviewer attempted to contact participants by phone to invite them to the interview. Effort was targeted at recruiting participants based on their levels of use, in an attempt to recruit similar numbers in each of the low, mid and high categories.

Following receipt of the completed consent forms, a telephone or Skype interview was arranged at a time suitable for the participants. Interviews typically lasted 30 to 60 minutes, followed by a short debrief. All participants were offered an optional follow-up call the next day to discuss any concerns arising from the interview.

All interviews (including verbal consent) were recorded with an encrypted digital recorder. Recordings were downloaded to the Lancaster University secure server and deleted from the audio device after each interview. Interviews were transcribed verbatim by a professional transcriber. Interviews were conducted between 8 September 2017 and 23 February 2018 by KP, a psychologist with a specialist research interest in mental health who had not been directly involved in the development of the REACT toolkit.

Data management

Hard copies of the consent form were kept in a lockable filing cabinet in a secure office at Lancaster University and were scanned as soon as possible upon receipt. All electronic consents and scanned copies were saved under the participant's randomisation number (given by Liverpool CTRC). Recordings of interviews were kept in folders and under the

participant's randomisation number on the same password-protected shared drive in both their original and wav formats.

Recordings were sent to the transcriber via ZendTo, a secure file transfer service, after being encrypted and password protected using 7-Zip. Transcripts were returned to the interviewer by email in the same encrypted and password-protected format (7-zip). Transcripts were also saved on the shared drive using participants' randomisation number.

All digital data from the study was stored on the Lancaster University shared network drive, in a resilient storage infrastructure which is dual-housed in the university data centres (on site). Multiple levels of redundancy are built into these storage arrays; snapshots and backups are automated and taken regularly. Files with identifying information (e.g. electronic copies of consent forms) were protected with an additional password. Data was accessed by the interviewer using an encrypted computer and was clearly labelled to avoid contamination of blinded researchers. Qualitative analysis was conducted using NVivo qualitative data analysis software, version 11 for Windows.

Analysis

Analysis of interviews followed the framework approach as described by Ritchie and Spencer.[143] The initial framework was created a priori, based on the research team's interest in answering the main research questions of how participants experienced the REACT toolkit, including patterns of use and experience of the website, and how the toolkit could be improved. This framework evolved during familiarisation and indexing to create the final themes used to understand the data.

We anticipated that high-level users would be more positively inclined towards REACT than low-level users and would be more motivated to share their insights. We were particularly keen to understand the reasons for forum use and what functions it served, although we were aware this would not be relevant to all participants. Finally, we expected that the experiences of the relatives would be applicable to online interventions for carers more widely than REACT.

Initial analysis of areas discussed on the forum consisted of grouping thread titles thematically into main topic areas. In addition, we used online software Wmatrix[144] to analyse the vocabulary used on the forum. This software allocates words to semantic fields, and makes it possible to obtain the most frequently used semantic fields in a dataset, and compare one's data to a larger "reference" corpus and thus obtain a ranked list of semantic

fields that are relatively more frequent in the former than the latter, to a statistically significant extent.

Results

Participant characteristics

Fifty-five eligible participants were approached: 10 declined, 10 did not respond and 11 were unavailable at the time or agreed but were then unreachable. Of the remaining 24 who took part, six were low users, four mid-level and 14 were high users.

All participants were invited to provide basic descriptive details, shown in *Table 51* (some participants were supporting more than one family member or close friend). Of the 24 participants, 20 were female and 21 were white British, with two Indian, one Irish, and one "any other white" background. The lack of ethnic diversity in the sample was consistent with the pattern in the overall trial sample in which over 95% of participants were white British, Irish or any other white. Average participant age was 51 years. Although we attempted to sample across the range of web usage, it was easier to recruit high users, and much more difficult to engage low users.

Table 51: Demographic and web-use characteristics of interview participants

Identifier	Relationship to person with mental health problem	Diagnosis of relative/friend	Age	Gender	Ethnicity	Web use
T0001	Mother	Schizophrenia	60	Female	Other white	High
T0002	Mother	Schizophrenia	57	Female	White British	High
T0003	Not completed	Undefined	54	Female	White British	Medium
T0004	Mother	Schizophrenia	65	Female	White British	Medium

T0005	Mother	Bipolar disorder	60	Female	White British	High
T0006	Mother, daughter	Schizophrenia, other	54	Female	White British	Low
T0007	Not completed	Undefined	42	Female	White British	Medium
T0008	Partner	Bipolar disorder	35	Male	White British	Low
T0009	Father	Schizoaffective disorder	57	Male	White British	High
T0010	Mother	Psychosis	48	Female	White British	High
T0011	Mother	Schizophrenia	58	Female	White British	Low
T0012	Sibling	Psychosis	30	Male	Indian	Low
T0013	Mother	Schizophrenia	57	Female	White British	High
T0014	Mother, partner	Bipolar disorder, schizophrenia	65	Female	White British	High
T0015	Sibling, wider family member	Psychosis, other	57	Female	White British	High
T0016	Partner	Bipolar disorder	43	Female	White British	High
T0017	Partner	Bipolar disorder	44	Female	White British	High
T0018	Partner	Bipolar disorder	43	Female	Irish	High

T0019	Mother, partner, wider family member	Bipolar disorder, other, schizophrenia	54	Female	White British	High
T0020	Mother	Schizophrenia	64	Female	White British	High
T0021	Mother, partner, friend	Bipolar disorder, other, other	69	Female	White British	High
T0022	Partner	Schizoaffective disorder	37	Female	White British	High
T0023	Partner	Bipolar disorder	48	Male	White British	Low
T0024	Sibling	Psychosis	26	Female	Indian	Low

Overview

Participants seemed to feel able to talk openly about both positive and negative aspects of their experience. Some interviewees chose to have the website open in front of them during the interview to help trigger their memories. All participants responded positively to the opportunity to share their experiences and thoughts about REACT and found the questions appropriate. During the debrief, no concerns were reported, other than queries about the future of REACT. Interviews typically lasted 30–40 minutes. Key themes reported below were derived from interpretation of the mapped data obtained from participants. This was informed by an initial framework of wanting to understand how relatives experienced REACT, and what improvements they would suggest. *Table 52* provides a summary of the a priori framework themes and the final framework themes and subthemes.

Table 52: Framework themes summary table

A priori framework themes	**Final framework themes and sub-themes**
How did people use REACT?	**Is REACT really needed?** Simple access to information

	Contrast to negative experiences with services Anonymity Single sources UK relevant information
Experience of REACT	**What facilitates use of REACT?** Incorporation of REACT into regular digital practice Free and flexible access Privacy of access across different devices
How could REACT be improved?	**What hinders use of REACT?** Impact of other competing demands Ad hoc engagement with site Improvement or deterioration in relative Level of identification with other relatives
	Who did REACT help? Consolidating knowledge of carers with mental health experience Benefits for people cared for
	How did REACT work ? Learning more about relative's condition and how to respond How to manage challenging situations Reducing sense of isolation Availability of tailored support Most useful earlier in carer journey

	Peer support: the active ingredient Empathic and effective support from specialist carers (REACT supporters) Support from, and offering support to, other relatives
	Ways to improve Overall feel of website Technical improvements Content improvement

Key themes

Is REACT really needed?

REACT was welcomed. For some relatives, this was because of a general lack of support experienced from services and lack of carer specific information online. For others, it was because the kind of help they had received was felt to be too demanding to be useful alongside the challenges of caring; thus the simplicity of access to REACT support was important.

> ***T0011 – mother, aged 58:*** *I did have a carer's assessment but it's proved to be more stressful than helpful…this lovely social worker came and spoke to me and then I said what I needed, which was practical help more than anything, and then he emailed me to say can you give me a timetable of your day and again me head started to explode and I'm thinking oh God this is too stressful, I can't cope with it. So I've decided not to bother with it because I don't think it's going to be that much help; I think it's just a paper exercise more than anything.*

Negative experiences with services and health professionals led to feelings of exclusion for many participants. Moreover, where support was offered, it commonly failed to acknowledge the systemic context for the service user and carer. This could create an additional burden

and trigger for the person suffering with mental health difficulties, leading at times to a vicious cycle of increasing distress in carer and service user.

> ***T0003 – female, 54:*** *Doctors, they…look at the medical side of things. I worked for a consultant psychiatrist when I was within the NHS so I know that their interests were the patient and getting the patient to feel better, but it wasn't so much around the family life and what was happening at home…In a way that's where people fail because if they don't look at the whole picture of what's going on then they can't assess what's going on with that patient.*

REACT was a useful support option even for individuals who had access to appropriate local support. A key attraction was that it was accessed anonymously, in contrast to local support groups where this was not possible. The need for anonymity was often driven by the service user more than the relative.

> ***T0004 – mother, 65:*** *He…made the request that I don't tell my family that he has bipolar one, so it curtails where I can get support. So I have a number of friends who know about it and they're very supportive and very understanding of it, but…to be able to go online whenever I needed to and know I…would probably get a reply within 24 hours was really helpful.*

REACT was compared to other mental health websites and seen as a useful addition. For some it was helpful to have information concentrated in one trusted site, while others found it helpful to have multiple websites that signposted to each other, of which REACT could be one. Furthermore, REACT was thought to address a gap in the written literature, which predominantly referred to systems in other countries, particularly the US, which were of limited relevance to these UK-based participants.

> ***T0023 – Male partner, 48:*** *I know that sounds really really bad, but the majority of the books seemed to be American and they definitely deal with things in a different way and the medication they have over there is different, the health service and the psychiatric system over there [are] very different to what we have here.*

What facilitates use of REACT?

Most participants were regular users of the Internet and familiar with accessing online material. This made incorporating REACT into their routine relatively straightforward in principle.

> ***T0019 – Mother, partner and wider family member, 54:*** *I do use online a lot and it's convenient for me 'cos you can go jump on and off whenever you [have] a spare moment.*

Participants liked the flexibility of being able to access REACT when and where they wanted, and being able to progress through the site at their own pace, which could be altered as other demands required. They also appreciated it being a free service. Relatives were encouraged to use REACT as often, and access as many of its features, as they found personally useful without feeling penalised or excluded. For example, access to the forum could vary from reading posts to responding to comments and creating new threads.

> ***T0003 – female, 54:*** *The great thing is that you can just go when you need to, as opposed to having to make appointments and get to a place.*

Flexibility was also appreciated in the range of media REACT used: relatives could focus on text, forum or video formats as they chose.

> ***T0004 – mother, 65:*** *I also have learning difficulties and dyslexia, so I actually found having both [text and videos] was more useful because sometimes I wouldn't always take the text in but watching the video as well kind of would reinforce and make it easier to understand.*

> ***T0024 – 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.*

The privacy and anonymity built into REACT were highly valued. Participants appreciated being able to have non-identifying usernames and to privately message REACT supporters, as well as having the option of posting in the community forum. The desire for anonymity was often a result of fear and stigma, and could be more prominent in certain communities and cultures. The ability to access REACT's information and personalised advice on a range of devices, especially the mobile phone, enhanced privacy and anonymity.

> ***T0002 – mother, 57:*** *You are anonymous. And you can leave when you want, whereas if you go to a group you tend to be there for at least a polite amount of time.*

> ***T0012 – brother, 30:*** *Certainly in the BME community it's very taboo, you're not allowed to talk about it, you pretend it doesn't exist, you ignore it, and therefore the more they deal with people like me the better I think.*

What hinders use of REACT?

Participants appeared to start off keen to explore the site, initially going through the modules one by one, for example. However, after an initial burst of curiosity other considerations began to affect use, especially lack of time, workload and levels of distress. One challenge people reported was that they would sometimes forget to use the site when under pressure or distressed. In those situations, email reminders or notifications of responses to a forum post could point them back to REACT as a resource that could help them address their current difficulties.

> ***T0020 – mother, 64:*** *I suppose I did need a little bit of reminding every now and again to keep going into the site to look…but that's probably because I had a lot on and couldn't find the time to do it.*

Participants varied in how they used the site. Some used it in a preventative way; others were more ad hoc, using it as they felt the need. Most appeared to return as needed, triggered by circumstances.

There were two key reasons for using REACT less than intended. Either the person they cared for became better; or the person(s) became unwell, and so the carer lacked time and energy to use REACT and, under stress, felt less able to process new information or even to remember their password.

> ***T0005 – mother, 60:*** *When things are a little bit more kind of stable and things are ticking along OK, you kind of forget about it [REACT] in the sense because you kind of don't need as much support.*

> ***T0002 – 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.*

Although most participants found it useful to read that others were in a similar situation, this was not always straightforward. Some seemed to suffer from "imposter syndrome", feeling that their situation was less complex than those of other contributors and that they therefore had less right to share their concerns online. Others identified so strongly with being a carer (professionally or personally) that asking for support for themselves felt very difficult.

> ***T0024 – sister, 26:*** *I am a support worker…[but] that wasn't something that I found that I wanted to use because when it comes to my carer's role it is very stressful, it is something that you do kind of just do, so when it comes to asking for the help, often you kind of do feel a little bit ashamed because you're sitting there and…you're meant to be helping.*

Who did REACT help?

To meet criteria for participation in the REACT study, relatives had to self-identify as a carer of a person with BD or psychosis, and to report experiencing significant levels of distress. In addition to being a carer, some of our participants worked in mental health-related jobs, and it was particularly interesting to hear how REACT helped them. Some felt familiar with much of the information shared, but found it helpful to be reminded of it and to read about other people's experiences. In particular, it reminded relatives to take care of themselves and encouraged them to reflect on their own mental health and wellbeing.

Clearly, having a professional mental health background is no guarantee of looking after oneself well, and in fact there was some evidence that this group faced additional hurdles (personal and practical) to opening up and getting the support they needed from local services. REACT's anonymity helped participants to address those needs.

> ***T0014 – mother and partner, 65:*** *When I first got it I read all the text of everything, and looked at my plan…My daughter's been ill for 17 years so I'm pretty clued up about all these things and I do research in mental health myself, so it reminded me of what to do and helped me stay positive and things like that you know. And reinforced things I should be doing and trying not to forget the important stuff, taking respite and keeping things in proportion.*

> ***T0002 – mother, 57:*** *I can't really get support in this area because I am a health professional for other people with mental health difficulties, so I would be on very dodgy ground confidentiality-wise if I went to a support group in this area…So in that sense, being able to tap into that [online] group was good. I'm a bit of a complex client, I think.*

For some participants, using REACT had a knock-on effect on those they cared for, or on other relatives. Some used information they had accessed on REACT to initiate discussions with their relative, or showed service-users or other family members elements of the site they had found useful.

> ***T0020 – mother, 64:*** *It had plenty of information in it…It obviously overall benefits the person that the relative's looking after if they're more informed.*

> ***T0016 – female partner, 43:*** *Yeah, he didn't feel as isolated…'cos there's still that kind of [stigma] and he's obviously felt isolated, he's not wanted to talk about it, and it did actually make him open up a bit more…so that had a really positive effect for him.*

How did REACT work?

Many participants expressed an interest in knowing more about their relative's condition and its consequences, as well keeping up to date with information on mental health in general. Consistent with the logic model for REACT (see *Chapter 2*), participants linked learning more about their relative's conditions to changes in how they perceived and responded to it.

> ***T0008 – male partner, 35:*** *The layout was quite easy to use and stuff like that, it broke down everything that you need from, you know, different kinds of mental illness – my wife was diagnosed with bipolar so…while I knew about depression or I had a little understanding of depression, bipolar I didn't know at all. And it was quite good to…get an eye-opener on different treatments and it was the first place I went to when my wife went through ECT treatment as well, because it kind of helped me cope with it.*

> ***T0010 – mother, 48:*** *In general I felt that I got a lot of information from it and I felt that it kind of changed my perspective.*

Most participants had very high levels of distress at inception and had been caring for someone for long periods of time. They said they valued gaining more knowledge and a more practical understanding of how to manage challenging situations.

Even with improved understanding, there was acknowledgement that it was a continuing challenge to respond constructively, and that REACT's round-the-clock availability helped. Much of the most valued content involved practical advice about services and processes, and about how to communicate effectively with a person experiencing a mental health problem. This was done most effectively by learning from other people's stories, which had the added benefit of reducing feelings of isolation.

> ***T0004 – mother, 65:*** *It's almost at the point at which their behaviour is most challenging, [that] you're sort of required to be most understanding, and that's*

> *when you sort of have the least capacity to be, you know, insightful and understanding about it. So that's where I went to the toolkit to almost try and force myself to have that.*
>
> *But you know it's incredibly difficult because their behaviour can be…intensely challenging and confronting, and so it's trying to get that balance of being passionate while also looking after yourself.*
>
> ***T0004 – 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.*

Even for participants who chose not to use REACT, knowing that it was available and accessible offered comfort and reassurance. Participants also appreciated the existence of a forum and the more private direct messaging service that allowed them to seek tailored information. The personalised nature of the intervention was highly valued and set REACT apart from other websites and professional advice.

A key purpose in accessing the forum or direct messaging was to offload frustrations with current services and to feel heard and supported in a non-judgemental environment. This may have been facilitated by the fact that REACT supporters were trained relatives, not health professionals.

> ***T0004 – mother, 65:*** *I think there's that sense of almost with the direct messaging of someone looking out for you, at I guess a more personal level, and in the forum that sense of shared community experience of being in the same boat and…that other people are unfortunately experiencing some pretty shitty things too.*
>
> ***T0001 – mother, 60:*** *Sometimes it's, it's like releasing the frustrations to say all this…and you know sometimes just having somebody say, That must be hard, that's…a difficult situation to be in, it's enough to at least relieve some of my distress that the system seems to be causing.*

Overall, participants reported that REACT helped them to cope better with difficult situations by offering emotional support in a safe space and practical advice, and by teaching them improved coping mechanisms, consistent with our logic model. However, a consistent message was that REACT was most useful when offered early in the recovery journey.

Introduced later in the journey, it was still helpful but mostly by confirming knowledge gained and by providing an outlet to offload pent-up feelings of loneliness and frustration.

> ***T0018 – 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.*

> ***T0001 – mother, 60:*** *I was eight years or seven years into my daughter's journey by the time I'd come into the REACT study and I think I had a lot of stored-up questions, topics, things that I had no-one to talk to about, so I got to get that all off my chest and I think it still took another while after my period of the study ended, but I do feel that that's parked now, I don't have to think about those things all the time anymore.*

There was some evidence to suggest that the needs of long-term carers are different, and more emotion-focused. For some, REACT had not been able to meet this need.

> ***T0001 – Mother, 60:*** *If I'd had the REACT toolkit when my daughter first went to hospital, I would have gotten a huge amount more out of it. I think the videos then would have been absolutely essential. [Now]…I didn't need that section as much because it was stuff I was familiar with because it's just a long trip. My problem is it's a long trip, that's forever as far as I can see, and that's the bit I was having trouble with. So it wasn't where to find some information, it was how to get that emotional support.*

Support: the active ingredient

REACT supporters were identified as different from health professionals, yet treated as a specialist, trained and knowledgeable group that stood apart from other relatives using the website. Access to them and peer support appeared to be the most highly valued aspect of the website. In particular, REACT supporters were given high praise for the advice they offered and their empathy in the forum and in direct messages. Furthermore, participants felt cared for, valued and safe when REACT supporters individually followed up with them if they were concerned, and for keeping a continuous yet not intrusive level of contact. The prompt responses of REACT supporters were particularly valued during periods of crisis.

> ***T0003 – Female, 54:*** *They got back to me really quick, and it was like sort of experts getting back to you and people that had been through things, people that knew more, different websites where I could go, they could offer more support that way.*

> ***T0004 – Mother, 65:*** *I think one of them even followed up with me 'cos I then wasn't on the forum for a couple of days, and she just…said something to the effect of I just want to check that you're OK. So it was a really sweet thing and it was just like, I am OK, I've just had my hands full.*

Participants also appreciated the support from other relatives. Even when they disagreed with responses, they valued receiving a plethora of opinions and thoughts. They also perceived benefits in sometimes being able to offer support themselves. This seemed to link to the logic model's proposal that REACT would increase relatives' sense of self efficacy, which in part would be realised through helping others.

> ***T0010 – Mother, 48:*** *It was quite encouraging to hear other people's points of views even though on some occasions I didn't actually agree with them.*

> ***T0004 – Mother, 65:*** *If I got a reply to a forum post then I would go and look at that because there's partly a sense of wanting to help other people who are in the same boat as you…Even if [their reply] was like three or four months afterwards, then I would reply to their post.*

Ways to improve

Participants were invited to suggest specific ways they would like to see REACT improved. These can be grouped under three headings: overall feel of the website, technical improvements and content improvement.

Overall feel of the website

Suggestions for improving the feel of the website included:

- Make the site more interactive
- Add less academic ways of learning, e.g. cartoons
- Update the interface – change fonts and colours (e.g. blue too clinical)
- Make tabs more visible

- Turn blog into newsfeed
- Offer opportunity to contribute to blogs and directory
- Use pop-up windows to attract attention to specific elements.

Technical improvements

These included:

- Easier navigation in the forum
- Direct links to comments in the notification emails
- A function to download or print personal or private discussions for future reference
- Extend search function to all pages including forum subsections
- Snooze function for reminder emails
- Make the site an app, obviating the need for multiple logins and problems with forgotten passwords.
- Support note making during videos
- Offer skype call option for support for those with dyslexia
- Allow recording of messages as alternative to typing

Content improvement

Most responses concerned the toolkit's content, with suggestions for:

- Additional teaching on coping strategies
- Help with deciding where a topic fits in a forum
- Positive topics
- Spaces for planned interaction that do not relate to problems
- More frequent blog updates, with email notifications
- More detail on how services work and different team roles function

- A module on improving communication with services (e.g. what to ask whom)
- More information on additional local sources of support, with email prompts for these events
- More medication information especially on supporting someone to manage side effects
- Updates on relevant news events such as legislation changes or topical TV programmes
- More information for children and adolescents
- Allow support workers and carers to interact on the forums to share good practice
- Allow creative input from participants.

Analysis of REACT forum topics

We also explored how participants in the REACT arm used the REACT forum and what sorts of topics were covered.

Thread titles

As of November 2018 – the forum contained 171 different threads. These could be grouped into the following main topic:

- Problems with the cared-for relative (e.g. “How to deal with verbal abuse and aggression”; “Think partner is getting worse again”)
- Medication (e.g. “Coming off medication”; “Medication changes and drug abuse”)
- Emotions and stress (e.g. “Blues after helping my wife through an episode”; “Stress and stressors”)
- Hobbies and leisure activities (e.g. “Swimming”; “The power of gardening”)
- Relationships (e.g. “Retaining a relationship while being your partner’s carer”)
- Work (e.g. “Disclosing mental illness at work”)
- Legal issues (e.g. “Mental health law”)
- Dealing with the health and social care system (e.g. “Can anyone support me with complaint?”; “Use and abuse of ‘confidentiality’ by NHS staff”)

- Communication (e.g. “The power of words”)
- The forum itself (e.g. “So I’m new to REACT…how am I feeling?”)

Preliminary corpus linguistic analysis

Corpus linguistic analysis revealed the following additional themes:

- Help and advice: needing, asking and receiving help; supporters not being allowed to give advice
- Obligation: talking about one’s responsibility, duty, etc.
- Hypothesising: possibilities and wishes, e.g. “If only I could live by the sea.”

This approach also provided more detail for themes suggested by thread titles, e.g.:

- Illnesses and symptoms: e.g. bipolar, illness, psychosis, symptoms, psychotic, depression, drugs, mental, physical, ill, disorder, paranoia, ADJ+ episode (e.g. psychotic episode)
- Medicine, medical actions**:** carers, psychiatrist, diagnosis, treatment, NHS, assessment, lithium, therapy, medications, valproate, confidentiality, meds, dose, anti-psychotic
- Problems/negative emotions**:** stress, delusion, anxiety, crisis, issues, anxious, difficult, challenging
- Strategies/positive emotions**:** Coping, managing, recover, wishes, exercise, hope, glad, love, wellbeing
- Kinship**:** son, relatives, husband, daughter, parent, wife, family, relationship.

Discussion

Chapter 2 reported on the development of REACT as an online toolkit, drawing on the insights of experts by experience at a series of workshops and the design brief created from this by the TMG. The logic model for REACT, based on well-established cognitive

behavioural principles, mapped out the challenges faced by relatives, the key features of REACT, the anticipated experiences of users and outcomes in response to such experiences. The in-depth interviews analysed above were broadly consistent with the logic model.

Relatives reported multiple challenges in understanding the behaviours of the relative they cared for and how best to respond to these, resulting in distress, isolation, stigma and shame. REACT offered them psychoeducational information and interactive support through the forum and direct messaging as well as additional information on where to seek further help on specific topics. Participants reported that they used REACT to learn more about BD and psychosis, to develop more effective ways of dealing with challenging situations, to share problems and solutions and to feel more able to manage their experiences.

A consistent message was that participants felt REACT would be most useful early on in their relative's recovery journey, when they were likely to be seeking information and strategies. Relatives later in this journey might need more emotion-focused interventions.

Relatives found prioritising time to use REACT difficult. The advantage of an online interventions is that it is always accessible. However, the corollary is that there is no dedicated time to engage. Overall, relatives reported feeling less isolated, more supported and, through better self-care, more able to attend to their own wellbeing without feeling ashamed to do so.

There were helpful suggestions about potential improvements and updates for REACT, consistent with digital formats rapidly evolving to become more interactive and integrated. Peer support and REACT supporter contributions were seen as crucial features of REACT, but not all participants accessed these. It is therefore crucial that future iterations of REACT optimise access to these elements. Linguistic analysis of the REACT forum indicated this platform was used to share information about living with mental health issues in a broad context including, but not limited to, the clinical and behavioural features of psychosis and BD. Consistent with REACT's recovery perspective there were also discussions about how both relative and individual with the mental health diagnosis could best live well alongside BD and psychosis.

A key limitation of our qualitative findings was the difficulty in recruiting low-level users for interview, resulting in a high proportion of high-level users in the final sample. This was despite the invitation's emphasis that we were very interested in talking to all participants in the trial, even those who had not used REACT at all. While the views of medium and low-

level users have contributed to each of the key themes, the predominance of high users is likely to be linked to the primarily positive views we received. There remains a real need to understand better the views of those who do not engage with DHIs, to ensure these do not increase inequalities in access to mental health services.

Chapter 7 Discussion

Introduction

In this chapter we summarise the main findings from the study and interpret these in light of other relevant research and the clinical context. We highlight the key strengths and limitations of the research that need to be taken into account when considering these findings. We draw out implications for policy, practice and future research. As this study was funded by a specific call by the HTA for efficient trial designs, we comment on how the lessons from this study can be used to inform future online trials. Finally, we draw out the main conclusions from this work.

Summary and interpretation of key findings

This was the first definitive RCT testing of an online DHI for relatives of people with severe mental health problems. The aim was to develop and test the clinical and cost effectiveness of an online supported self-management toolkit for relatives of people with psychosis and BD (which included a comprehensive resource directory), compared to a comprehensive RD alone. At baseline, participants reported very high levels of distress and low levels of wellbeing, both of which improved significantly, but there was no evidence of a difference between the groups. There was some evidence that those receiving REACT felt better supported than those receiving the directory, but the difference was small and, after accounting for missing data, failed to reach statistical significance (p0.051).

REACT appeared to be highly acceptable, with users reporting feeling safe and supported. No serious adverse events were reported. REACT cost an estimated £142.95 per participant, including full development and delivery costs. These costs would reduce as the number of users grew. There was no evidence that REACT increased QALYs, (incremental QALYS adjusted for baseline EQ-5D-5L, age and gender was -0.0024, 95%CI -0.0088–0.0039), or would save money (incremental cost adjusted for baseline age and gender was £286.77, 95% CI -£858.81–£1432.36, p=0.624).

REACT was originally designed as a paper-based intervention for relatives of people with psychosis in EIP services,[2] and we were able to adapt it to create an online DHI that also supported relatives of people with BD. Modules relevant to understanding and managing bipolar experiences were added, and a forum to facilitate a peer support community was established, along with a confidential direct messaging system, both of which were

successfully moderated by trained relatives with lived experience of supporting someone with psychosis or BD. The textual content was updated, and made more interactive through the use of videos of service users, relatives, and professionals sharing their experiences and knowledge, and the use of reflective exercises to help relatives to think about how to apply the information they were gaining to their specific situations. Making the toolkit available online made it easier to disseminate widely, and to update content as required.

REACT was made available to relatives across the UK who agreed to take part in an online trial. Recruitment, eligibility, consent, randomisation, data collection and follow-up all occurred primarily online (with some face-to-face recruitment and some telephone or postal reminders for follow-up). A bespoke data collection system was built. Despite the huge increase in development and testing of DHIs for mental health problems across the world, to our knowledge, this was the first definitive RCT test in Europe of an online DHI for relatives of people with severe mental health problems. In the US, Glynn *et al*[145] and Rotondi *et al*[146, 147] both report proof-of-concept trials for online psychoeducation programs for relatives of people diagnosed with schizophrenia, but neither groups reported a fully powered definitive evaluation.

There was a lot of interest in using REACT from relatives. Our aim was to recruit 666 relatives over 18 months. We recruited 800 relatives fairly easily within the recruitment phase of the study. This might indicate substantial unmet need in this area, and the potential for widespread use of an online support tool. Many more relatives were keen to take part, but 43% of those who completed the eligibility criteria questionnaire failed on at least one item, most commonly (81% of those failing) on the requirement to report “being strung up and nervous all the time” “rather more than usual ” or “much more than usual”. This item was chosen as having the highest item-total correlation with total GHQ-28 scores in our feasibility study and was included to avoid a floor effect at baseline. However, as a consequence, most relatives in the trial were in crisis at the beginning of the study, but relatives who had been distressed for longer periods and so responded “no more than usual” were ineligible.

Baseline GHQ-28 scores (mean 40.2, SD 14.3) were much higher than those reported for previous samples in studies of relatives of people with psychosis or BD who were seeking help,[13, 119] including our feasibility trial (mean 34.14, SD 24.63).[2] The same pattern was evident for wellbeing and support scores, which were significantly lower than in our feasibility trial.

Over the study's 24-week follow-up period there was a big reduction in distress and increase in wellbeing and support in all relatives across both arms. This is likely to be a result of the fact that circumstances change over time and for people recruited in crisis, the crisis is likely to have abated by follow-up, at least for some participants. This statistical regression to the mean makes it harder to see any impact from an intervention, as any difference needs to be significant, over and above the effect of time.

Further, reducing distress using an online psychoeducation approach might have been an overly ambitious goal. Although psychoeducation has been reliably shown to improve knowledge outcomes, and is recommended by NICE,[53, 54] there is no evidence it reduces distress, even when delivered face-to-face.[43] There is evidence that face-to-face interventions designed to improve outcomes for relatives are generally less effective for those with higher levels of distress.[39] While many people flourish alongside psychosis or BD, these are potentially chronic mental health problems that for some people can have a devastating effect on their lives, and those of their family and friends. REACT provides information and strategies to support relatives, but did not offer a cure for either condition, which might be what relatives were initially seeking to reduce their distress.

Although REACT showed no benefit over only the RD in reducing distress (GHQ28), relatives who received REACT did report feeling more supported than those who received RD only at 12 weeks (2.50, 95% CI 0.87–4.12) and 24 weeks (1.65, 95% CI 0.04–3.27). However, this was a small effect and after accounting for missing data in a longitudinal model, the difference between groups was no longer statistically significant at the cut-off of $p<.05$ (1.51, 95% CI -0.005–3.01, $p=0.051$), and unlikely to be of clinical significance. This is because, although similar numbers of relatives dropped out of follow-up in each arm of the trial, dropout in the RD arm was not linked to outcome, while those in the REACT arm who felt less supported were more likely to drop out. This pattern of informative dropout was consistent across all the outcome measures, and highlighted the importance of adequately accounting for missing data in RCTs.

We were able to test the hypothesised logic model that REACT would reduce distress by providing relatives with a working cognitive model of psychosis or BD (assessed using the Brief IPQ), and more adaptive coping (using the Brief COPE). Relatives in both arms of the trial developed more benign perceptions of illness and reported feeling more able to cope over the 24-week period. However, these changes did not differ between those receiving REACT and those receiving the RD only, and there was no evidence they played a causal role in reduced levels of distress. Coping strategies assessed using the Brief COPE showed

little change over time, but already favoured active coping, planning and acceptance at the outset.

REACT was valued by relatives for being comprehensive, relevant, easy to access, private and anonymous. The proactive support from REACT supporters was appreciated, as was the opportunity to learn about how best to support someone with a mental health problem through a variety of different mediums (text, video, forum). Relatives provided useful feedback about the content and design of REACT, all of which should be used to further develop the toolkit. A consistent message was that REACT would be most useful to relatives early on in the recovery journey, when they were likely to be seeking information and strategies. This suggested that more recruitment through GP surgeries and EIP teams would be beneficial. Some relatives found seeking help for their own needs difficult, and most found it hard to prioritise time to use REACT.

The problem of low levels of use is common across many DHIs. The flexibility of DHIs in that they can be used anytime, anywhere (with an internet connection), may paradoxically limit their effectiveness. The median (IQR) time spent on REACT (excluding the RD) in the REACT arm was 50.8 minutes (12.4–172.1), with a large variation between individuals (range 0.1–4505.5 minutes). The median (IQR) time spent on the RD in the RD only arm was 0.5 minutes (0–1.6), again with wide variation from 0 to 42.9 minutes. However, as the purpose of the RD was to signpost relatives to other sources of support, and we do not have data on how much they used these alternative supports, these figures cannot be directly compared.

Causal analysis suggested a small but non-significant association between website use and outcome, suggesting the need to better understand factors that affect engagement with REACT and DHIs more broadly.

All relatives were free to use REACT at their own convenience. The modules were openly accessible and we did not specify any ideal levels or order of use (though there was a logic to the presentation order). Although relatives were sent periodic reminders in response to low levels of activity, they did not report their levels of use to anyone directly. The REACT supporters moderated activity on the forum and responded to direct messages from relatives, but did not support use of the psychoeducation modules. The content was easy to follow, and each module had self-reflection exercises built in, to help relatives to think about how the information might apply to their specific situation. However, as Mohr *et al* reflect,[148] it may be that users will more effectively engage with DHIs if there are clear expectations of

use, and the presence of a respected individual to whom the individual is accountable. This may be similar to the effect of personal trainers for exercise: it's not that we don't know how to exercise, or that we need to exercise, but that, for some people, being accountable to a respected person at a dedicated time and specific place makes us more likely to do it. This might in part account for evidence to suggest greater efficacy of supported interventions,[149] and suggest that broadening the role of the REACT supporters to support all relatives to engage with all parts of REACT, including the modules, and as occurred in the feasibility study, might increase levels of use.

There were several ways in which this study differed from the REACT feasibility trial, which might account for the differences in findings. These differences might provide valuable insights into factors that affect the effectiveness of DHIs, but all require further testing.

1. Relatives in this study were more distressed at the outset and more likely to be in crisis.
2. Relatives had been caring for longer, and the information in REACT might have come too late.
3. REACT was online, rather than in paper form, and so might have been less accessible or visible, reducing triggers for use.
4. Relatives did not receive as much support to use REACT in general. Only the forum and direct messaging were supported, and relatives not engaging with these components did not receive any support in using REACT.
5. REACT was offered in addition to treatment as usual, but not as an integral part of a clinical service, in which clinicians working with relatives were also aware of the nature of the problems experienced by the people they were caring for.
6. REACT was supported by trained relatives rather than members of the clinical team.
7. REACT was compared to an active control (the RD).

Strengths of the study

Despite the recent interest in use of DHIs in mental health, and the government's backing of this agenda,[150, 151] there is still lack of a robust evidence base to support their effectiveness. 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 protocol to manage any direct contact with participants, and a pre-published analysis plan that appropriately addresses missing data.

As a result of these strengths, our findings highlight three key dangers of current research in this area. The first is assuming that interventions adapted from those delivered face-to-face will be equally effective: REACT was shown to be effective when offered in paper form and supported by telephone by staff linked to the relevant clinical team.

The second is the use of uncontrolled pre-post comparison to argue for effectiveness: REACT would have appeared very effective without comparison to an active control group.

The third is the need to appropriately manage missing data. Dropout in online trials is often higher than in offline trials, and cannot be assumed to occur at random: Relatives in the REACT arm who were more distressed were also more likely to drop out of follow-up. This may be true for other online interventions, as it may be harder to adapt the intervention better to meet individual user needs than would be the case in face-to-face support.

Limitations of the study

The study also had several limitations that need to be taken into account in interpreting the findings.

Accepting the need for rigour, there were limitations in selecting a traditional RCT design to evaluate REACT. RCTs were developed to test the effectiveness of static stand-alone interventions that can be easily defined (e.g. dose of a drug). DHIs, including REACT, are often designed to be one component of a comprehensive package of care, and their effectiveness should be evaluated as such. Their impact is likely to be very different when offered as part of service, rather than in isolation. For example, REACT is one part of the support that NICE recommend to relatives, and may only be effective for relatives able to access other elements of this support (e.g. appropriate clinical and social support for the person with psychosis or bipolar; and/or family intervention). REACT educates relatives about the services they should be receiving. If they are unable to access these, it could increase rather than decrease distress. Alternatively, awareness that a relative is accessing REACT, could lead to changes in behaviour in clinical staff who may reduce other forms of input that they perceive as no longer necessary. Testing an intervention that is designed to be part of a package of care, using an RCT design, maximises internal validity, but is inherently problematic in ignoring the impact of the changes throughout the wider system. As

recommended by the new guidance being developed by the Medical Research Council and NIHR for developing and evaluating complex interventions, study designs that take a more systems-based approach to the evaluation of interventions like REACT, which are just one component of a more complex healthcare package, may be more appropriate than traditional RCTs.[152]

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Developing and Evaluating Complex Interventions
Draft of updated guidance: Updated Guidance: Developing and Evaluating Complex Interventions [DRAFT FOR CONSULTATION]

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DHIs also need to be able to evolve and adapt at pace. The REACT trial took three years to deliver and by the end of the study, the toolkit looked dated, but had not been adapted during the study in an attempt to standardise the intervention across all participants. The way in which people used technology had evolved, such as increased use of mobile apps, and the content needed updating to reflect advances in the way in which mental health problems were understood and managed over time. REACT participants provided excellent ideas for updates as part of the qualitative data collection, described in *Chapter 6*. However, health research currently adopts a model of "definitive" testing, using a large expensive trial lasting several years, and testing between group differences. If a trial shows no overall group benefit for the intervention after a defined period, it is likely to become very challenging to attract further investment to develop it further.

This is in contrast to the iterative dynamic model of design, evaluate, adapt[153] seen in other areas of digital development, in which real-time data collection informs continuous adaptations over time. Because DHIs can similarly facilitate collection of large amounts of real-time data, within-person variation in the impact of the intervention can be explored, to identify what works for particular individuals in particular contexts.

Further limitations of this study included failure to recruit a broader range of relatives. Despite designing a broad recruitment strategy incorporating a wide range of online and offline recruitment strategies, our sample predominantly comprised white British females. There was some evidence of a greater proportion of partners than in previous studies.[2, 13, 119] It is possible that the predominance of female participants partially reflects the continuing burden of care falling to women, but the lack of relatives from ethnic minority groups is likely to result from lack of cultural adaptation in content and language, both of which were beyond the scope of this study. Cultural adaptation should be a key focus of future work in this area, to ensure DHIs do not exacerbate existing inequalities in access to healthcare.

Treatment as usual was not well measured and therefore cannot be reliably defined. There were also some technical issues in data collection online using the CSRI which meant that information about medication use and some service use was not reliable and could not be

used. This made it difficult to understand exactly what services relatives were receiving, and if and how these changed as a result of being offered REACT or accessing the RD. Given both interventions were designed to be one component of a care package, and a key function of both is to inform and signpost relatives to other sources of support available, more rigorous and detailed data on how these additional data sources were accessed and used would have allowed us to better understand the impact of both REACT and the RD.

Retention to follow-up played a very important role in this study. Online trials have historically reported higher dropout rates than those conducted face to face.[77] In anticipation of this, we over-recruited to the trial to ensure the final analysis was adequately powered. This strategy was successful and there was no evidence of differential rates of drop out between the two groups. However, those who dropped out of the REACT arm were more distressed than those that remained. This was not the case in the RD arm. This meant that data could not be assumed to be missing at random in both groups. When missing data were taken into account, any statistically significant benefits of REACT over the RD were lost. We don't know why relatives who were more distressed were more likely to drop out in REACT, but it may have been low satisfaction with the intervention. Those in the RD group may have been less dissatisfied, or had lower expectations of the RD and remained involved for the promise of access to the REACT modules at the end of the study (even though these were also made available to those who dropped out).

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Recruitment to the nested qualitative study within this trial was also limited by failure to interview those in the RD arm, and those who dropped out of the study prior to 24 week follow-up. The focus was on understanding relatives' experiences of using REACT, and as the RD was one component of REACT, we did not recruit additionally from this group. However, we acknowledge that their experiences of the RD may have been very different. We recruited only those who had completed 24-week follow-up as we were keen to prioritise collection of the primary outcome data and so did not want to overburden those from whom we were still seeking data. However, given that retention was not random (see below) this biased us to interview relatives who were less distressed at baseline.

Our intention was to recruit a sample across the range of levels of use of REACT so we could understand what factors might impact on engagement. Inevitably it proved easier to recruit those with higher levels of use and hence our findings are likely to be positively biased in their impressions of REACT.

Practical limitations of this study included underestimating the amount of IT resources needed to build and host the REACT toolkit and the online trial methodology. Part-time support meant we could not always address issues immediately, and led to protocol deviations outlined in *Chapter 4*. Finally, patient and public involvement in the REACT trial was challenging. Despite extensive involvement of relatives in the clinical delivery of REACT (from REACT supporters and supervisor), it was much more difficult to engage relatives in the RAG or the oversight committees. Consistent with the online design of the trial, this work was conducted remotely via digital or telephone communication, and it was harder to create a sense of engagement.

Finally, this trial is not an independent evaluation as members of the research team were also involved in the design and delivery of REACT. This may have led to bias in interpretation of the findings. Extensive peer review has been used to mitigate this, but it is important this remains acknowledged.

Implications for online trials

This study was funded as part of a specific call by the HTA for efficient trial designs. A previous version of the study that tested the clinical and cost effectiveness of REACT using a traditional offline trial design with data collected face-to-face was rejected by the NIHR HTA board at the final hurdle because it was deemed too expensive (cost £2,032,667). We redesigned the trial online, and delivered this for one-third of the original cost (at £633,404). Notwithstanding previous comments about whether an RCT is the best design to evaluate DHIs, we learned some key lessons about running online trials that might be useful to other researchers.

The key challenges and our suggested solutions are provided in *Table 53* below. These recommendations build directly on previous research in this area.[77]

Table 53: Challenges and solutions to delivery of online trials

Task	Challenge	Solution

Recruitment	Reaching people who may not use the Internet regularly.	A combination of offline and online recruitment strategies was needed to reach our recruitment target, and there was no evidence that recruitment avenue affected dropout.
	Cost-effective advertising through social media, specifically Facebook.	We outsourced Facebook advertising to an expert, which proved to be a very successful recruitment strategy. This is an example of new skills and expertise that are needed within the research team to deliver online trials.
Registration engagement	Ensuring online registration effectively encourages trial participation.	Based on PPI feedback on our landing page we limited text, included videos and highlighted requirement of commitment to follow-ups. Strategies to enhance engagement beyond the landing page Included: lay language to explain processes and encourage continuation; a progress bar; automated reminder emails 24 hours after consent and phone number activation, and 7 days after baseline questionnaires were started; and the option to contact the trial manager personally by telephone.
Eligibility checks	Randomised participants must meet strict eligibility criteria in order to adhere to protocol.	Participant eligibility was validated using online check boxes. Pop-ups were set up to explain to participants who failed to meet criteria why they could not take

		part, and direct them to alternative opportunities.
Participant identification and contact	Participants should be contactable throughout the trial to encourage follow-up and in case of risk.	We ensured the collection of complete and valid contact details to be sure that participants were identifiable, contactable and real. Participants could not progress without providing email, postal address and contact number. These details were also validated.
Consent	Valid informed consent must be obtained online for all participants in line with ethical standards.	We adhered to the British Psychological Society guidelines and received NHS ethical approval.
Monitoring intervention usage	Assessing the amount of intervention use accurately.	Web use was measured by Google Analytics data showing activity on webpages (page downloads, number of logins, and time spent on a page). Such data were limited as they did not tell us anything about how this information was being processed or used.[158] We tried to account for pages that could have been left open and inactive, by restricting maximum time, but it was always possible the page was open but not being actively engaged with, or was being used by another person.
Retention	The remote nature of contact may reduce retention to follow-up – "out of sight, out of mind".	A combination of email reminders at follow-up points along with additional postal, text and telephone contact increased retention rates. Another possible solution to low retention rates in online trials is to

		offer financial incentives for follow-up. We tested the effectiveness of higher/lower and conditional/unconditional financial incentives in our SWAT (see *Appendix 2*). We found no effect for this population from varying the amount or conditionality of incentives to complete follow-up (see *Appendix 2 Table 55*). This finding was in contrast to previous studies, so may vary depending on population.
Participant withdrawal	Studies must inform participants about times at which, and ways in which, they can withdraw from a study.	Information regarding withdrawal was included in the participant information sheet. A link to withdraw was contained in all follow-up reminder emails. Different levels of withdrawal were provided (data collection, intervention use, reminders etc). We tried to collect data on reasons for withdrawal.
PPI	PPI in online trials may require some new strategies to enhance engagement and ensure meaningful involvement.	Relatives involved in the clinical delivery of REACT (REACT supporters and supervisors) were physically located with the research team, and consequently had high levels of face-to-face contact with other members of the team. Online strategies to communicate with the Relatives' Advisory Group (RAG) and oversight committees (TSC and DMEC) were less effective at engaging members.

		Some face-to-face involvement of PPI participants is advisable.
Risk management	Identifying and responding to risk during an online trial needs careful consideration due to the remote nature of contact.	Clear risk strategy and protocol are needed. In REACT this included: *Identification*: Red flags items on GHQ automatically triggered an automated email to participants and a notification to trial manager. Risk could be identified by supporters through direct messaging or forum or by the trial manager when contact made for follow-up. *Recording and decision-making:* Any risk identified was recorded on an online dashboard. Clinical contacts were provided within the team for advice on risk. High risk events were recorded on the dashboard and reported to the lead clinical contact, the TSC chair, sponsor and NHS research ethics committee.

Implications for healthcare delivery

Services have to find a way to offer relatives education and support as recommended by NICE, regardless of whether or not this is effective in reducing GHQ-28 scores. In the absence of more effective alternatives, REACT can be justified as one component of a comprehensive care package that addresses NICE guidelines to offer relatives information and support; as such, it provides a credible base for further development and investigation. Relatives felt safe and well-supported using REACT, which might facilitate better engagement with other aspects of the service.

Key developments should include: redesigning the content and presentation using feedback from participants; making the technology more interactive and user-friendly; increasing the role of REACT supporters to include support to use the modules; specifying recommended levels of use; and offering REACT to relatives earlier in the recovery journey, alongside other components of care, particularly for those with high levels of distress. REACT can also help services to meet the NICE recommendation to increase involvement of service users (including relatives) in peer-worker roles to support delivery of healthcare services.[54] However, in its current form, REACT is unlikely to reduce relatives' distress or save money in other healthcare costs.

The need for DHIs to enhance but not replace face-to-face support is consistent with findings across other groups[154] including young people,[155] who are often assumed to be more likely to embrace digital technology.

Recommendations for further research

1. Given the apparent unmet need and high acceptability of REACT, further work is needed to make the content of REACT more effective, by iteratively codesigning and testing each of the key developments including: redesigning the content and presentation using feedback from participants; making the technology more interactive and user-friendly; increasing the role of REACT supporters to include support to use the modules; specifying recommended levels of use; and offering REACT to relatives earlier in the recovery journey, alongside other components of care, particularly for those with high levels of distress.

2. Psychoeducation and support are important and valued by relatives, but distress (GHQ-28) may not be the most appropriate outcome to evaluate their effectiveness. Understanding more about a chronic health problem for which there is no immediate cure is important, but unlikely to reduce distress without additional therapeutic input. Therefore, effectiveness of psychoeducation interventions may be better tested against alternative outcomes such as whether they support relatives to feel more knowledgeable, more empowered, better able to cope, and more engaged with services, rather than on reducing distress. Further research could focus on working with relatives to understand their views about what should be the primary outcomes for future psychoeducation programs.

3. Research is needed to understand how to increase the amount of engagement and use of REACT and other DHIs, to maximise their potential to improve outcomes.
4. Research is needed to understand how to improve uptake and reach of REACT (and other DHIs) by groups that currently show low levels of use of mental health services and support, including ethnic minority groups and men.
5. The impact of effective psychoeducation interventions for relatives on service-user outcomes needs to be tested.
6. RCTs can be delivered online at less cost. However, this methodology presents new challenges in keeping participants engaged throughout long-term follow-ups, and managing high-quality PPI; both need to be addressed by further research

Conclusions

Despite being informed by evidence-based theory, extensive user-informed design, and having previously shown positive outcomes on relatives' distress in a pilot study, REACT did not reduce relatives' distress significantly more than a comprehensive resource directory listing nationally available support services for relatives, nor did it save resources in other areas of health and social care. Distress reduced significantly in both arms, but as there was no treatment as usual-only group, it is possible that both interventions were effective, but equally possible that neither were and that this change was a function of time.

There are several reasons why REACT may have failed to show the benefits suggested in the feasibility study: the relatives taking part included those caring for people with bipolar disorder, had been caring for longer and were more highly distressed at baseline; REACT was online rather than in paper form; REACT was supported by trained relatives rather than staff within the participant's clinical team; REACT was tested against an active control (the resource directory) of unknown effectiveness; and there was less support targeted at using the modules rather than the forum. It is impossible to know which of these factors was crucial in determining these findings.

Notwithstanding these findings, relatives using REACT also reported feeling safe and supported and no serious adverse events were reported. Qualitative feedback was very positive. Relatives need access to information and emotional support [53, 54]even if it does not reduce their distress scores assessed using the GHQ-28.
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Rossella Iraci Capuccinello (Division of Health Research, Faculty of Health and Medicine, Lancaster University) provided health economics analysis.

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Sonia Johnson (Division of Psychiatry, University College London) was co-investigator advising on intervention content and the design and implementation of the trial.

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Ceu Mateus (Division of Health Research, Faculty of Health and Medicine, Lancaster University) provided health economic analysis.

Barbara Mezes (Spectrum Centre for Mental Health Research, Division of Health Research, Faculty of Health and Medicine, Lancaster University) provided trial management and administrative support.

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Katerina Panagaki (Spectrum Centre for Mental Health Research, Division of Health Research, Faculty of Health and Medicine, Lancaster University) conducted and analysed qualitative interviews with relatives in the REACT arm of the trial.

Naomi Rainford (Clinical Trials Research Centre, Institute of Child Health, Alder Hey Children's NHS Trust) was a statistician supporting management of trial data.

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Paula Williamson (Clinical Trials Research Centre, Institute of Child Health, Alder Hey Children's NHS Trust) was co-applicant and advisor on trial design and statistical analysis.

Publications

Lobban, F, Robinson, H, Appelbe, D, Barraclough, J, Bedson, E, Collinge, L, *et al* (2017). Protocol for an online randomised controlled trial to evaluate the clinical and cost-effectiveness of a peer-supported self-management intervention for relatives of people with psychosis or bipolar disorder: Relatives' Education And Coping Toolkit (REACT). *BMJ open*, 7(7), e016965.

Honary, M, Fisher, NR, McNaney, R, & Lobban, F (2018). A Web-Based Intervention for Relatives of People Experiencing Psychosis or Bipolar Disorder: Design Study Using a User-Centered Approach. *JMIR mental health*, 5(4).

Lobban, F, Collinge, L, Robinson, H, Flowers, S, Minns, V, & Jones, S (2018, March). Approaches to service user engagement in the relatives education and coping toolkit (REACT) RCT. In *Bipolar Disorders*, 20, 31–31.

Appelbe, D, Robinson, H, Dodd, S, Walker, A, Williamson, P, Lobban, F (2017). "Implementing and running an online trial-a case study using the react trial." In *Trials*, vol. 18.

Robinson, H, Lobban, F, and Honary, M (2016). "Relatives Education and Coping Toolkit (REACT) Lessons Learnt from Developing a National Online Trial for Relatives/Friends of People with Psychosis or Bipolar Disorder." In *Early intervention in psychiatry*, 10, pp. 70-70.

References

1. Honary M, Fisher NR, McNaney R, Lobban F. A Web-Based Intervention for Relatives of People Experiencing Psychosis or Bipolar Disorder: Design Study Using a User-Centered Approach. *JMIR mental health* 2018;**5**.
2. Lobban F, Glentworth D, Chapman L, Wainwright L, Postlethwaite A, Dunn G*, et al.* Feasibility of a supported self-management intervention for relatives of people with recent-onset psychosis: REACT study. *The British Journal of Psychiatry* 2013;**203**:366-72. https://doi.org/10.1192/bjp.bp.112.113613 last accessed 23 August 2019.
3. Lobban F, Glentworth D, Haddock G, Wainwright L, Clancy A, Bentley R. The views of relatives of young people with psychosis on how to design a Relatives Education And Coping Toolkit (REACT). *Journal of Mental Health* 2011;**20**:567-79.
4. McGrath JJ, Saha S, Al-Hamzawi AO, Alonso J, Andrade L, Borges G*, et al.* Age of onset and lifetime projected risk of psychotic experiences: cross-national data from the World Mental Health Survey. *Schizophrenia bulletin* 2016;**42**:933-41.
5. Johns LC, Kompus K, Connell M, Humpston C, Lincoln TM, Longden E*, et al.* Auditory verbal hallucinations in persons with and without a need for care. *Schizophrenia bulletin* 2014;**40**:S255-S64.
6. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE*, et al.* Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *The Lancet* 2013;**382**:1575-86.
7. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M*, et al.* Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Archives of general psychiatry* 2007;**64**:543-52.
8. McCrone PR, Dhanasiri S, Patel A, Knapp M, Lawton-Smith S. *Paying the price: the cost of mental health care in England to 2026*: King's Fund; 2008.
9. Paykel ES, Abbott R, Morriss R, Hayhurst H, Scott J. Sub-syndromal and syndromal symptoms in the longitudinal course of bipolar disorder. *The British Journal of Psychiatry* 2006;**189**:118-23.
10. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Archives of general psychiatry* 2005;**62**:975-83.
11. Drancourt N, Etain B, Lajnef M, Henry C, Raust A, Cochet B*, et al.* Duration of untreated bipolar disorder: missed opportunities on the long road to optimal treatment. *Acta Psychiatrica Scandinavica* 2013;**127**:136-44.
12. Awad AG, Voruganti LN. The burden of schizophrenia on caregivers. *Pharmacoeconomics* 2008;**26**:149-62.
13. Barrowclough C, Gooding P, Hartley S, Lee G, Lobban F. Factors associated with distress in relatives experiencing recent onset psychosis in a family member. *J Nerv Ment Dis* 2014;**202**:40-6.
14. Kingston C, Onwumere J, Keen N, Ruffell T, Kuipers E. Posttraumatic stress symptoms (PTSS) in caregivers of people with psychosis and associations with caregiving experiences. *Journal of Trauma Dissociation* 2016;**17**:307-21.
15. Onwumere J, Bebbington P, Kuipers E. Family interventions in early psychosis: specificity and effectiveness. *Epidemiology and Psychiatric Sciences* 2011;**20**:113-9.
16. Tennakoon L, Fannon D, Doku V, O'ceallaigh S, Soni W, Santamaria M*, et al.* Experience of caregiving: relatives of people experiencing a first episode of psychosis. *The British Journal of Psychiatry* 2000;**177**:529-33.
17. MacDonell MD, Short RA, Berry CM, Dyck DG. Burden in Schizophrenia Caregivers: Impact of Family Psychoeducation and Awareness of Patient Suicidality. *Family Process* 2003;**42**:91-103.

18. Magliano L, Fadden G, Madianos M, Caldas de Almeida JM, Held T, Guarneri M*, et al.* Burden on the families of patients with schizophrenia: reasults of the BIOMED I study. *Social Psychiatry and Psychiatric Epidemiology* 1998;**33**:405-12.
19. Möller–Leimkühler AM. Burden of relatives and predictors of burden. Baseline results from the Munich 5–year–follow–up study on relatives of first hospitalized patients with schizophrenia or depression. *European Archives of Psychiatry and Clinical Neuroscience* 2005;**255**:223-31.
20. Lobban F, Barrowclough C, Jones S. Does Expressed Emotion need to be understood within a more systemic framework? *Social Psychiatry and Psychiatric Epidemiology* 2006;**41**:50-5. https://doi.org/10.1007/s00127-005-0993-z last accessed 23 August 2019.
21. Onwumere J, Lotey G, Schulz J, James G, Afsharzadegan R, Harvey R*, et al.* Burnout in early course psychosis caregivers: the role of illness beliefs and coping styles. *Early intervention in psychiatry* 2017;**11**:237-43.
22. Kuipers E, Watson P, Onwumere J, Bebbington P, Dunn G, Weinman J*, et al.* Discrepant illness perceptions, affect and expressed emotion in people with psychosis and their carers. *Social Psychiatry and Psychiatric Epidemiology* 2007;**42**:277-83. https://doi.org/10.1007/s00127-007-0165-4 last accessed 23 August 2019.
23. Chessick CA, Perlick DA, Miklowitz DJ, Dickinson LM, Allen MH, Morris CD*, et al.* Suicidal ideation and depressive symptoms among bipolar patients as predictors of the health and well-being of caregivers. *Bipolar disorders* 2009;**11**:876-84.
24. Ostacher M, Nierenberg A, Iosifescu D, Eidelman P, Lund H, Ametrano R*, et al.* Correlates of subjective and objective burden among caregivers of patients with bipolar disorder. *Acta Psychiatrica Scandinavica* 2008;**118**:49-56.
25. Steele A, Maruyama N, Galynker I. Psychiatric symptoms in caregivers of patients with bipolar disorder: a review. *Journal of affective disorders* 2010;**121**:10-21.
26. Chessick CA, Perlick DA, Miklowitz DJ, Kaczynski R, Allen MH, Morris CD*, et al.* Current suicide ideation and prior suicide attempts of bipolar patients as influences on caregiver burden. *Suicide and Life-Threatening Behavior* 2007;**37**:482-91.
27. Fletcher K, Parker GB, Manicavasagar V. Coping profiles in bipolar disorder. *Comprehensive psychiatry* 2013;**54**:1177-84.
28. Hosang GM, Uher R, Maughan B, McGuffin P, Farmer AE. The role of loss and danger events in symptom exacerbation in bipolar disorder. *Journal of psychiatric research* 2012;**46**:1584-9.
29. Morriss R, Yang M, Chopra A, Bentall R, Paykel E, Scott J. Differential effects of depression and mania symptoms on social adjustment: prospective study in bipolar disorder. *Bipolar disorders* 2013;**15**:80-91.
30. Lowenstein J, Butler D, Ashcroft K. The efficacy of a cognitively orientated carers group in an early intervention in psychosis service–a pilot study. *Journal of Psychiatric and Mental Health Nursing* 2010;**17**:628-35.
31. Zendjidjian X, Richieri R, Adida M, Limousin S, Gaubert N, Parola N*, et al.* Quality of life among caregivers of individuals with affective disorders. *Journal of affective disorders* 2012;**136**:660-5.
32. Chen F-p, Greenberg JS. A positive aspect of caregiving: The influence of social support on caregiving gains for family members of relatives with schizophrenia. *Community mental health journal* 2004;**40**:423-35.
33. Veltman A, Cameron JI, Stewart DE. The experience of providing care to relatives with chronic mental illness. *The Journal of nervous and mental disease* 2002;**190**:108-14.
34. Andrew A, Knapp M, McCrone P, Parsonage M, Trachtenberg M. *Effective interventions in schizophrenia- the economic case. A report prepared for the Schizophrenia Commission.* London: Rethink Mental Illness; 2012.
35. Buckner L, Yeandle S. *Valuing carers 2015*: Carers UK; 2015.
36. Lowyck B, De Hert M, Peeters E, Wampers M, Gilis P, Peuskens J. A study of the family burden of 150 family members of schizophrenic patients. *European Psychiatry* 2004;**19**:395-401.

37. Perlick D, Rosenheck RR, Clarkin JF, Sirey JA, Raue P, Greenfield S*, et al.* Burden experienced by care-givers of persons with bipolar affective disorder. *The British Journal of Psychiatry* 1999;**175**:56-62.
38. Pharoah F, Mari J, Rathbone J, Wong W. Family intervention for schizophrenia. *Cochrane Database of Systematic Reviews* 2010;**12**.
39. Lobban F, Postlethwaite A, Glentworth D, Pinfold V, Wainwright L, Dunn G*, et al.* A systematic review of randomised controlled trials of interventions reporting outcomes for relatives of people with psychosis. *Clinical psychology review* 2013;**33**:372-82.
40. Miklowitz DJ, George EL, Richards JA, Simoneau TL, Suddath RL. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. *Archives of general psychiatry* 2003;**60**:904-12.
41. Perlick DA, Miklowitz DJ, Lopez N, Chou J, Kalvin C, Adzhiashvili V*, et al.* Family-focused treatment for caregivers of patients with bipolar disorder. *Bipolar disorders* 2010;**12**:627-37.
42. Yesufu-Udechuku A, Harrison B, Mayo-Wilson E, Young N, Woodhams P, Shiers D*, et al.* Interventions to improve the experience of caring for people with severe mental illness: systematic review and meta-analysis. *The British Journal of Psychiatry* 2015;**206**:268-74.
43. Sin J, Gillard S, Spain D, Cornelius V, Chen T, Henderson C. Effectiveness of psychoeducational interventions for family carers of people with psychosis: A systematic review and meta-analysis. *Clinical Psychology Review* 2017;**56**:13-24.
44. Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. *The Lancet* 2013;**381**:1672-82.
45. Reinares M, Colom F, Sánchez-Moreno J, Torrent C, Martínez-Arán A, Comes M*, et al.* Impact of caregiver group psychoeducation on the course and outcome of bipolar patients in remission: a randomized controlled trial. *Bipolar disorders* 2008;**10**:511-9.
46. Miklowitz DJ. *Bipolar disorder: A family-focused treatment approach*: Guilford Press; 2010.
47. Addington J, McCleery A, Addington D. Three-year outcome of family work in an early psychosis program. *Schizophr Res* 2005;**79**:107-16.
48. Lorig KR, Holman HR. Self-management education: history, definition, outcomes, and mechanisms. *Annals of behavioral medicine* 2003;**26**:1-7.
49. Butzlaff RL, Hooley JM. Expressed emotion and psychiatric relapse: a meta-analysis. *Archives of General Psychiatry* 1998;**55**:547-52.
50. Miklowitz DJ, Goldstein MJ, Nuechterlein KH, Snyder KS, Mintz JJAoGP. Family factors and the course of bipolar affective disorder. 1988;**45**:225-31.
51. Kim EY, Miklowitz DJ. Expressed emotion as a predictor of outcome among bipolar patients undergoing family therapy. *Journal of Affective Disorders* 2004;**82**:343-52.
52. HM Government. *The Care Act 2014*. London: The Stationary Office; 2014.
53. National Institute for Health and Care Excellence (NICE). *NICE Clinical Guideline*. *Bipolar Disorder: the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care* NICE Clinical Guideline; 2014.
54. National Institute for Health and Care Excellence (NICE). *Psychosis and schizophrenia in adults (CG178)* no. CG178. London: National Institute for Health and Care Excellence; 2014.
55. Healthcare Quality Improvement Partnership (HQIP), Royal College of Psychiatrists. *Report of the Early Intervention in Psychosis audit*. London: NHS England; 2016.
56. Vermeulen B, Lauwers H, Spruytte N, Van Audenhove C. P. 1. k. 038 Experiences of family caregivers for persons with severe mental illness: an international exploration. *European Neuropsychopharmacology* 2015;**25**:S374.
57. Eassom E, Giacco D, Dirik A, Priebe S. Implementing family involvement in the treatment of patients with psychosis: a systematic review of facilitating and hindering factors. *BMJ open* 2014;**4**:e006108.
58. Department of Health. *Achieving better access to mental health services by 2020*. London: Department of Health; 2014.

59. Worthington A, Rooney P, Hannan R. *The Triangle of Care. Carers Included: A Guide to Best Practice in Mental Health Care in England.* London; 2103.
60. Lobban F, Glentworth D, Wainwright L, Pinfold V, Chapman L, Larkin W*, et al.* Relatives Education And Coping Toolkit - REACT. Study protocol of a randomised controlled trial to assess the feasibility and effectiveness of a supported self management package for relatives of people with recent onset psychosis. *Bmc Psychiatry* 2011;**11**:100-6. https://doi.org/10.1186/1471-244x-11-100 last accessed 23 August 2019.
61. Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. *Psychol Med* 1979;**9**:139-45. https://doi.org/10.1017/S0033291700021644 last accessed 23 August 2019.
62. Quirk A, Smith S, Hamilton S, Lamping D, Stahl D, Pinfold V*, et al. Development and Validation of the Carer Well-Being and Support (CWS) Questionnaire: Report for the National Institute for Health Research Service Delivery and Organisation Programme*: HMSO; 2009.
63. Quinn J, Barrowclough C, Tarrier NJAPS. The Family Questionnaire (FQ): a scale for measuring symptom appraisal in relatives of schizophrenic patients. 2003;**108**:290-6.
64. Wainwright L, Lancaster University. *Relatives' Experiences of Supporting and Caring for a Family Member with First Episode Psychosis; with or without a Self-management Intervention.*: Lancaster University; 2015.
65. Gafoor R, Nitsch D, McCrone P, Craig TK, Garety PA, Power P*, et al.* Effect of early intervention on 5-year outcome in non-affective psychosis. *The British journal of psychiatry* 2010;**196**:372-6.
66. Bertelsen M, Jeppesen P, Petersen L, Thorup A, Øhlenschlæger J, le Quach P*, et al.* Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: the OPUS trial. *Archives of general psychiatry* 2008;**65**:762-71.
67. Arnberg FK, Linton SJ, Hultcrantz M, Heintz E, Jonsson U. Internet-delivered psychological treatments for mood and anxiety disorders: a systematic review of their efficacy, safety, and cost-effectiveness. *PLoS One* 2014;**9**:e98118. https://doi.org/10.1371/journal.pone.0098118 last accessed 23 August 2019.
68. Alvarez-Jimenez M, Alcazar-Corcoles M, Gonzalez-Blanch C, Bendall S, McGorry P, Gleeson J. Online, social media and mobile technologies for psychosis treatment: a systematic review on novel user-led interventions. *Schizophrenia research* 2014;**156**:96-106.
69. Hidalgo-Mazzei D, Mateu A, Reinares M, Matic A, Vieta E, Colom F. Internet-based psychological interventions for bipolar disorder: review of the present and insights into the future. *Journal of affective disorders* 2015;**188**:1-13.
70. Scott JL, Dawkins S, Quinn MG, Sanderson K, Elliott K-EJ, Stirling C*, et al.* Caring for the carer: a systematic review of pure technology-based cognitive behavioral therapy (TB-CBT) interventions for dementia carers. *Aging and Mental Health* 2016;**20**:793-803.
71. Ziebland S, Wyke S. Health and illness in a connected world: how might sharing experiences on the internet affect people's health? *The Milbank Quarterly* 2012;**90**:219-49.
72. Sin J, Henderson C, Spain D, Cornelius V, Chen T, Gillard S. eHealth interventions for family carers of people with long term illness: A promising approach? *Clinical psychology review* 2018.
73. Repper J, Carter T. A review of the literature on peer support in mental health services. *Journal of Mental Health* 2011;**20**:392-411.
74. Faulkner A, Basset T. A helping hand: taking peer support into the 21st century. *Mental Health and Social Inclusion* 2012;**16**:41-7.
75. Walker G, Bryant W. Peer Support in Adult Mental Health Services: A Metasynthesis of Qualitative Findings. *Psychiatric Rehabilitation Journal* 2013;**36**:28-34.
76. National Institute for Health and Care Excellence. *Implementing the early intervention in psychosis access and waiting time standard: Guidance* National Institute for Health and Care Excellence London; 2016.

77. Murray E, Khadjesari Z, White IR, Kalaitzaki E, Godfrey C, McCambridge J*, et al.* Methodological challenges in online trials. *Journal of Medical Internet Research* 2009;**11**:e9.
78. Mathieu E, McGeechan K, Barratt A, Herbert R. Internet-based randomized controlled trials: a systematic review. *Journal of the American Medical Informatics Association* 2013;**20**:568-76.
79. Department of Health. *A Framework for Mental Health Research*. London: Department of Health; 2017.
80. Wainwright LD, Glentworth D, Haddock G, Bentley R, Lobban F. What do relatives experience when supporting someone in early psychosis? *Psychology and Psychotherapy: Theory, Research and Practice* 2015;**88**:105-19.
81. Eysenbach G, with the Consort-EHEALTH Group. CONSORT-EHEALTH: improving and standardizing evaluation reports of Web-based and mobile health interventions. *Journal of medical Internet research* 2011;**13**.
82. Norman DA. Cognitive engineering. In: Norman DA, Draper SW, editors. *User centered system design*Hillsdale, NJ: Lawrence Erlbaum Associates Inc.; 1986:61.
83. Honary M, Fisher NR, McNaney R, Lobban F. Designing Accessible Web-Based Interventions for Relatives of People experiencing Psychosis or Bipolar Disorder using a User-Centered Approach. *Journal of Medical Internet Research – Mental Health* In press.
84. Anderson CM, Reiss DJ, Hogarty GE. *Schizophrenia and the family: A practitioner's guide to psychoeducation and management*. New York: Guilford Press; 1986.
85. Barrowclough C, Tarrier N. *Families of Schizophrenic Patients: Cognitive Behavioural Intervention*: Stanley Thornes; 1992.
86. Falloon IR. *Handbook of Behavioural Family Therapy*. London: Routledge; 1988.
87. Kuipers L, Birchwood M, McCreadie R. Psychosocial family intervention in schizophrenia: a review of empirical studies. *The British Journal of Psychiatry* 1992;**160**:272-5.
88. McFarlane WR. *Family therapy in schizophrenia*. New York: Guilford Press; 1983.
89. NHS England. *Five Year Forward View* NHS England; 2014.
90. Berry N, Lobban F, Emsley R, Bucci S. Acceptability of Interventions Delivered Online and Through Mobile Phones for People Who Experience Severe Mental Health Problems: A Systematic Review. *Journal Of Medical Internet Research* 2016;**18**:e121-e. https://doi.org/10.2196/jmir.5250 last accessed 23 August 2019.
91. O'Connor S, Hanlon P, O'Donnell CA, Garcia S, Glanville J, Mair FS. Understanding factors affecting patient and public engagement and recruitment to digital health interventions: a systematic review of qualitative studies. *BMC medical informaticsdecision making* 2016;**16**:120.
92. Van Dijk J. Digital divide: Impact of access. In: *The International Encyclopedia of Media Effects*; 2017:1-11.
93. Christensen H, Griffiths KM, Farrer L. Adherence in internet interventions for anxiety and depression: systematic review. *Journal of medical Internet research* 2009;**11**.
94. Andersson G, Cuijpers P. Internet-based and other computerized psychological treatments for adult depression: a meta-analysis. *Cognitive behaviour therapy* 2009;**38**:196-205.
95. Kaufman L, Brooks W, Steinley-Bumgarner M, Stevens-Manser S. Peer specialist training and certification programs: A national overview. *University of Texas at Austin Center for Social Work Research* 2012;**10**:07-011.
96. New Zealand Mental Health Commission. *Blueprint II: Improving mental health and wellbeing for all New Zealanders*: Mental Health Commission; 2012.
97. National Institute for Health and Care Excellence. *NICE Guideline 53: Transition between inpatient mental health settings and community or care home settings*. London: National Institute for Health and Care Excellence; 2016.
98. Joint Commissioning Panel for Mental Health. *Guidance for commissioners of acute care – inpatient and crisis home treatment* JCP-MH; 2012.
99. Joint Commissioning Panel for Mental Health. *Guidance for commissioners of community specialist mental health services* JCP-MH; 2012.

100. Mental Health Commission of Canada. *Changing directions, changing lives: the mental health strategy for Canada* Mental Health Commission of Canada,; 2012.
101. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMC medicine* 2010;**8**:18.
102. Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B*, et al.* Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* 2008;**337**:a2390.
103. Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). *Journal of medical Internet research* 2004;**6**.
104. Lobban F, Appleton V, Appelbe D, Barraclough J, Bowland J, Fisher NR*, et al.* IMPlementation of A Relatives' Toolkit (IMPART study): an iterative case study to identify key factors impacting on the implementation of a web-based supported self-management intervention for relatives of people with psychosis or bipolar experiences in a National Health Service: a study protocol. *Implementation Science* 2017;**12**:152.
105. Gu LL, Skierkowski D, Florin P, Friend K, Ye Y. Facebook, Twitter, & QR codes: An exploratory trial examining the feasibility of social media mechanisms for sample recruitment. *Computers in Human Behavior* 2016;**60**:86-96.
106. O'Connor A, Jackson L, Goldsmith L, Skirton H. Can I get a retweet please? Health research recruitment and the Twittersphere. *Journal of advanced nursing* 2014;**70**:599-609.
107. Bailey JV, Pavlou M, Copas A, McCarthy O, Carswell K, Rait G*, et al.* The Sexunzipped trial: optimizing the design of online randomized controlled trials. *Journal of medical Internet research* 2013;**15**.
108. Morgan AJ, Jorm AF, Mackinnon AJ. Internet-based recruitment to a depression prevention intervention: lessons from the Mood Memos study. *Journal of Medical Internet Research* 2013;**15**.
109. British Psychological Society. Ethics guidelines for internet-mediated research. In. Leicester: The British Psychological Society; 2013.
110. Harvey K, Catty J, Langman A, Winfield H, Clement S, Burns E*, et al.* A review of instruments developed to measure outcomes for carers of people with mental health problems. *Acta Psychiatrica Scandinavica* 2008;**117**:164-76.
111. Whittaker W, Sutton M. *Mental health, work incapacity and State transfers: an analysis of the British Household Panel Survey*: HEDG, c/o Department of Economics, University of York; 2010.
112. Whittaker W, Sutton M, MacDonald S, Maxwell M, Smith M, Wilson P*, et al.* The effect of mental ill health on absence from work in different occupational classifications: analysis of routine data in the British Household Panel Survey. *J Occup Environ Med* 2012;**54**:1539-44.
113. Whittaker W, Sutton M, Maxwell M, Munoz-Arroyo R, MacDonald S, Power A*, et al.* Predicting which people with psychosocial distress are at risk of becoming dependent on state benefits: analysis of routinely available data. *BMJ* 2010;**341**:c3838.
114. Russ TC, Stamatakis E, Hamer M, Starr JM, Kivimäki M, Batty GD. Association between psychological distress and mortality: individual participant pooled analysis of 10 prospective cohort studies. *BMJ* 2012;**345**:e4933.
115. Quirk A, Smith S, Hamilton S, Lamping D, Lelliott P, Stahl D*, et al.* Development of the carer well-being and support (CWS) questionnaire. *Ment Health Rev* 2012;**17**:128-38.
116. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. *J Psychosom Res* 2006;**60**:631-7.
117. Carver CS. You want to measure coping but your protocol'too long: Consider the brief cope. *Int J Behav Med* 1997;**4**:92.
118. Beck JS. *Cognitive behavior therapy: Basics and beyond*: Guilford press; 2011.
119. Szmukler G, Herrman H, Bloch S, Colusa S, Benson A. A controlled trial of a counselling intervention for caregivers of relatives with schizophrenia. *Social psychiatry and psychiatric epidemiology* 1996;**31**:149-55.

120. Woods RT, Bruce E, Edwards R, Elvish R, Hoare Z, Hounsome B*, et al.* REMCARE: reminiscence groups for people with dementia and their family caregivers–effectiveness and cost-effectiveness pragmatic multicentre randomised trial. *Health Technol Assess* 2012;**16**:48.
121. Brueton V, Tierney J, Stenning S, Meredith S, Harding S, Nazareth I*, et al.* Strategies to improve retention in randomised trials: a Cochrane systematic review and meta-analysis. *BMJ open* 2014;**4**:e003821.
122. Khadjesari Z, Murray E, Kalaitzaki E, White IR, McCambridge J, Thompson SG*, et al.* Impact and costs of incentives to reduce attrition in online trials: two randomized controlled trials. *Journal of Medical Internet Research* 2011;**13**.
123. David MC, Ware RS. Meta-analysis of randomized controlled trials supports the use of incentives for inducing response to electronic health surveys. *J Clin Epidemiol* 2014;**67**:1210-21.
124. Nonnecke B, Andrews D, Preece J. Non-public and public online community participation: Needs, attitudes and behavior. *Electronic Commerce Research* 2006;**6**:7-20.
125. Gleeson JF, Lederman R, Wadley G, Bendall S, McGorry PD, Alvarez-Jimenez M. Safety and privacy outcomes from a moderated online social therapy for young people with first-episode psychosis. *Psychiatric services* 2014;**65**:546-50.
126. Lobban F, Robinson H, Appelbe D, Barraclough J, Bedson E, Collinge L*, et al.* Protocol for an online randomised controlled trial to evaluate the clinical and cost-effectiveness of a peer-supported self-management intervention for relatives of people with psychosis or bipolar disorder: Relatives Education And Coping Toolkit (REACT). *BMJ Open* 2017;**7**:e016965. https://doi.org/10.1136/bmjopen-2017-016965 last accessed 23 August 2019.
127. GL Assessment. *General Health Questionnaire*. URL: https://www.gl-assessment.co.uk/products/general-health-questionnaire-ghq/ last accessed 23 August 2019. (accessed).
128. Goldberg D. *Manual of the general health questionnaire*: NFER Nelson; 1978.
129. Jones CJ, Hayward M, Brown A, Clark E, Bird D, Harwood G*, et al.* Feasibility and participant experiences of a written emotional disclosure intervention for parental caregivers of people with psychosis. *Stress and Health* 2016;**32**:485-93.
130. National Institute for Health and Care Excellence. *Guide to the Methods of Technology Appraisal 2013*. London: National Institute for Health and Care Excellence; 2013.
131. Frick KD. Micro-costing quantity data collection methods. *Medical care* 2009;**47**:S76.
132. Li J, Parrott S, Sweeting M, Farmer A, Ross J, Dack C*, et al.* Cost-Effectiveness of Facilitated Access to a Self-Management Website, Compared to Usual Care, for Patients With Type 2 Diabetes (HeLP-Diabetes): Randomized Controlled Trial. *Journal of medical Internet research* 2018;**20**:e201.
133. Curtis L, Burns A. *Unit Costs of Health and Social Care 2017*. Canterbury: Personal Social Services Research Unit, University of Kent; 2017. https://doi.org/10.22024/UniKent/01.02/65559 last accessed 23 August 2019.
134. NHS Improvement. *National schedule of reference costs 2017/18*. London: NHS Improvement; 2017.
135. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. *Health economics* 2018;**27**:7-22.
136. Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *Pharmacoeconomics* 2014;**32**:1157-70.
137. Department for Business, Energy & Industrial Strategy. *Ethicity facts and figures: average hourly pay*. London: Department for Business, Energy & Industrial Strategy; 2018.
138. Iribarren SJ, Cato K, Falzon L, Stone PW. What is the economic evidence for mHealth? A systematic review of economic evaluations of mHealth solutions. *PLoS One* 2017;**12**:e0170581.
139. Bhandari A, Wagner T. Self-reported utilization of health care services: improving measurement and accuracy. *Medical Care Research Review* 2006;**63**:217-35.

140. Petrou S, Murray L, Cooper P, Davidson LL. The accuracy of self-reported healthcare resource utilization in health economic studies. *International journal of technology assessment in health care* 2002;**18**:705-10.
141. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D*, et al.* Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. *Value in Health* 2013;**16**:231-50.
142. Livingston G, Barber J, Rapaport P, Knapp M, Griffin M, King D*, et al.* Long-term clinical and cost-effectiveness of psychological intervention for family carers of people with dementia: a single-blind, randomised, controlled trial. *The Lancet Psychiatry* 2014;**1**:539-48.
143. Spencer L, Ritchie J. Qualitative data analysis for applied policy research. In: *Analyzing qualitative data*: Routledge; 2002:187-208.
144. Rayson P. Wmatrix: a web-based corpus processing environment. 2009.
145. Glynn SM, Randolph ET, Garrick T, Lui A. A proof of concept trial of an online psychoeducational program for relatives of both veterans and civilians living with schizophrenia. *Psychiatric rehabilitation journal* 2010;**33**:278.
146. Rotondi A, Haas G, Anderson C, Newhill C, Spring M, Ganguli R*, et al.* A clinical trial to test the feasibility of a telehealth psychoeducational intervention for persons with schizophrenia and their families: Intervention and 3-month findings. *Rehabilitation psychology* 2005;**50**:325.
147. Cohen AN, Glynn SM, Murray-Swank AB, Barrio C, Fischer EP, McCutcheon SJ*, et al.* The family forum: directions for the implementation of family psychoeducation for severe mental illness. *Psychiatric Services* 2008;**59**:40-8.
148. Mohr DC, Cuijpers P, Lehman K. Supportive accountability: a model for providing human support to enhance adherence to eHealth interventions. *Journal of medical Internet research* 2011;**13**.
149. Baumeister H, Reichler L, Munzinger M, Lin J. The impact of guidance on Internet-based mental health interventions—A systematic review. *Internet Interventions* 2014;**1**:205-15.
150. Mental Health Taskforce. *The five year forward view for mental health*. London: NHS England; 2016.
151. NHS Digital. *Health Secretary: My tech vision will help build most advanced health and care system in the world*. Press release, 17 October 2018.
152. Developing and Evaluating Complex Interventions. Draft of updated guidance: Updated Guidance: Developing and Evaluating Complex Interventions [DRAFT FOR CONSULTATION]. In.
153. Mohr DC, Schueller SM, Riley WT, Brown CH, Cuijpers P, Duan N*, et al.* Trials of Intervention Principles: Evaluation Methods for Evolving Behavioral Intervention Technologies. *J Med Internet Res* 2015;**17**:e166. https://doi.org/10.2196/jmir.4391 last accessed 23 August 2019.
154. Perle JG, Langsam LC, Randel A, Lutchman S, Levine AB, Odland AP*, et al.* Attitudes toward psychological telehealth: Current and future clinical psychologists' opinions of Internet-based interventions. *Journal of clinical psychology* 2013;**69**:100-13.
155. Hollis C, Falconer CJ, Martin JL, Whittington C, Stockton S, Glazebrook C*, et al.* Annual Research Review: Digital health interventions for children and young people with mental health problems–a systematic and meta-review. *Journal of Child Psychology and Psychiatry* 2017;**58**:474-503.
156. Deci E, Ryan RM. *Intrinsic motivation and self-determination in human behavior*: Springer Science & Business Media; 1985.

Appendix 1 Changes to protocol and statistical analysis plan

Protocol

The REACT study protocol was published before the end of data collection and is available at https://bmjopen.bmj.com/content/7/7/e016965, last accessed 28 October 2019.

The following amendments and clarifications were made to the published protocol paper:

- We aimed to recruit 666 relatives. Ethical approval was granted to continue recruiting throughout the recruitment phase to ensure the we had an adequate sample size to test our primary and secondary hypotheses.
- The RAG was involved in the development of REACT and the recruitment strategy for the trial. However, it was not involved in the data analysis or interpretation, and has not yet been involved in dissemination. The challenges of PPI in an entirely online trial are described in *Chapter 7*.

Our protocol stated that one of the inclusion criteria was “a score” of ≥3 on the GHQ-28 item “I feel nervous and strung up all the time”. This should read eligibility requires a response on the 3rd (rather more than usual) or 4th (much more than usual) option. The items were not scored. If they had been, this would have been a score of 2 or more as the GHQ items are scored 0–3.

Protocol deviations

Full details of all the technical issues that arose during the trial are listed in *Report Supplementary Material File 1, Table 6-6*. *Table 54* summarises where this led to a protocol deviation and the number of participants affected in each arm. In addition, the University of Liverpool server which hosted the data collection was inaccessible from 9pm on 15 November 2017 until 8.45am on 16 November 2017 which would have interrupted use of REACT for all participants.

Table 54: Protocol deviations

Protocol specification	Potential deviation(s)	REACT (n=399)	RD (n=401)	Total (n=800)
Baseline demographic information	Missing baseline demographic information	31 (7.8%)	31 (7.7%)	62 (7.8%)
12-week outcome measures	Missing 12-week outcome measures	112 (28.1%)	94 (23.4%)	206 (25.8%)
24-week outcome measures	Missing 24-week outcome measures	107 (26.8%)	94 (23.4%)	201 (25.1%)
Email participants follow-up reminders or secondary randomisation allocation	Any inaccuracies associated with email contact with participants	26 (6.5%)	20 (5.0%)	46 (5.8%)
Access to intervention	Times when participants unable to access assigned intervention (e.g. during maintenance or bug-fixing)	3 (0.8%)	2 (0.5%)	5 (0.6%)
Web-usage data will be recorded	Protocol to measure web usage was only activated on 15 June 2017	51 (12.8%)	49 (12%)	100 (12.5%)

Statistical analysis plan

A full statistical analysis plan was published on 22 March 2017, before the start of data collection, and updated on 20 December 2017, before the end of data collection. Both versions are available at https://figshare.com/account/home#/projects/19975.

Updates were:

- Clarification that the time spent on the final webpage of a given login session for a participant would not be available; therefore this would imputed. If there was a

video on this webpage, video feedback data would allow calculation of the time spent on this page accurate to within 5 seconds. If there is no video on this page, it would be assumed that the time spent on this page is equal to the mean time that they have spent on all previous webpages to date.

- Clarified that p-values would be reported to four decimal places (changed from "three decimal places (unless<0.00001, in which the exact p-value will be reported up to a maximum of five decimal places, i.e. minimum reporting threshold of p<0.00001)").
- To maximise retention, participants who did not complete GHQs online were sent postal versions. When completion dates were missing for postal GHQ-28 questionnaires, we estimated them by calculating the midpoint between dates of sending and receiving the questionnaires. If not recorded, the date of receipt was imputed using the mean number of days between sending and receiving questionnaires for all postal GHQ-28 questionnaires with accurately recorded sending and receiving dates.
- An additional exploratory analysis was added to test the impact of "lurking" in the forums, as this became a topic of growing interest during the period of the study (see details below).

All analyses were done using SAS version 9.4 and Stata version 14.

Appendix 2 Study within a trial

We embedded a methodological study within the REACT trial on the impact of higher incentives and conditional rewards on recruitment and registered it as a study within a trial (SWAT) protocol, available at http://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/, last accessed 28 October 2019.

The strongest evidence exists for payment incentives as supporting effectiveness in increasing follow-up completion rates.[121, 123] However, the amount paid, and whether it is offered conditionally or unconditionally remain areas of uncertainty. We tested the relative effectiveness and costs associated with a lower value (£10) compared to a higher value (£20) of reward, and whether the reward was conditional or unconditional. We embedded this SWAT in the REACT randomised trial, for the 24-week follow-up.

At 24 weeks' follow-up, participants underwent a second randomisation to one of the following four intervention groups:

- Intervention 1: £10 conditional (dependent on completion of the follow-up questionnaire)
- Intervention 2: £10 unconditional (offered with the request and so available even without completion)
- Intervention 3: £20 conditional
- Intervention 4: £20 unconditional

To assess the impact of this second randomisation, the number (proportion) of participants providing 24-week follow-up data was calculated, presented and compared between groups using the χ^2 test. The independent impact of intervention group on retention rates over and above that of reward, was explored by including the intervention group along with the value of the reward (or un/conditional nature of the reward) as an explanatory variable in logistic regression.

Outcome

Table 55 shows the number of people completing GHQ-28 questionnaires at 24-week follow-up in each arm of the trial, and in each category of £10 versus £20 reward, and unconditional versus conditional reward. A chi-squared test showed that there was no significant benefit in offering people a higher level of reward, or a conditional reward.

Table 55: Retention rates at 24 weeks according to randomised value/nature of reward

	Completed GHQ		Did not complete GHQ	
	REACT	RD	REACT	RD
Overall	292	307	96	83
Value of the reward				
£10	148	146	51	44
£20	144	161	45	39
Nature of the reward				
Unconditional	145	158	41	45
Conditional	147	149	55	38

The independent impact of intervention group on retention rates was explored by including intervention group along with value of the reward (or un/conditional nature of the reward) as an explanatory variable in logistic regression. There was no significant impact of intervention group on retention when allowing for either the value of reward (odds ratio 0.825, 95% CI 0.590–1.154), or the nature of reward (odds ratio 0.825, 95% CI 0.590–1.154) (see ***Report Supplementary Material File 1****, Section 6.6.11*).

Discussion

Retention to online trials is always a challenge. We used several strategies to maximise retention, including multiple strategies for follow-up, which showed some success. However, our SWAT showed that, for this population, there was no effect from varying the amount of financial incentive to complete follow-up or from making the incentive conditional on completion. This finding was in contrast to previous studies, such as the “Sexunzipped” online trial, in which higher financial rewards (£20 versus £10) increased response rates for both online self-report data, and urine samples by post,[107] and might reflect differences in the populations, highlighting the importance of understanding the motivations of the population being recruited.[122] It is possible that older relatives in a caring role are more motivated to take part in the study by having access to the intervention and the opportunity to improve care for other relatives; whereas younger people recruited to a sexual health study may have less disposable income and be more motivated by the financial reward. However, this remains speculative and is an important area for future research, especially as misunderstanding motivation could result in retention strategies that in fact have negative impact on retention.[156]