TITLE

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)

REACT Trial Protocol Version 1.9 Dated 17.06.19

Study Sponsor:

Lancaster University
Research Support Office
Bowland Main
Balrigg Campus
Lancaster
LA1 4YT

Trial identifier: The REACT Trial

ISRCTN number: 72019945

Funder reference: HTA Project: 14/49/34

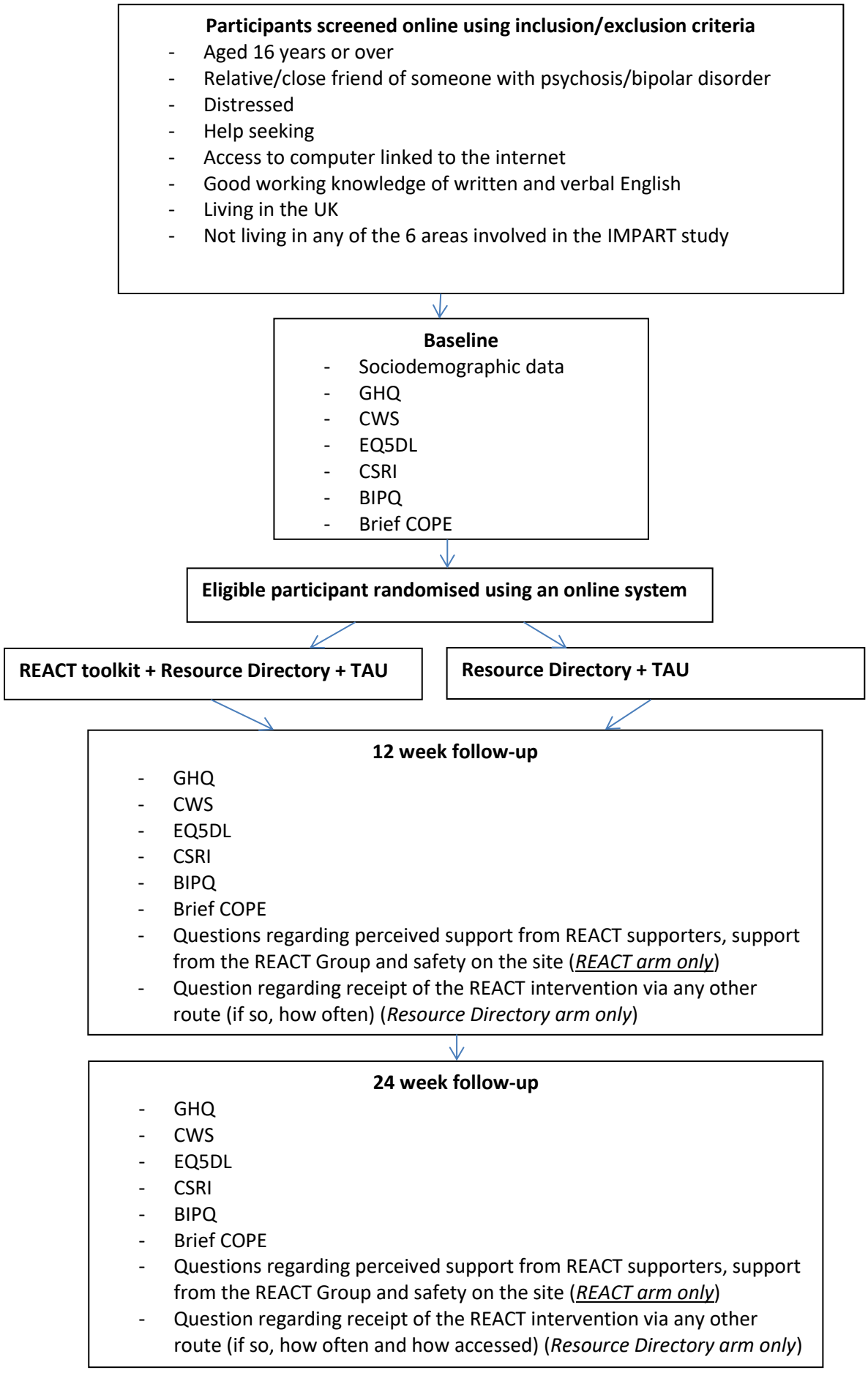
Sponsor reference: HRM7891

CONTENTS

TRIAL SUMMARY

Title	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)
Population	Minimum of 666 relatives of people with psychosis / bipolar disorder Inclusion criteria: • Aged 16 years or over • Relative/close friend of someone with psychosis/bipolar disorder • Distressed • Help seeking • Access to computer linked to the internet • Good working knowledge of written and verbal English Exclusion criteria: • Living outside the UK • Living in any of the 6 areas involved in the IMPART study
Study setting	Online trial, recruitment through NHS and non-NHS sites across the UK
Study duration	24 weeks per participant
Intervention	This trial will compare the clinical and cost effectiveness of 1. REACT intervention + Resource Directory + TAU 2. Resource Directory + TAU
Primary outcome	Relatives' distress at 24 weeks assessed using the General Health Questionnaire (GHQ-28).
Secondary outcomes	- Relatives' distress at 12 weeks assessed using the General Health Questionnaire (GHQ-28). - Relatives' wellbeing at 12 and 24 weeks assessed using the Carers' Well-Being and Support Measure (CWS) - Costs of delivering the intervention versus NHS and productivity cost savings in use of health services and paid work (adapted version of the CSRI) - Cost effectiveness – cost of significant unit change (defined as 3 point reduction) in primary outcome (GHQ-28) - Cost utility – marginal cost of any changes in marginal change in quality adjusted life years (QALYs) (making use of the EQ-5D-5L, as recommended by NICE)

TRIAL FLOW CHART



NOTE ON TERMINOLOGY

The term "relative" is used rather than "carer" as our PPI Group felt it better captured the complex nature of this relationship – which is often not just about caring. "Relative" includes family members or close friends.

SUMMARY OF RESEARCH

We will conduct a single blind 2 arm pragmatic online RCT to compare "REACT (including Resource Directory) +Treatment As Usual (TAU)" versus "Resource Directory +TAU ".

REACT is an online self-management intervention for relatives (defined as family or friends) of people with psychosis/BD, supported by Expert Relatives (REACT Supporters). The Resource Directory (RD) provides information on how to access all currently available online support. Eligibility criteria are as inclusive as possible and require relatives to be over 16, living in the UK, supporting someone with psychosis/BD, distressed, help seeking, and connected to the internet. Recruitment will be national through a wide range of routes including NHS services (starting with NHS Trusts in England), third sector organisations, and self-referral. Following online consent relatives will complete baseline measures prior to individual randomisation. Twelve and twenty four weeks after randomisation, relatives will be invited to repeat the measures and analysis will be a direct comparison under the intention to treat principle between the 2 arms, adjusting for baseline scores. The primary outcome is relatives' distress (GHQ-28) at 24 weeks and the secondary outcomes are relatives' distress (GHQ-28) at 12 weeks and carer well-being and support (CWS) at 12 and 24 weeks. An adapted version of the Client Service Receipt Inventory (CSRI) will assess treatment as usual, and inform a cost effectiveness analysis. Cost utility using quality adjusted life years will be assessed using the EQ-5D-5L. Towards the end of the study the resource directory arm will be able to view the content of the toolkit modules providing information to relatives.

Based on feasibility data, and accommodating for design adaptations, we estimate the mean difference between arms to be 5.0 units (s.d. 16.60). A conventional power calculation shows us that a total sample of 466 participants would give us 90% power to reject the null hypothesis ($p<.05$) when the true effect size is 5.0 units. Based on a review of online trials [1] we allow for a 30% dropout rate, although we describe a number of strategies we will employ to reduce this. We require a minimum of 666 participants for sufficient power. Our estimated total population size of relatives of people with psychosis/BD (total 750,000), regularly using the internet (76%), and showing significant levels of distress (approx. one third) is 190,000 relatives. Our recruitment strategy is broad, and over 18 months so, based on recruitment rates from other online trials, we are confident we can achieve this. Our team has extensive methodological experience in conducting large RCTs, specifically in mental health and in online trial methodology. We include a relative with expertise in using her lived experience to inform research, and clinical service development.

Our study allows us to also address important methodological questions about online trial design. An additional randomisation will occur at 24 week follow-up to determine the relative effectiveness and costs associated with a lower value (£10) compared to a higher value (£20) of reward, and conditional compared to unconditional reward, in improving retention to the REACT RCT.

INTRODUCTION

Rationale for the REACT trial

Relatives of people with psychosis/BD provide a large amount of vital unpaid care [2], but at huge personal cost in terms of high levels of distress, a significant practical/financial/emotional burden [3, 4], and increased use of healthcare services [5, 6]. The UK Government recognises the need to support relatives in a caring role [7] and NICE recommends that this is done by providing them with structured information and support [8, 9]. However, evidence shows very poor levels of implementation of interventions to support relatives [10-12]. A recent review of the quality of mental health services has identified improving support for relatives as a national priority [13].

REACT (Relatives' Education And Coping Toolkit) is an online supported self-management toolkit for relatives of people with psychosis/BD that has been developed to meet this need. REACT is recovery focussed, co-produced with relatives,

and already has feasibility evidence to support its use in Early Intervention Services [14] – see above. To date there have been only two small feasibility studies in the US which have evaluated online interventions for relatives of people with psychosis [15, 16] and none for BD. One pilot RCT of an online intervention specifically aimed at siblings of people with psychosis is currently underway in the UK [17]. All studies show online interventions are feasible and usability data from openly available sites such as the Australian based www.bipolarcaregivers.org show high traffic (this site reports approximately 5,000 visits per month [18]).

If effective, REACT could meet the support needs of relatives of people with psychosis / BD across the UK, who currently provide free informal care that saves the NHS over £1.2 billion per year [19, 20]. However, the impact of caring can also have a significant personal and financial cost as many seek health care services due to the impact of the caring role. If effective support can be offered, it has the potential to save the NHS a considerable amount of money in sustaining a vital support system and reducing health care needs. We will test the clinical and cost effectiveness of REACT to achieve this aim.

Evidence why now

The intervention is particularly timely as the new UK Care Act 2014 makes it a legal right for all carers to have an assessment of need and a support plan, whilst at the same time constraints on NHS service and local authority budgets means they will face difficulty in delivering these plans. REACT has the potential to meet the most commonly identified needs for information, guidance, and emotional support for relatives of people with severe mental health problems, at low cost. The intervention is also consistent with the recently revised NICE Guidelines for both psychosis (which cites the REACT feasibility study as evidence to support the recommendations) and BD, and a research recommendation from NICE to evaluate the "clinical and cost effectiveness of peer support interventions in people with psychosis and schizophrenia" [8, 9].

This online RCT design is particularly appropriate to evaluate an online intervention, and is timely in offering the opportunity to also address important methodological issues in online trial design. The internet offers many advantages when designing healthcare interventions including making them: of standardised quality; easy to access; flexible for users; inexpensive to deliver; easy to update; and adaptable to personal needs. Data from the Office for National Statistics show that in 2014, 22 million households (84%) had internet access, and 38 million people (76%) accessed the internet every day. Data from the US, suggests that 59% of all US adults have looked online for health related information in the past year, and use of web-based health resources is particularly high in carers [21]. Recent studies of web-based interventions for people with mental health problems have shown them to be a potentially effective way to address the challenge of increasing access [22], including for psychosis [23] and BD [24]. However, because of the ease of delivery, there is a danger that online interventions are developed and offered without rigorous evaluation of both potential benefits and harm they could cause. Online trials offer an ecologically valid way to evaluate online interventions, but this trial methodology is still in its infancy and presents some challenges [25]. This study offers a timely opportunity to address these issues, including identifying effective ways to maximise retention, which is arguably the greatest threat to the validity of findings.

Background

REACT Feasibility Study

This study provided preliminary evidence for the feasibility and effectiveness of REACT in a real world clinical setting. One hundred and three relatives from Early Intervention Service (EIS) teams across 3 NHS Trusts were individually randomised to receive TAU or REACT + TAU. Compared to similar studies recruiting families of people with psychotic disorders, relatives were keen to take part in the study; we over recruited, and follow-up rates at 24 weeks (83%) were high [26-28]. The estimated intervention effects (regression coefficient) indicate that relatives who received REACT showed a greater reduction in distress, negative experiences of caregiving, and concern about psychosis, along with increased positive experiences of caregiving, carer wellbeing and support, and perceived ability to cope (a high score indicates feeling less able to cope) compared to those in TAU. However, only reduction in distress, and increases in sense of being supported and perceived coping were statistically significant ($p<.05$). Qualitative feedback from relatives who used REACT was extremely positive. Relatives reported feeling less isolated and more supported as a result of REACT *"Oh, very reassuring. It [REACT 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'*.

Rationale for changes made since the feasibility study

Qualitative feedback from the feasibility study, input from our PPI group, and expertise within our clinical academic team have led us to make important adaptations to the intervention

1. We will make REACT suitable for a broader range of relatives, including those outside EIS and those supporting people with BD. Whilst the focus on developing targeted early interventions has been successful in improving outcomes, these improvements are not sustained when service users move from specialist EI Services into routine mental health services [29, 30]. Relatives are often managing worsening symptoms with less support. There is an urgent need to develop interventions which can be extended beyond EI Services, and to include a broader range of diagnoses. Much has been written questioning the validity of diagnosis in severe mental health problems, and specifically highlighting the overlap between psychosis and BD [31]. Many of the challenges of supporting someone with a serious mental health problem remain the same, though clearly some targeted information is also required. The modular structure of REACT offers us the opportunity to add additional modules specific to Bipolar Disorder and extend support to relatives supporting someone with this diagnosis.
2. REACT will be made available online directly to relatives. In the feasibility study REACT was available in paper and online form, and only through EIS teams. Due to the increase in general use of the internet to access healthcare interventions, the advantages of being able to update information as required, and the opportunity to add more interactive components and multimedia formats such as video clips, we have chosen to deliver REACT as an online intervention. We also make it available directly to all relatives as limiting access to relatives supported by EI services excludes some relatives with the greatest needs, including those supporting people who are reluctant to engage with services.
3. REACT will be supported by expert relatives (REACT Supporters) who will facilitate the website, moderate the REACT Group (a peer discussion board), contribute to an "Ask the Experts" function, and provide direct messaging contact where needed. Participants in our REACT feasibility study highlighted the wish to share their experiences with other relatives, and learn from the experiences of others. Given these changes, we are careful not to extrapolate too much from the feasibility study.

Given these adaptations, we use the findings from our feasibility study to inform this trial, but have reduced the estimated effect size to account for differences in the way in which REACT is supported and the population, inflated estimated attrition rates in line with data from online trials, and we have included an additional internal pilot.

Aim

To evaluate the clinical and cost effectiveness of an online peer supported self-management intervention for relatives of people with psychosis/BD: Relatives' Education And Coping Toolkit (REACT).

Objectives

The key objectives are:

i. To determine the clinical effectiveness of REACT on the following outcomes:
    a. Primary outcome is relatives' distress at 24 weeks assessed using the General Health Questionnaire (GHQ-28 [32]).
    b. Secondary outcomes are relatives' distress at 12 weeks (GHQ) and relatives' wellbeing at 12 and 24 weeks assessed using the Carers' Well-Being and Support Measure (CWS [33])

ii. To determine the cost effectiveness of REACT in reducing distress for relatives using the following measures:
    a. Costs of delivering the intervention versus NHS and productivity cost savings in use of health services and paid work (adapted version of the CSRI [34])
    b. Cost effectiveness – cost of significant unit change (defined as 3 point reduction) in primary outcome (GHQ-28)
    c. Cost utility – marginal cost of any changes in marginal change in quality adjusted life years (QALYs) (making use of the EQ-5D-5L [35], as recommended by NICE)

POTENTIAL RISKS AND BENEFITS

Potential risks and burden to participants

The most likely risk to participants in this trial is increased distress (note that participants must be distressed in order to meet inclusion criteria). If a participant experiences increased distress during the study they are encouraged to contact the REACT Supporter. The REACT team also includes an Expert Relative, a GP, a Consultant Psychiatrist and a Consultant Clinical Psychologists who will supervise the REACT Supporters and offer support if needed. The PIS and Resource Directory will also provide participants with contact details of appropriate support services should they need additional support or information.

Risks to privacy will be protected by ensuring the site is a closed site, available only to relatives taking part in the trial and linking posts to self-selected pseudonyms to ensure confidentiality, anonymity and participant safety.

Potential benefits to participants

In our experience of conducting similar research it is likely that participants will value the opportunity to talk about and explore their personal experiences and to make an important and valued contribution the development of an intervention to improve outcomes for relatives of people with psychosis or bipolar disorder.

Relatives in both arms of the trial will receive the Resource Directory. After the final participant's follow-up is complete the resource directory arm will be able to view the content of the toolkit modules providing information to relatives (without peer support through the REACT Group forum or direct support online from the REACT Supporters).We hope that participants will develop a better understanding of bipolar disorder and psychosis and potential avenues for support as a relative of someone with mental health problems.

Participants will be given high-street voucher(s) in appreciation of their contribution to this research.

METHODS

Trial Design - Online methodology

The trial will be primarily online. Online trials are particularly suited to evaluating self-management interventions using self-report measures [1]. Our team have considerable expertise in developing and evaluating online interventions and we draw on this experience and on relevant literature in designing this study. Advantages of online trial design include the potential: to reach a greater number and range of participants who may be underrepresented in face to face trials, and are more representative of the population likely to use an online intervention; to recruit more people over a shorter timeframe as many people can register and be assessed simultaneously; for secure randomisation and data entry without need for complex blinding protocols; and for a much cheaper trial due to fewer staff required [25]. There are also important disadvantages regarding identity checking at recruitment, and retention which our design attempts to overcome (see Participant Timeline section). Some of our strategies require the use of email / telephone which is why we describe our trial as *primarily* online [1]. All of these strategies will be developed with our Relatives Advisory Group (RAG) to ensure they are carried out appropriately and sensitively.

Recruitment and retention

Recruitment and retention feasibility

In our feasibility study, we recruited 103 relatives from a potential pool of 914 relatives accessing support from the participating EI teams over the recruitment period. Therefore our recruitment rate was 1 relative out of every 9 available. In England alone, there are estimated to be over 1.5 million people in the UK in 2014 with psychosis/BD [19]. If we assume that: at least half have contact with an adult relative; relatives broadly reflect the general population in internet use (estimated as 76% daily users http://media.ofcom.org.uk/facts/); and that more than one third will be experiencing clinically significant levels of distress and burden for which they are likely to seek help [36, 37-41], we have an estimated total population of 1,500,000 /2 *.76 / 3 = 190,000 just in England, and obviously more UK wide. Even excluding relatives linked to the 6 NHS Trusts excluded for the IMPART study, this is a large population for which to recruit our target sample.

Relatives seek support through NHS services, charities, and online searches. Our recruitment strategy will target all of these options. Therefore we need to recruit 1 relative out of every 285 relatives available. Our recruitment period

spans months 7-24. We need a minimum of 666 relatives for sufficient power, an average rate of 37 relatives per month. Our online recruitment strategy is very different from our feasibility study (which recruited locally face to face in EI teams in 3 NHS Trusts in North West England) and therefore we also draw on published data from online trials to inform our estimates.

A recent systematic review of 50 internet based RCTs reported recruitment rates with a median=231, IQR=75–594 per month [1]. Those with higher recruitment rates employed strategies that we propose in our design including: building in a "lead-in" period during which people can register interest in the trial; using online recruitment strategies to target those already using the internet to seek help; and paying participants. Payment for participation is common practice in mental health trials, and more than doubles the odds of completion of online survey data [42]. There is no evidence it has a detrimental effect on the quality of data.

Our previous work demonstrates our team is able to achieve recruitment rates at the top end of this range. For example, one of our recent trials was able to recruit over 2000 adults into an online sexual health intervention trial in just five months, primarily through an advertisement on Facebook [43]. Referrals coming through NHS routes, and through carer networks / charities tend to be slower as they often depend on communication through third party informants. No other study has tried to recruit our target population using the range of strategies we propose, making it very difficult to estimate the pattern of recruitment over time. Therefore, we set our criteria using an average monthly rate of over 37 relatives per month over 18 months recruitment period.

Differential attrition is a potential threat to internal validity of the trial, but recent evidence suggests rates may be lower than anticipated, even in health behaviour change interventions [44, 45]. In our online sexual health trial comparing an interactive intervention website with an information only site, we were able to achieve 77.2% follow-up of 2036 young people, with no differential attrition [43]. A further trial assessing "Health on the Web" has achieved 80% follow-up with no differential dropout [46]. Ensuring participants understand the importance of completing the follow-up measures even if they stop using the intervention, may help reduce differences [47]. Our feasibility study for REACT showed no significant differential dropout between arms (REACT arm n = 51, unable to contact n=4, withdrew n = 6: TAU n = 52, unable to contact n = 3, withdrew n = 4). In order to decrease attrition rates in the control arm we will allow the resource directory arm to view the content of the toolkit modules providing information to relatives after the final follow-up.

Recruitment process

To broaden recruitment as widely as possible, we will develop a social media strategy to promote our study using Twitter, Facebook, and blogging. We will build on links with national carer networks and work with national organisations such as MIND, Carers Trust, Rethink Mental Illness, Carers UK, SANE, Bipolar UK, and NHS Choices to create links to the study on their websites, and promote the study to their members through newsletters, local groups, and national conferences. These organisations will all be listed in the Resource Directory in our trial. We will work with the national Science Media Centre and our own University press offices to engage with the news media where possible including local and national radio, BBC online, and Health Correspondents of national newspapers. We will recruit through relevant NHS trusts and Clinical Commissioning Groups (CCGs), working closely with the Clinical Research Network (CRN) to ensure information about the study is made widely available. The CRN have agreed to support database searches in GP practices, and research nurses to recruit within secondary care Mental Health Trusts. Relatives living in the UK will be eligible to take part in the trial (also dependant on other criteria). To maximise efficiency of resources within NHS services we plan to initially focus our recruitment in England and then move into Wales, Scotland Northern Ireland depending on recruitment numbers.

We will attempt to create interest in the study from the very beginning. A study website informing people about the aims of the study, the REACT intervention and the eligibility criteria will be set 6 months before the start of randomisation. Relatives will be invited to register their interest and leave an email contact. When the recruitment phase starts, we will contact these relatives and invite them to complete the online consent process. This "lead in" period has been used successfully in a previous online trial [24] and can lead to increased retention rates as those who still wish to take part respond to the email, demonstrating a greater commitment to the trial than those who don't respond.

As part of this trial, we aim to determine the effectiveness of targeted recruitment strategies to increase recruitment from under-represented groups to the REACT RCT. This objective will be met using descriptive methods, and our

comparator will be published data from previous trials of interventions for carers of patients with psychosis [48-50]. The intervention will be multiple, different, targeted recruitment strategies, designed in partnership with Patient Public Involvement (PPI) representatives from our target groups. We are fortunate that our existing PPI panel is already diverse, and we will specifically recruit additional members from our target groups, e.g. BME, young people, men. Having recruited a diverse PPI panel, we will work with them to identify appropriate routes for recruitment to the trial. For example, for younger people, we may use banner advertising on online chatroom websites and social media websites such as Facebook and Instagram, advertising in local newspapers in high BME urban areas, distributing flyers or posters distributed at places the target group is likely to frequent, such as colleges or community centres. Similar strategies have been successfully used to recruit young people and BME groups to web-based sexual health studies, [13, 16, 22] but have not so far been used to recruit for trials of online support interventions for relatives and friends of people with psychosis and BD. Older people from BME groups may respond better to community-based recruitment e.g. through voluntary groups [26]. We will monitor the success of our various strategies by asking potential participants who access the REACT trial website to indicate on a drop-down menu how they heard about the trial. This will occur at registration and again for those who consent into the trial. The primary interest will be the overall demographic characteristics of the trial participants. Secondary outcomes will be the relative characteristics of participants by route of entry, with particular attention paid to routes that generate a high yield of BME participants, younger people, and men.

Retention process

The biggest challenge to online trials is dropout from the intervention and/or follow-up assessments. Consistent with evidence based recommendations we have built in several design features to address this challenge [47, 51]. We have feasibility tested the intervention and shown the content to be acceptable and positively received by relatives [14, 52]. Our current work in online interventions has highlighted "out of sight, out of mind" as a common problem and participants have suggested reminder emails may be helpful, with the option to opt out of these if desired. Flexibility in amount and timing of use of the site is an important aspect of the intervention which we do not wish to impinge on. Dropout from follow-up is the biggest challenge to the validity and power of the trial, and rates ranging from 8%-83% (mean = 36%) have been reported for online trials, though loss is generally lower in those with alternative follow-up strategies such as described below (mean 30% loss to follow-up) [1, 43]. To maximise retention we will: only randomise participants once they have completed assessment measures at baseline; include detailed explanations in our recruitment materials to explain to participants why data completion at follow-up is so important; require email, telephone and postal contact details at registration so we have multiple methods of contact for follow-up; send participants up to 3 automated email reminders at 5 day intervals, followed by telephone and/or postal requests (and the opportunity to complete the primary outcome measure over the phone/by post); and pay participants a token of gratitude of a high-street voucher(s) for completing the measures at each time point. Payment incentive has the strongest evidence to support its effectiveness in increasing completion rates [51, 42]. However, the amount of payment, and whether it is offered conditionally or unconditionally remains an interesting methodological question which we can answer in this trial. We will test the relative effectiveness and costs associated with a lower value (£10) compared to a higher value (£20) of reward, and conditional compared to unconditional reward, in improving retention to the REACT RCT as part of a sub-study, but only at the 24 week FU time point. To increase retention in the control arm we will allow the resource directory arm to view the content of the toolkit modules providing information to relatives after the final follow-up. Finally we have inflated our sample size estimate to allow for 30% DO rate, based on mean rates in previous online trials [1].

Internal pilot

This trial differs from our feasibility study in significant ways, and therefore we have designed an internal pilot of our recruitment and retention strategies. We will monitor recruitment and retention rates on a monthly basis. The accrual rate into online trials is very different to conventional face to face trials, which often start slowly and increase as clinical sites are setup. Recruitment online is often very fast in response to initiation of specific recruitment strategies. Given that we are using both strategies, and there is no data on which to estimate accrual rates for this population using our range of recruitment strategies, we set our criteria using an average monthly rate of over 37 relatives per month over 18 months recruitment period.

After 4 months we have set a target of at least 148 relatives. If we are behind this, we will review pathways by which people have found the study site and identify additional ways to promote the study to relatives.

After 9 months we have set our STOP-GO-AMEND criteria for success of the internal pilot.

GO - If we achieve 100% or above of our anticipated recruitment at 9 months (333+ participants), we continue as planned

AMEND - If we achieve 80-100% of our anticipated recruitment (267 - 333 participants), we will review and amend our recruitment strategies in collaboration with the TSC. The focus will be on identifying strategies that have led to spikes in recruitment to create more related opportunities. The monthly rate of recruitment will continue to be reviewed to see if the current recruitment rate would lead to the full sample being recruited.

STOP - If we recruit below 80% of the target for 9 months (<267 relatives), we will consider with the NIHR HTA whether the trial should be closed.

The sample of participants who have completed 24 week follow up at this stage (9 months into the trial) will be used to estimate the standard deviation (SD) of GHQ scores. If the SD is higher than the estimated 16.6 units, the required sample size will be recalculated and recruitment targets increased accordingly. If the SD is lower, consistent with good practice the sample size will remain unchanged.

Retention (in terms of follow up of the primary outcome GHQ-28 at 24 weeks) will also be assessed as part of the internal pilot after 9 months from trial opening. If follow up for the primary outcome at 24 weeks is less than the anticipated 70% rate, the recruitment target will be inflated to reflect the updated follow up rate. This will be necessary in order to ensure that 466 patients will ultimately provide 24 week primary outcome data achieve, thus providing sufficient power to assess change in primary outcome among those patients who provide follow up data at 24 weeks.

Although online trials offer the potential for significant efficiency savings to research funders, the methodology is relatively new and more evidence is needed regarding accrual rates, and strategies to solve low recruitment and retention rates. Given that continuing the trial is a relatively cheap option (compared to a face to face trial), it may be that this offers an opportunity to investigate the causes of low recruitment and high dropout in online trials. This understanding is vital to improve the success of future trials and cannot be achieved if the trial is terminated. The TSC will be asked to take this into consideration when reviewing the results from the internal pilot described above, though ultimately this decision will be made by HTA.

Study setting and target population

This study will take place online with a minimum of 666 relatives of people with psychosis or BD living in the UK (confirmed via valid postal address). Relatives are defined as family, partners or close friends. The online site will explain that the study is designed to test the effectiveness of an intervention for relatives of people with particular kinds of difficulties. People visiting the site will be asked to complete a short checklist to indicate whether they meet the inclusion criteria listed below.

Inclusion / exclusion criteria

Inclusion:

1. **Aged 16 years or over.**

The toolkit is written for adults. We acknowledge the very important role that young carers play in supporting people with psychosis. However, we feel that the toolkit would need to be adapted significantly to meet the needs of this group and therefore we have excluded them for the purposes of this study.

2. **A relative/close friend providing regular support for someone with a mental health problem.**

Any attempts to specify the amount of time required to meet this definition was very arbitrary as support is delivered in many different ways and the importance of it to the receiver is not defined by frequency. For example, someone

may have a close friend who they spend a week with every few months which provides substantial support but would not meet the criteria. Therefore we have specified participants should be a relative / close friend providing regular support – and have asked participants to tell us the nature and frequency of the support, and how close they perceive the relationship to be. We can then describe the participants in detail, and explore whether the type of relationship impacts on use and effectiveness of the intervention.

3. Their relative has psychosis or BD.

Relatives will be asked to indicate which of a list of terms have been used to describe their relatives' mental health problems, or whether any of the descriptions apply. Each term will be linked to a brief description of the characteristic symptoms. The list will include psychosis / schizophrenia / schizophreniform disorder / psychotic disorder / schizoaffective disorder / bipolar disorder / manic depression / cyclothymia.

4. Distressed (according to GHQ item score)

The intervention is designed to reduce distress associated with supporting someone with a mental health problem. Potential participants will be asked to indicate the extent to which they feel distressed by their relatives' mental health problems using a single item question from the GHQ which showed highest item-total score correlation in our feasibility data. Those showing no distress will be excluded as they are unlikely to be motivated to use the site, or show any reduction in distress.

5. Help-seeking

Potential participants will be asked if they would like to receive help with their distress through an online toolkit. A brief description will be provided. Only those confirming they would like to try this kind of intervention will be eligible.

6. Regular access to a computer which is connected to the internet.

7. A good working knowledge of written and spoken English language.

Exclusion:

1. Living outside the UK

Relatives will be required to be living in the UK and provide a UK address. Whilst internet interventions have the potential to broaden access across the world, this is limited by the applicability of the content. REACT is currently available in English, and much of the content focuses on understanding UK health services (including variation between countries within the UK). Adaptations could be made for other countries in the future but not for the purposes of this trial.

3. Living within any of the 6 areas involved in the IMPART study

Six NHS Trusts are taking part in a parallel study investigating the implementation of the REACT intervention as part of routine clinical services. The study is called IMPART (IMPlementation of A Relatives' Toolkit) and is funded by the NIHR HS&DR stream and is a small iterative case study. Relatives who are receiving clinical support from services in the geographical areas covered by participating Trusts will be excluded from the trial as they may receive the intervention through their service. Therefore at registration relatives will be asked to provide the first 5 digits of their service user relative's postcode. It will be made clear that this information is not stored. If they do not know their service user relative's postcode they will be provided with the name of the NHS Trusts taking part in IMPART. They will be asked if their relative lives in this area, or they recognise the name of the Trust as the provider of care. Those relatives who are in areas taking part in IMPART will be excluded from REACT and directed to a separate website which will explain why they are not eligible and what is happening in the IMPART study. As a final check that contamination has not occurred, relatives in both arm of the REACT trial will be asked at 6 month follow-up to indicate whether or not they have received REACT through any other route outside the trial,.

NB: We have chosen not to require that relatives live with the person with mental health problems, or a minimum amount of contact. Some relatives are very distressed because this relationship has broken down to the extent there is currently no

contact. These relatives need support and REACT is an appropriate intervention for them. Given that these relatives often face the most difficulties getting help from mental health services, this may be the only kind of support they are able to access.

Participant withdrawal

Patients are free to withdraw consent at any time without providing a reason, although we will ask participants if they would like to tell us why they have withdrawn so that we can take this into consideration in future studies. Participants will be given the option to withdraw from providing follow-up questionnaire data and/or use of the website. It will be made clear in the PIS that any questionnaire data provided up until this point can only be removed if requested within 2 weeks of data collection. Web usage data, online forum posts and direct messages cannot be cannot be retracted and may be used in analysis. Participants who choose to withdraw from *both* the follow-ups and use of the website will have their login details deleted and will no longer be able to access the website.

Participant timeline

1. Expression of interest

A study website informing people about the aims of the study and the REACT intervention will be set up at the very beginning of the study, 6 months before the start of randomisation. This will provide a brief summary of the aims of the REACT intervention and the trial. Relatives will be informed of the eligibility criteria of the study and invited to register their interest by leaving their email address. When the recruitment phase starts, we will contact these relatives and invite them to complete the online consent process.

2. Screening and online informed consent

Relatives who are interested will first be assessed for eligibility based on the location of the support services they receive. This will be done by asking if their relative with mental health problems lives in one of the postcodes of the six participating Trusts. Relatives who tick yes to this question will be redirected to the IMPART study site and will not be eligible for the REACT trial. The IMPART study assess the implementation of REACT through NHS Early Intervention services. All relatives not redirected to IMPART will be directed to an online Participant Information Sheet (PIS). They will indicate by checking a series of statements that they have read this, meet the eligibility criteria (checklist), and give consent to take part. In doing so, they will be required to provide multiple forms of contact including email, mobile / landline, and postal address. The PIS will include a detailed description of the study process, including any potential risks to taking part. It will also emphasise the following key points

1- The reason why it is important that they agree to complete the assessments at follow-up
2- Why the identity checks are carried out (see below)
3- The importance of not sharing access to the toolkit with anyone outside the household.

3. Identity check

A reliable way to identify participants to prevent multiple registrations, and invalid entries, and to ensure the same person is completing data entry at each time point is essential. We will do this by checking for any overlap in registered details (postal address/telephone number/email), and by asking for mobile phone number at consent. Verification of identity will be checked by sending a code by text message to the phone which is then input by the relative into the website. The same process will be used at follow-up assessments. Whilst it is fairly easy to generate multiple email accounts, mobile phone numbers are more reliable unique identifiers. If any of the 7% of the UK population without a mobile phone take part, or there are any concerns identified through matching registration details, we will ask for a landline/postal address and verify identity using a code delivered by telephone/post. We will use post codes to check all participants are living in the UK. We will request date of birth and gender at baseline and also at 12 and 24 week follow-up, on the assumption that, if those facts were falsified at baseline, participants would be unlikely to accurately recall them 12 and 24 weeks later. Similar strategies have been used successfully in previous trials [56]

4. Baseline

Following identity verification, relatives will be asked to complete all the baseline measures and demographic information online (see Assessment section).

NB: All measures assess outcomes for relatives. No data are collected that would require consent from service users, and which could therefore exclude relatives where service users refuse to consent. Many previous studies evaluating family interventions that require both service user and relatives' participation struggle to recruit sufficient dyads because they have to exclude relatives in families where the service user is refusing to take part. These are often the relatives most in need of support. A key strength of REACT is that it is available to all relatives who wish to use it.

5. Randomisation

Following baseline assessments, participants who fulfil the eligibility criteria and have given online consent will be randomised to "REACT (including RD) + TAU" versus "RD+TAU" by the Clinical Trials Unit (CTU). We will use variable block randomisation in which the unit of randomisation is the relative. We are interested in exploring the effect modification of several variables including diagnosis of service user, length of time since problems started, relationship to person with mental health problem, whether or not they live with the person, and whether or not they are receiving support from NHS services. However, there is no convincing evidence that any of these will have an effect and therefore we have not stratified randomisation. Following assignment to REACT+TAU or RD+TAU the Trial Manager (TM) will be blind.

All data are self-report and imputed directly online by participants. Data will be uploaded directly to a data base securely stored at the CTU. The REACT Supporters will be aware of who is taking part in the study, and the TM may become unblinded during telephone conversations with participants who need to be contacted for follow-up data. However, neither will be involved in any assessments, data entry, or analysis so this will not influence outcome.

We have included an additional randomisation at 24 week follow-up. The aim is to determine the relative effectiveness and costs associated with a lower value (£10) compared to a higher value (£20) of reward, and conditional compared to unconditional reward, in improving retention to the REACT RCT. This sub-study will use a randomised factorial design, with participants randomised to either £10 or £20 reward and to the reward being conditional (i.e. dependent on completion of follow-up questionnaires) or unconditional (i.e. offered with the initial request for follow-up data). The reward will be a shopping voucher (either Amazon or High Street vouchers, which can be used at multiple stores – final decision to be worked out with our PPI group). To minimise costs, and maximise benefit to the REACT RCT, we have opted to offer these different incentives at the primary outcome point (24 weeks). We did consider randomising at the three month point and using these data to inform follow up at 24 weeks, but this is not feasible as the recruitment phase is staged over 18 months. The primary outcome will be retention rate (completion of the primary outcome measure). Subgroup analysis will be undertaken to determine whether results vary by demographic characteristics (e.g. age, gender, ethnicity).

6. REACT intervention vs Resource Directory

Participants randomised to REACT will receive a link to the REACT intervention site and login details. They will be invited to change their login details to something personally memorable at the first visit. Contamination can occur when the intervention is shared with other people who could be taking part in the trial. Participants allocated to the REACT intervention will receive additional information prior to accessing the intervention to explain why it is important not to share their log-in details with anyone else. We will encourage relatives to share knowledge from REACT with immediate members of the family living in the same household, including the service user if they are interested. This shared knowledge can indirectly impact on relatives' distress and is a valid part of the intervention. However, we will explain why it is essential only one member of the family and/or household takes part in the study, and will chase up any indicators that this may not be the case (matching registration details).

Over the next 24 weeks, they will receive email/text reminders to visit the site which they can opt out of if they wish. These reminders are part of the intervention and as such they will be designed to look like the intervention site, and clearly different in style/tone/sender from emails sent regarding the trial process and data collection. See 'The Intervention' section for more details about the website.

Participants randomised to the control arm will receive a link to a copy of the Resource Directory (see 'Resource Directory' section below for more detail).

7. Follow-up assessments and incentives

Twelve and twenty four weeks after randomisation, all participants will be sent an email to remind them to log on to the site to complete the follow-up measures. This reminder will reiterate the reasons why this follow-up data is important. It will also give the option for people to choose not to complete the measures, and will ask them to provide a reason if possible. After completing the 12 week follow-up measures, participants will be sent a thank you email with a £10 Amazon voucher. At 24 week follow-up participants randomised to either £10 or £20 reward and to the reward being conditional (i.e. dependent on completion of follow-up questionnaires) or unconditional (i.e. offered with the initial request for follow-up data). Non-responders will receive up to 3 automated emails sent at 5 day intervals, followed by phone/post contact (and the opportunity to complete the primary outcome measure over the phone/by post).

The intervention - REACT (Relatives' Education And Coping Toolkit)

The REACT intervention is a facilitated online intervention for relatives of people with psychosis/BD.

Validation of the intervention content

The development of REACT was informed by:

- a systematic review of interventions reporting on outcomes for relatives of people with psychosis [44],
- the NICE Guidelines for BD [9] and psychosis[8];
- a series of focus groups with relatives [53];
- clinical and personal expertise within the research team (consisting of relatives, clinicians, and academics);
- extensive feedback from service users and relatives throughout the development process.

Updated content of the intervention

a) Modules

The toolkit is comprehensive and modular in format so that the content is divided into manageable sections which can be used flexibly depending on the individual needs of the relative. These include: Introduction to REACT; What is Psychosis?; Managing Positive Symptoms; Managing Negative Symptoms; Dealing with Crises; Dealing with Difficult Behaviour; Managing Stress – Thinking Differently; Managing Stress – Doing Things Differently; Understanding Mental Health Services (how to get the help you need); Treatment Options; The Future; Resource Directory; Jargon Buster. Although the information is by necessity standardised, the toolkit is designed to help relatives tailor this information to make it more specific to their family. Case examples, activity tasks (including quizzes), and self-assessment tasks are used extensively to aid illustration.

In response to feedback from our feasibility study additional modules currently being added include: What is Bipolar Disorder? Managing Changes in Mood. The BD modules are currently under development with input from the BD Advisory Panel at the Spectrum Centre, Lancaster University, and will be piloted and finalised before the start of the study.

b) REACT Group (Discussion Board) and "Ask the Experts"

To enhance peer support and interactivity we are also developing the REACT Group (a peer support discussion board) and an "Ask the Experts" facility, which will feed into a "Frequently Asked Questions" information page.

The REACT Supporters

The REACT website will be facilitated by "REACT Supporters" with experience of caring for someone with psychosis or BD. Specifically, they will: 1) respond to technical queries about how to use the site, and guide users to get the most out of the modules available; 2) moderate the REACT Group discussion board and input to threads to ensure the site is active; and 3) respond to the "Ask the Experts" questions as part of the multidisciplinary research team. Users will be able to message the REACT Supporter directly, and will be directed to relevant parts of the site as appropriate as well as encouraged to draw on the peer support from other relatives available through the REACT Group. The site will be a closed site, available only to relatives taking part in the trial. Posts will be linked to self-selected pseudonyms to ensure confidentiality, anonymity and participant safety.

It is not feasible at this stage to translate the toolkit into other languages, however the REACT Supporters will be trained in how to offer the REACT toolkit and support in a culturally sensitive way, taking into consideration different explanatory models for mental health, individualistic versus collectivistic orientations, and issues of conceptual equivalence across cultures. Regular clinical supervision for the REACT Supporters and moderation of the REACT Group will be used to manage challenges arising and risk issues. The toolkit does not offer crisis support but does include a module on "Dealing with Crises" and will direct relatives to appropriate clinical services. See 'Ethical Considerations' for more information about managing risk.

Resource Directory

The control group will receive a Resource Directory which lists details of how to access the full range of support currently available to relatives. The Directory will include websites of the main national organisations including MIND, Carers Trust, Rethink Mental Illness, Carers UK, SANE, Bipolar UK, Samaritans, and NHS Choices. It will also explain how to access support through NHS health services. This information is included in the resource directory which will be available within the REACT site and to control participants via a separate login. This ensures that all relatives in the trial have access to current best practice. We are therefore testing the clinical and cost effectiveness of adding REACT to current best practice.

After the final follow-up the resource directory arm will be able to view the content of the toolkit modules providing information to relatives (without peer support through the REACT Group forum or direct support online from the REACT Supporters).

Treatment as Usual (both arms of the trial)

We will assess current treatment using our adapted CSRI which will include contact with health, social and voluntary sector services. We will not make any direct changes to current treatment as part of the trial. Relatives will be informed that taking part in the trial will not affect any support or services that they, or their relative, receive.

Recently revised NICE guidelines for psychosis and for BD recommend that all relatives receive an assessment of their own needs (by mental health services) and a care plan to meet these needs which is reviewed annually. They should all receive written and verbal information in an accessible format about: diagnosis and management of psychosis and schizophrenia; positive outcomes and recovery; types of support for carers; the roles of teams and services; getting help in a crisis. They should also be offered support where needed. Both our REACT development work [53] and the feasibility trial [14] are cited in the guideline to support this recommendation. However, the extent to which these recommendations are implemented in clinical services is poor. This study compares the addition to treatment as usual of a standardised way to deliver this intervention via the REACT website (including Resource Directory), with treatment as usual plus a Resource Directory which signposts relatives to currently available support in the NHS and voluntary sector.

Assessments

Validity of measures delivered over the internet is a potential problem in online trials, but in this study we use measures which are already designed as self-report checklist responses. The only exception is the CSRI which is more commonly used face to face. However, the inventory is designed to be adapted to suit the needs of each study and we have successfully developed an online version for a trial of an online relapse prevention intervention in BD which is currently underway [54]. We will follow the same process, liaising with our RAG to specify clearly the potential NHS and work related costs which need to be included in the online inventory. Mental health research predominantly relies on self-report in all settings and there is no evidence to suggest that this is less reliable when conducted online compared to face to face.

Outcome measures

The outcomes have been selected for being well developed, standardised measures with good psychometric properties and which assess outcomes identified as important by relatives. This is important as previous work shows that people are more likely to complete multi-item measures in online trials if they feel they are personally relevant [55]. Our decisions about which measures to use were informed by previous trials, our clinical expertise and the NIHR SDO funded review of carer outcome measures [56]. We have also taken into account sensitivity to change in previous intervention

studies and our own REACT feasibility study. There are no CORE measures recommended for assessing our outcomes in relatives of people with psychosis. Finally, we have limited the measures as far as possible to ensure that they do not place undue burden on participants. We estimated time needed to complete measures at each time point will be approximately 30 minutes.

Assessments of distress (GHQ-28) and carers' wellbeing and support (CWS) will be made online at baseline (prior to randomisation) and 12 and 24 weeks after randomisation to assess clinical effectiveness, and measures of quality of life (EQ-5D-5L) and service use (CSRI) at the same time points will assess cost effectiveness.

1. *The General Health Questionnaire (GHQ)* [32] is chosen as the primary outcome because it has been used extensively in previous research and shown to have significant associations with important functional outcomes including: more frequent GP visits [57]; increased absence from work [58]; claiming incapacity benefits up to 2 years hence [59]; and severe adverse health outcomes, including deaths [60].
2. *The Carer Well-Being and Support Questionnaire (CWS)* [33] is designed to cover all aspects of the carer's experience of caring for someone with a serious mental health problem including relationships, roles, financial concerns, physical/ emotional health, stigma, worries about safety, their satisfaction with support offered and ease of obtaining information. It is a self-report tool which can be used online.
3. *The Client Service Receipt Inventory* (*CSRI)* [19] collects retrospective information about the interviewee's use of health and social care services, accommodation and living situations, income, employment and benefits in the preceding 12 weeks. We will also include use of other free interventions including relatives support groups and websites, so we can accurately describe TAU. Costs will include the direct costs of offering and supporting the intervention in the REACT arm, and health care contacts, medications prescribed, and time off (or ability to) work for the relative in both arms. Unpaid informal care by the relatives will be measured by asking relatives how many hours of care they provide supporting the person with mental health problems, and costing these on an hourly basis based on national mean age and gender specific wage rates available from the Office for National Statistics. Days lost by relatives from work, and reduced hours while at work due to the caring role will also be recorded and costed as part of the CSRI. Wherever possible, unit costs for medication and health care resources will be taken from national sources such as the British National Formulary and the PSSRU Costs of Health and Social Care. Adaptations to the CSRI will be based on feedback from the Relatives Advisory Group and made to ensure that the structure and wording of items is clear and no important areas are missing.
4. *The EQ-5D-5L* [35] will be used to assess quality of life from which Quality Adjusted Life Years (QALYs) can be derived. The EQ-5D-5L is an established, standardised health-related quality of life instrument used extensively in clinical studies. It comprises five items covering the domains of mobility, self-care, usual activity, pain/discomfort and anxiety/depression.

Sociodemographic measures

1. *Sociodemographic data* will be collected at baseline and updated at follow-up as appropriate.

Mediator measures (completed at 0, 12, 24 weeks)

To test the proposed mechanism of change for the REACT intervention we will include a measure of understanding of psychosis/bipolar disorder; insight into the service users' experiences; and measure of perceived ability to cope:

1. *The Brief Illness Perception Questionnaire (BIPQ*): a 15-item likert scale assessing dimensions of beliefs consistent with the Self-Regulation Model.
2. *Single item added to the BIPQ* to assess perceived coping: How able do you feel to cope with your relatives' mental health problem? (0=not at all able to cope; 10 = completely able to cope)
3. *Brief COPE*: this is a widely used measure of actual coping styles.

Relatives' experiences of the intervention

These items are based on previous published work investigating perceived safety and satisfaction with online interventions [70]. Only the REACT arm will receive these questions at 12 and 24 weeks post randomisation:

1. To assess whether relatives feel supported by the REACT supporters: 'I always feel supported by the REACT Supporters (strongly disagree, disagree, agree, strongly agree)

2. To assess whether relatives feel supported by the REACT Group: 'I always feel supported by the REACT GROUP (strongly disagree, disagree, agree, strongly agree)
3. To assess whether relatives feel the site is safe: 'I always feel the REACT site was a safe and confidential environment (strongly disagree, disagree, agree, strongly agree)

Appropriate use of the site

The following data will be collected automatically via the site:

1. Number of times a relative flagged content as requiring attention
2. Number of times the REACT Supporter deleted a comment from the site
3. Number of participants' accounts suspended

The following data will be recorded by REACT Supporters:

1. Number of times the REACT Supporters identify a clinical risk and escalated this to research team.

Web usage data

Web usage data will be collected in order to inform statistical analyses linking actual resource use to efficacy of intervention. This will allow us to explore whether the way in which people use the intervention, is linked to its effectiveness in reducing distress.

Specifically we will measure the detailed web usage for each individual participant at each entry to the site (time, duration and modules and videos or pages accessed by each user throughout the study). This needs to be a detailed report for each individual on the study, not a general summary. Participants are informed in the PIS that this monitoring of web usage will take place.

Appropriate causal analysis will usefully supplement the primary ITT analysis (which assesses the effectiveness of the *offer* of REACT versus usual resources) in order to inform on the efficacy of REACT as received. Causal analyses will be employed to prevent introducing selection bias (inherent to more basic efficacy analysis techniques, such as per protocol or as treated analyses) due to the likely correlation between intervention use and underlying stress levels (and hence prognosis). Instrumental variable regression (using randomisation and any other baseline factors linked to resource use but independent of outcome to act as instruments to predict compliance) will be used to determine the impact of web usage on outcome. Web usage data are vital to inform these analyses, and will also provide a useful summary of the extent to which participants actually utilised the available resource.

Qualitative methods

Peer support

Employing REACT Supporters, and building in the REACT Group (a peer support discussion board) is consistent with recent NICE Guideline research recommendations to further explore the effectiveness of peer support in psychosis. We will explore qualitatively the way in which the support functions are used by the relatives, in particular what issues they primarily seek help for, and the impact of the different responses from the REACT Supporter (via PhD funding applied for separately). Previous work in evaluating Expert Peers with service users has shown that, although there are practical challenges in employing and supporting people in this role, the support offered by peers with a shared lived experience is highly valued and as effective as that delivered by health professionals [61, 62]. Peer support for relatives has not been formally investigated to the same extent, however evidence for the effectiveness of multifamily groups which incorporates peer support [63], the popularity of offline support groups in the UK, and the data from our feasibility study suggest this is a promising way forward [14]. Informed by the work of Repper and colleagues [62] we will employ experts by experience (REACT Supporters) who, consistent with the cognitive behavioural theoretical underpinnings of the intervention, will encourage relatives to share a range of alternative perspectives on their experiences, and problem solving and coping strategies consistent with those outlined in the toolkit. To complement this, we hypothesise that the REACT Group discussion board will provide a non-stigmatising confidential space in which relatives can find acceptance and empathy from those with shared experiences.

Intervention use

The NHS Digital Strategy promotes digital technology to improve healthcare effectiveness and reduce cost. Online self-management interventions offer potential for high quality, standardised, accessible information, at low cost. However, uptake is low, many people don't benefit, and we have little understanding of how to improve digital intervention use and outcomes. The REACT trial currently assess the clinical and cost effectiveness of the intervention. By adding some qualitative interviews with the participants, and combining this with the quantitative data already collected, we can answer some important additional questions that are relevant for all digital health interventions:

1. What factors influence HOW participants engaged with the REACT toolkit?
    a. Level and pattern of website visits
    b. Use of forum
    c. Use of direct messages
    d. Do reminders to visit the site / modifications make any difference?
2. How was REACT experienced by participants? What aspects did they find helpful and why?
3. How was support from peer supporters experienced?

Eligible participants will be identified by the Information Systems lead at the CTRC Liverpool in order to keep the TM blind. Between approximately twenty to twenty five participants who meet the following eligibility criteria will be contacted by the interviewer and sent a letter of invite (Qualitative interview latter of invite v1.0 16.03.17), PIS (Qualitative interview Participant Information Sheet V1.0 16.03.17), consent (Qualitative interview consent form v1.0 16.03.17) by the interviewer: 1) Randomised to the intervention arm; 2) Completed 24 week follow-up; 3) Consented to be contacted about future research as part of the REACT trial consent. Participants will be given at least 24 hours to decide whether they wish to participate and will be given the opportunity to ask any questions.

Following receipt of completed consent form an interview will be arranged. Interviews will be recorded using an encrypted digital recorder and verbal consent to record the interview will be taken prior to the interview commencing. The interview will last up to 1 hour and will be conducted over the phone or Skype, depending on the participants' preference. If a participant chooses Skype, they will be informed that we cannot ensure a secure connection. Participants will be debriefed following the interview.

As soon as possible following the interview the recording will be downloaded to Lancaster University secure server and deleted from the audio device. If this is not possible immediately, the audio device will be locked in a cabinet in a secure office until download is possible. Interviews will be transcribed by a professional transcriber who will have undergone DBS check and signed a confidentiality agreement.

The qualitative data will be analysed using a framework analysis approach (Ritchie and Spencer 1994). The initial framework will be structured around responses to the key issues identified in the research questions above, but will be flexible to accommodate other important issues that arise during the interviews. This approach is particularly suited for pragmatic research in which specific questions are answered by a pre-determined sample, within a limited timeframe. The aim is not to achieve an in-depth interpretative analysis of individual experiences, but rather to identify key factors relevant to the pre-specified questions. Analysis will follow familiarisation with the data, finalising the thematic framework, indexing data, charting data within the framework, and mapping and interpreting the data to identify the answers to the research questions above. We will look for what is consistent across participants, but can use the framework (which retains individual level data across each row) to explore differences in individual experiences.

Following the interview, participants will be encouraged to contact the interviewer if they have any further questions about the research, and to access support via the REACT toolkit for any needs linked to their caring role.

Statistical considerations

Sample size calculation

The sample size is calculated to ensure that we are able to accurately test the primary hypothesis that there will be a significant difference ($p<.05$) between the 2 arms of the trial in GHQ-28 scores at 24 week follow-up, controlling for baseline scores. Our feasibility study showed a mean difference in GHQ scores between groups at 6 months (controlling for baseline) of 6.59 units (standard deviation 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, we reduce our estimate of the mean difference in this trial to 5.0 units (s.d. 16.6). REACT retains its integrity as a supported self-management intervention for relatives of people with severe mental health problems, but to accommodate feedback from the feasibility study, the way in which support is delivered has been adapted, and the target population has been broadened. We do not know whether these changes will impact on the effectiveness of the intervention but have allowed for a reduction from 6.59 units to 5 units. A detailed qualitative and quantitative analysis of our feasibility data suggests that a reduction of 3 units on the GHQ can be used to indicate clinically meaningful change (see detail below). We retain our estimate of standard deviation of 16.60 from the feasibility study, as it is consistent with other studies using this measure with relatives in EI services (n = 79, s.d. = 14.42) [64], and somewhat higher than those from mental health services (none EI) (n = 47, s.d.=12.8) [36], or relatives of people with dementia recruited in the community (n = 488 s.d.= 11.9) [65]. A conventional power calculation shows us that a total sample of 466 participants would give us 90% power to reject the null hypothesis ($p<.05$) when the true effect size is 5.0 units.

In our feasibility study, 17% of people had missing data at 6 months. However, we have allowed for this to be higher as retention has historically been lower in online trials. Our estimate of 30% dropout rate is based on the mean dropout rate across 14 online trials that used the same offline follow-up strategies as this design [1]. Therefore we have inflated the sample size to account for this 466 / 0.70 = 666 (minimum). This is likely to be a conservative estimate as online trial methodology is improving and in our most recent trials we were able to achieve follow-up rates of 77.2% [43] and 80% [46].

Defining clinically meaningful change on primary outcome

There is no previous data to suggest what a clinically meaningful change would be on the GHQ-28 for this population. We have therefore used our feasibility data to explore this question and demonstrated that a change of 3 units can be justified. Firstly, we used the qualitative data from the feasibility study to identify those people who clearly described clinically meaningful change and found that this was present in people with change scores as low as 3 units on the GHQ-28 (e.g. "*It changed everything for me,.... it made a big difference to my life*"; "*I was overly anxious, I was petrified. That was one of the biggest helps to me, and therefore to Edward because once I could relax, and stop being such a pain, do you know what I mean, and it has worked for me ever since*"; "*it basically allays your fears. It gives you enough knowledge to relax*"). We then divided the pilot sample into 2 groups – those whose GHQ-28 scores fell more than 3 points and those that didn't. We then compared these groups on changes scores on other outcomes used: Carer Well Being Scale and the Experience of Caregiving Inventory. Using independent samples t-tests we found a trend for a greater increase in wellbeing ($p = .061$) and a greater reduction in negative caregiving experiences ($p<.001$) in those experiencing at least a 3 point reduction on the GHQ-28.

Data analysis

The analysis of the primary outcome will follow the intention to treat approach, and include both a complete case analysis and a sensitivity analysis to examine the effect of missing outcome data. GHQ score at 24 weeks will be compared between the two arms of the trial, adjusting for baseline score. Missing data will be monitored and strategies developed to minimise its occurrence, however as much data as possible will be collected about the reasons for missing data and this will be used to inform the handling of missing data. We will ask participants to indicate online why they have declined to respond to the email reminders, and the TM will also ask participants when they call them. Since we will have two assessment points, at 12 and 24 weeks, we will carry out a sensitivity analysis using a joint modelling approach to check whether there is any difference in outcome (here the longitudinal outcome rather than the outcome at 24 weeks alone) between the randomised arms adjusted for dropout/missingness.

In order to investigate the relationship between resource use and outcome, data will be recorded on baseline covariates (related to both resource use and outcome) and relevant resource use (from participants in both randomised arms). Appropriate causal methods will be implemented to estimate efficacy of actual resource use, supplementing ITT estimates of effectiveness.

Our analysis will also include a test of the relative effectiveness and costs associated with a low value reward (£10) vs. a higher value (£20) and a conditional vs. unconditional reward. The sample size required in REACT RCT for sufficient power is 666 (minimum). This was calculated expecting a 70% retention rate, for a conditional reward of £10. All available evidence suggests that increasing the reward, and making it unconditional, will both increase the retention

rate. This sample will give us 84% power at the 5% significance level to determine a 10% absolute difference (from 70% to 80%) in retention between conditional or unconditional reward and lower value vs. higher value reward.
Finally, we will compare the effect of tailored recruitment strategies (e.g. media advertising; Facebook; chat rooms) in the REACT RCT by examining the association between strategy and the number of participants recruited to the RCT. We will also examine differences in demographic characteristics of participants entering the RCT via each of the recruitment strategies (age, sex, ethnic group, education level, income level).

Clustering

As we will not individually identify service users in this study, it is theoretically possible that multiple family members could sign up to take part in the study. It is also theoretically possible that relatives from the same support group sign up to the study, which could also lead to a clustering effect if factors associated with the group impact on distress levels. We will aim to minimise this by explaining in detail to relatives (and potential referrers) why it is very important that only one relative per service user takes part in the study. This will include a lay description of the concepts of clustering and contamination on the registration site and recruitment materials. Relatives are required to indicate at registration that to the best of their knowledge, they are the only relative of the person they care for who is taking part. Thus we cannot eliminate, but will aim to minimise, any risk of clustering. However, evidence to date regarding clustering effects suggests that even if this does occur, it is unlikely to have a major impact on the power of the study.
For example, The design effect is 1+p(m-1), where p is the ICC and m is the average cluster size. If we assume an ICC of 0.05 (based on Baldwin et al 2011 doi: 10.1080/16506073.2010.520731 as the only relevant estimate), and an average cluster size of 2 (a worst case scenario meaning all the service users have two relatives included), the design effect would be 1.05. Our target sample size after dropouts is 466, so the effective sample size would be 466/1.05=444 and the power only slightly reduced to 88%.
The Client Service Receipt Inventory already assesses service use, including support groups. By asking for detail about these groups, we can examine whether there is any evidence of clustering if relatives are attending the same group. If there is evidence of clustering, we will undertake sensitivity analyses that allow for any such clustering at the end. If however we are convinced that clustering is minimal, we would then argue that the effect of clustering is negligible and no sensitivity analysis is required.
If it is not possible to determine the exact ICC for the analysis, a sensitivity approach will be applied, either by multiplying the resulting standard error by sqrt(1.05) or by taking a good approximation to the significance level of 4.5% rather than 5%.

A full Statistical Analysis Plan will be developed before any comparative analysis is undertaken.

Cost Effectiveness

For the health economics analysis cost comparisons between the 2 arms at 24 weeks will be made using linear regression models exploring bootstrap methods to generate confidence intervals around the cost differences. Cost-effectiveness from an NHS perspective at 24 weeks will use a unit change (defined as 3 points) on the GHQ. The EQ-5D-5L will be used to generate QALYs. If the intervention has higher costs and improved outcomes than usual treatment then cost-effectiveness will be expressed in the form of incremental cost-effectiveness ratios, estimated by dividing the incremental costs by the incremental benefits of the intervention. Uncertainty around cost-effectiveness estimates will be explored using cost-effectiveness planes (through generating a large number of cost-outcome combinations using bootstrap methods) and cost-effectiveness acceptability curves (showing the probability of the intervention being cost-effective at various levels of willingness to pay for health benefits). This is important as it allows any uncertainty in the costs or outcomes to be reflected in the results presented, making them as transparent and generalisable as possible. NICE HTA guidance will be followed. However, the costs of informal support can have a significant impact on cost-effectiveness when it constitutes a substantial part of the support provided, so we will account for this by providing results from the NHS, and from the wider societal perspective. The focus will remain (as in NICE guidelines) on publically funded aspects of care. We feel it is important to collect and present the information on the wider implications as well to allow full transparency.

ETHICAL CONSIDERATIONS

Ethical approval

Before the study commences we will gain ethical approval through the National Research Ethics Service (NRES), and the Sponsor (Lancaster University). The study will require Research and Development approval at each site. All our staff will be up to date with training in Good Clinical Practice (GCP), information governance training / information security, and assessing risk. The Trial Management Group and the Trial Steering Committee will ensure all activity is carried out according to protocol. The CTU will oversee all data collection, storage, and management and ensure that this is anonymous and secure and consistent with the Data Protection Act (1998). Access will be restricted to preserve confidentiality and blindness. The trial will be registered and given an ISRCTN number. Once finalised, a protocol paper and statistical analysis protocol will be published.

Informed consent

Valid informed consent must be taken online. Here we follow British Psychological Society guidance [66] including providing a detailed (but not overly long) online Participant Information Sheet (PIS) which includes clear instructions regarding withdrawal rights and risks to taking part, and a series of explicit consent statements each requiring a response.

TRIAL MONITORING

Data management

Data will be collected online using a secure web application and stored in a database on one of the CTRC servers following the appropriate CTRC Information Systems SOPs. This server is located in a secure (access controlled) server room. Data regarding your use of the REACT site, online forum posts and direct messaging to the REACT Supporters will be stored on a secure university server at Lancaster University.

Risk assessment

Three levels of risk within the REACT RCT have been identified and are addressed here: 1) online safety; 2) clinical safety; and 3) privacy protection.

Online safety

- The REACT site will include a set of Ground Rules regarding use of the REACT site e.g. how to ask a question on the forum without revealing personal identifiable information and what kind of language is/is not appropriate for use on the site.
- Participants will be made aware of the consequences of inappropriate online communication in the PIS and will be asked to agree to follow the Ground Rules as part of the online consenting process.
- The REACT supporters will act as moderators of the site and will ensure the Ground Rules are being adhered to. If the REACT Supporters identify posts that are inappropriate (e.g. hostile or offensive language) they will contact the participant via direct messaging and notify them that the post has been removed. If a participant continues to use the REACT site inappropriately despite repeated notification, their account will be suspended.
- The REACT site will also include a function which allows participants to flag inappropriate or concerning posts to the REACT Supporters. Depending on the nature of such posts the REACT supporter will either deal with the issue themselves via direct messaging with the participant or, where there is a clinical risk issue, report the post immediately to CI who is a Clinical Psychologist for guidance. The Trial Management Group (TMG) includes 2 Consultant Clinical Psychologists, a Consultant Psychiatrist and a Primary Care GP. They will ensure clinical risk issues are picked up and managed quickly.
- The REACT Supporters will have regular supervision (initially weekly, moving to fortnightly if appropriate) with the CI or co-I (Clinical Psychologists), both based at the same site.
- Unauthorised access to the site will be prevented by providing participants with unique login details (see section below). The PIS will emphasise that is important participants do not share these details.

Clinical safety

a) Via the REACT site

- The REACT forum will be monitored by the REACT Supporters who will check the forum regularly. Moderators will be online during office hours. However, it will be made clear to site users that the site is not managed 24/7 and therefore there may be a delay in response.
- It will be made clear on the website that the forum and direct contact with the REACT Supporters should not be used for people requiring urgent crisis support. In the unlikely event that a participant posts something on the REACT site that causes the REACT supporters concern for the participants' (or someone else's) safety the REACT Supporter will signpost the participant to contacts for crisis support (these contacts are listed on the PIS). The site will provide details of how to access urgent support through Emergency services, NHS Direct, the police, or crisis helplines such as Samaritans as appropriate.
- Where low risk (no indication of immediate or serious threat of severe harm or risk to life but either: 1) clear evidence of high levels of distress; or 2) concerns for risk of harm or abuse towards participants or others) is identified either an automated email/text will be sent to the participant to signpost to support services or advice will be sought from Lancashire Care NHS Foundation Trust (LCFT) Safeguarding team.
- Where high risk (i.e. clear evidence of immediate and serious risk to life or child welfare) is identified the REACT Supporter will alert the police or social services. The participant information sheet (PIS) will clearly state limits to confidentiality. We will be able to link participant login details to their personal details at registration. In the unlikely event of clear evidence that someone participating in the trial is intending to harm themselves or someone else, or at serious risk of harm, this information, along with personal contact details, will be passed to local police services as quickly as possible.

b) Via contact with the Trial Manager (TM)

- The TM will have (email/phone) contact with non-responders to encourage follow-up completion. Should a low risk issue arise during this contact the TM will send an automated email/text to signpost the participant to contacts for support or seek advice from LCFT on safeguarding issues. In the case of high risk issues, the TM will inform the police or social services as appropriate.

Privacy protection (confidentiality)

a) The REACT site

- The REACT website is a private, closed site. Participants will be provided with unique login details and asked to use a 'fake' username when logging on so that all activity is anonymous.
- Participants can post information by using the REACT Group – which is an online forum shared with all other relatives in the intervention arm of the study, or the REACT Supporters – which can be communicated with individually using Direct Messaging.
- Participants will be advised not to use personal details in referring to any friend or relative they are supporting when using the REACT Group as we cannot guarantee this information will not be shared with people outside the site by other users.
- Discussions with the REACT Supporters will be private and confidential. Participants will have the choice over whether they also wish to share these discussions (or parts of) on the REACT Group discussion board in order to involve other REACT users.
- The REACT Group will be monitored by the REACT Supporters. If certain questions are repeatedly asked in discussions with the REACT Supports we may post these under Frequently Asked Questions (FAQs) to help other users who may have the same question in the future. Again, the FAQs will be completely anonymous.

b) Research data

- All responses to the study questionnaires will be strictly confidential and unidentifiable by use of a unique study number in place of participant names.
- All study data will be anonymised and pooled prior to analysis and any data used in the write up of the study will not be identifiable.
- The data collected for this study will be stored securely on encrypted password protected computers and only the research team will have access to this data.
- Confidentiality of information will only be broken if a participant is at risk to themselves or others. This will be made clear in the Participant Information Sheet.
- Content of the REACT Group and REACT Supporter messaging will be used for analysis by the research team. Participants will be asked to consent to this on entry into the study. This data will be downloaded from the REACT site and stored securely at Lancaster University.

Identifying, reporting and clinical management of (serious) adverse events

Definitions

Low risk adverse event (AE): 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)

The most likely adverse event to occur in this study is participant experience of distress. Distress is an expected adverse event because participants must be distressed on entry to the study to meet inclusion criteria. Reading about psychosis may exacerbate distress (though our aim is to reduce distress).

High risk serious adverse event (SAE): clear evidence of immediate and serious risk to life or child welfare

*NB: Suicide, threat to life/serious abuse and hospitalisation due to participation in this study are ALSO identified as **unexpected SAEs** because we would not expect any of these outcomes for participants during the period of the study.*

Identification

Low and high risk (S)AEs will be identified in the following ways:

a) System identifies "red flag" item in response to General Health Questionnaire (GHQ) or Relative's wellbeing and Support Questionnaire (CWS) items (Trial Manager (TM) notified through interface)

OR

b) Risk is identified by the REACT Supporters through the forum or direct messaging

OR

c) Risk is identified by the TM when contacting none responders for follow-up(NB This is with both arms and needs to follow strategies to ensure blinding is not broken)

Reporting Procedures

1. **Low risk events** should be documented on the relevant databse within 1 working day
2. **High risk events** should be documented on the relevant database AND reported to an unblinded Clinical Psychologist co-applicant (SJ) within 1 working day

- SJ will collect relevant info about the event and forward this to TSC chair
- The TSC chair will decide whether the high risk event is related or unrelated to the study.
- IF RELATED then CI and TM will be unblinded.
- The TM will report the high risk related event to TSC Chair, the Sponsor and the NHS REC within 15 days of the event.

3. The lead statistician to provide a summary report of all low and high risk (S)AEs to the DMEC and TSC at every meeting.

Clinical management

LOW RISK - distress

a) Automated email/text* is sent to participant (TM alerted that this has been sent)

OR

b) REACT Supporter sends standardized email/text* to participant

OR

c) TM sends standardized email/text* to participant

LOW RISK - safeguarding

REACT supporter is the most likely person to identify safeguarding issues through interaction with participants.

a) REACT supporter will ask for guidance from a named co-applicant clinician whilst maintaining blinding for the CI and TM
b) REACT supporter will use Lancashire Care NHS Foundation Trust safeguarding team to get advice on safeguarding risks (contact details in risk management protocol)
c) Any safeguarding concerns **must** be reported to the relevant local authority (the local authority of the person for whom you have concern). It must be reported to the authority's safeguarding team (for adults) or children's social care team (contact in risk management protocol).

HIGH RISK

If an immediate risk is identified the either then police (immediate risk to life) or social services (other risk to child) will be contacted as appropriate

Data monitoring

Data from the trial will be reviewed by an independent Data Monitoring & Ethics Committee (DMEC). The DMEC will prioritise safety of participants and alert an independent Trial Steering Committee (TSC) to any concerns regarding safety or other ethical issues. The DMEC will be completely independent and consist of a Chair, a clinician, a relative, and a trial statistician.

Quality Assurance

- The study will be conducted in accordance with procedures identified in the protocol.
- The trial will be overseen independently by the DMEC and the TSC.
- The DMEC will evaluate data for compliance with protocol, data accuracy and data consistency.
- The TSC will evaluate the process for consent, recruitment and randomisation for compliance with the protocol.

Record retention

Data will be uploaded directly to a database securely stored at the CTU, Liverpool University (with access for the TM to contact non-responders for follow-up) and transferred to Lancaster University as sponsor once the study has finished. Personal data will be stored for 15 years after the study has finished allowing us to understand results in relation to personal characteristics, and storage of consent for the time in which analyses take place. As part of the consent process participants are given the option to sign up to Spectrum Connect (already approved) where their personal data will be stored for longer if the participant consents. This allows them to be contacted about future research and updates at Spectrum with their consent. Research data will be stored in anonymised form on Lancaster University secure network on password protected, encrypted university computers indefinitely following completion of the study. This is in line with NIHR requirements for open access.

INDEMNITY

REACT is sponsored by Lancaster University. Lancaster University legal liability cover will apply to harm to participants arising from the management of the research; the design of the research; and the conduct of the research. Lancaster University will not pay compensation in the event of harm to participants where no legal liability arises.

FINANCIAL ARRANGEMENTS

This trial is funded by the National Institute of Health Research (NIHR), Health Technology Assessment (HTA). Contractual agreements will be in place between sponsor (Lancaster University), the CTU (Liverpool University) and University College London, and Lancashire Care NHS Foundation trust, which will incorporate financial arrangements. The REACT trial will automatically be adopted into the NIHR portfolio an NIHR funded study. Support from the Comprehensive Local Research Network (CLRN) will therefore be covered by research support costs.

Participants will be given a token of appreciation for their participation (£10 at baseline and 12 week follow-up and either £10 or £20 at 24 week follow-up depending on random allocation).

TRIAL COMMITTEES

Trial Management Group (TMG)

The TMG (all co-applicants, TM, Chair of the Relatives' Advisory Group, CTU supervising statistician) will meet monthly during the pre-award period and for the duration of the trial (using face to face and teleconferencing as appropriate). The CTU trial statistician will provide data to monitor progress of the trial on a monthly basis to the TMG. This group will ensure that all the milestones are being met on time and problem solve any issues arising at any of the sites.

Trial Steering Committee (TSC)

The TSC will oversee the progress of the trial, provide guidance as required, ensure that it is being carried out according to protocol and will make decisions regarding the continuation of the trial. They will liaise directly with the trial sponsors. The TSC will meet prestart, 10 months progress review, 15 months internal pilot, and then annually. The Committee will include an independent Chair, clinician and relative, along with the CI, and CTU staff as required.

Data Monitoring & Ethics Committee (DMEC)

Data from the trial will be reviewed by an independent DMEC. The DMEC will prioritise safety of participants and alert an independent TSC to any concerns regarding safety or other ethical issues. The DMEC will be completely independent and consist of a Chair, a clinician, a relative, and a trial statistician. The DMEC will meet prestart, 10& 15 months (see internal pilot) and then annually timed to feed reports into TSC. All data required by the DMEC will be provided by the supervising statistician at the CTU.

DISSEMINATION AND PROJECT OUTPUTS

Key outputs

1) A fully tested online supported self-management intervention (REACT) for relatives that delivers NICE Guideline recommended treatment for psychosis and bipolar disorder;
2) Evidence for clinical and cost effectiveness of REACT;
3) Data to inform the design of future online trials, including recruitment and retention rates, predictors of attrition and dropout, and the effectiveness of strategies to maximise retention.
4) If REACT is shown to be effective, we will ensure it can continue to be successfully implemented in the NHS by providing: full costing details; a co-produced manual for training and supervising the REACT Supporters; and converting the most common queries submitted to "Ask the Experts" into a "Frequently Asked Questions" page.

Dissemination

All products will be widely disseminated to all relevant stakeholders including service users, relatives, NHS managers and frontline clinical staff including GPs; clinical academics; the general public. A study website will provide updates and outputs from the study and links to all publications and presentations.

Publications

Journal articles outlining the main findings will be written for open access in academic journals (such as Lancet, British Medical Journal, British Journal of Psychiatry), and leading specialist internet journals (Journal of Medical Internet Research). Publications aimed at service users and carers will be targeted at appropriate web and print forums (such as Carers UK, Your Voice (Rethink), Pendulum (Bipolar UK)). All articles will be adapted to suit the relevant audience and input from the whole research team will ensure these are accessible, appealing and informative.

Conferences

Findings will be presented at key national and international conferences in each of the stakeholder forums, for example to the RCPsych Congress, British Association of Behavioural and Cognitive Psychotherapy (BABCP), American Association for Behavioral and Cognitive Therapies (ABCT), and Rethink Mental Illness conference.

Social media

To broaden dissemination as widely as possible, we will develop a social media strategy to promote our findings using Twitter, Facebook, and blogging. We will build on links with carer networks to promote findings to local groups and work with national organisations such as MIND, Carers Trust, Rethink Mental Illness, Carers UK, SANE, Bipolar UK, McPin Foundation and NHS Choices to promote findings through their networks. Finally, we will work with the Science Media Centre and University press offices to engage with the news media where possible.

Abroad

Although the intervention is currently written specifically for relatives in the NHS in the UK, it could easily be adapted to meet the needs of relatives in other countries. Since publication of the REACT feasibility trial, we have had interest from clinical teams from Norway and New Zealand and we are collaborating to help them adapt REACT for use in their own services.

Clinical services

The IAPT programme (Increasing Access to Psychological Therapies) is currently expanding from depression and anxiety to include more severe and enduring mental health problems including psychosis. The lack of supported self-management interventions has already been highlighted as a significant issue, especially given the success such approaches have had in increasing access to therapy for people with depression and anxiety. It is not clear to what extent “low intensity” interventions are suitable for service users with more severe mental health problems, but our pilot data suggest that supporting relatives with supported self-management interventions is highly acceptable and feasible, but not currently available. Filling this gap by developing REACT must be followed by ensuring it is disseminated within these organisations that will determine wide clinical use. Our research team include members of both the NICE Guideline Development Group (Johnson) and the IAPT Expert Advisory (Jones) and IAPT Training Task Groups (Lobban, Jones).

BENEFICIARIES

The main direct beneficiaries of this research will be relatives, who will receive the information and support they need. As well as reducing distress and improving outcome for relatives, the intervention is likely to have a significant indirect impact on other family members including the service user. If relatives feel more able to cope, have more information and strategies to manage psychosis/BD and are involved as partners in the care team, they are more likely to continue to care. There is good evidence that where relatives are involved, service users have a significantly improved outcome [11], and that working with families is a clinically and cost effective way to reducing frequency of relapse and hospital admissions, and improve social functioning for service users with psychosis [67-69]. The other direct beneficiaries will be clinical staff, who by directing relatives to this intervention, make their own role more manageable. NHS Trusts will benefit from being able to meet their clinical targets to provide widely accessible support to relatives. Indirectly, the

whole of society will benefit from the improved wellbeing of a significant part of the population, and the costs saved by the improved mental health of service users and relatives. Given the potential for REACT to be adapted for relatives of people with other kinds of mental health problems, the indirect beneficiaries of this research are extensive.

DECLARATION OF INTEREST

Some members of the applicant team (FL and VM) were also involved in the development and feasibility testing of REACT. The applicant team are further developing the REACT intervention as part of the study. This study is therefore not an independent evaluation.

PROTOCOL AMENDMENTS

Version 1.0 18.08.15
Version 1.1 01.02.16
Version 1.2 08.03.16
Version 1.3 25.08.16
Version 1.4 11.11.16
Version 1.5 09.01.17
Version 1.6 20.03.17
Version 1.7 19.05.17
Version 1.8 06.12.17

REFERENCES

1. Mathieu, E., et al., *Internet-based randomized controlled trials: a systematic review.* Journal of the American Medical Informatics Association, 2012: p. amiajnl-2012-001175.

2. Buckner, L. and S. Yeandle, *Valuing Carers 2011 Calculating the value of carers' support.* Carers UK; Centre for International Research on Care, Labour & Equalities; University of Leeds, 2011.

3. Lowyck, B., et al., *A study of the family burden of 150 family members of schizophrenic patients.* European Psychiatry, 2004. **19**(7): p. 395-401.

4. Perlick, D., et al., *Burden experienced by care-givers of persons with bipolar affective disorder.* The British Journal of Psychiatry, 1999. **175**(1): p. 56-62.

5. Gallagher, S.K. and D. Mechanic, *Living with the mentally ill: effects on the health and functioning of other household members.* Social Science & Medicine, 1996. **42**(12): p. 1691-1701.

6. Perlick, D.A., et al., *Use of mental health and primary care services by caregivers of patients with bipolar disorder: a preliminary study.* Bipolar Disorders, 2005. **7**(2): p. 126-135.

7. HM Government, *The Care Act 2014*. 2014, HM Government: The Stationery Office: London.

8. *NICE Clinical Guideline 178: Psychosis and Schizophrenia in Adults - Treatment and Management*. 2014, National Institute for Health and Care Excellence.

9. *NICE Clinical Guidline (CG185). Bipolar disorder: the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care*. 2014, National Collaborating Centre for Mental health.

10. Haddock, G., et al., *An investigation of the implementation of NICE-recommended CBT interventions for people with schizophrenia.* Journal of Mental Health, 2014(0): p. 1-4.

11. Garety, P., *Testing a cognitive model of psychosis - studies of emotional and cognitive processes in the first 100 patients*. 2003: BABCP Annual Conference 2003: York.

12. Tetley, D. and S. Ordish, *Core interventions in the treatment and management of schizophrenia.* Lincolnshire Partnership NHS Trust, 2005.

13. The Schizophrenia Commission, *The abandoned illness: a report from the Schizophrenia Commission* 2012, Rethink Mental Illness: London.

14. Lobban, F., 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**(5): p. 366-372.

15. Glynn, S.M., et al., *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**(4): p. 278-287.

16. Rotondi, A., et al., *Web-based psychoeducational intervention for persons with schizophrenia and their supporters: one-year outcomes.* Psychiatric Services, 2010. **61**(11): p. 1099-1105.

17. Sin, J., et al., *The E Sibling Project–exploratory randomised controlled trial of an online multicomponent psychoeducational intervention for siblings of individuals with first episode psychosis.* BMC psychiatry, 2013. **13**(1): p. 123.

18. Berk, L., et al., *Evaluation of the acceptability and usefulness of an information website for caregivers of people with bipolar disorder.* BMC medicine, 2013. **11**(1): p. 162.

19. McCrone, P., *Paying the price: the cost of mental health care in England to 2026.* 2008.

20. Mangalore, R. and M. Knapp, *Cost of schizophrenia in England.* Journal of Mental Health Policy and Economics, 2007. **10**(1): p. 23.

21. Fox, S., M. Duggan, and K. Purcell. *Family caregivers are wired for health*. 01/09/2014].

22. Lal, S. and C.E. Adair, *E-Mental Health: A Rapid Review of the Literature.* Psychiatric Services, 2014. **65**(1): p. 24-32.

23. van der Krieke, L., et al., *E–Mental Health Self-Management for Psychotic Disorders: State of the Art and Future Perspectives.* Psychiatric Services, 2014. **65**(1): p. 33-49.

24. Todd, N., et al., *A web-based self management intervention for Bipolar Disorder "Living with Bipolar": a feasibility randomised controlled trial.* Journal of Affective Disorders, in press.

25. Murray, E., et al., *Methodological challenges in online trials.* Journal of medical Internet research, 2009. **11**(2).

26. Barrowclough, C., et al., *Randomised controlled effectiveness trial of a needs-based psychosocial intervention service for carers of people with schizophrenia.* British Journal of Psychiatry, 1999. **174**: p. 505-511.

27. Szmukler, G., et al., *An exploratory randomised controlled trial of a support programme for carers of patients with a psychosis.* Social Psychiatry and Psychiatric Epidemiology, 2003. **38**(8): p. 411-418.

28. Leavey, G., et al., *A randomized controlled trial of a brief intervention for families of patients with a first episode of psychosis.* Psychological Medicine, 2004. **34**(3): p. 423-431.

29. Gafoor, R., et al., *Effect of early intervention on 5-year outcome in non-affective psychosis.* The British Journal of Psychiatry, 2010. **196**(5): p. 372-376.

30. Bertelsen, M., 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**(7): p. 762-771.

31. Bentall, R.P., *Madness explained: Psychosis and human nature*. 2004: Penguin UK.

32. Goldberg, D.P. and V.F. Hillier, *A scaled version of the General Health Questionnaire.* Psychological medicine, 1979. **9**(01): p. 139-145.

33. Quirk, A., et al., *Development of the carer well-being and support (CWS) questionnaire.* Mental Health Review Journal, 2012. **17**(3): p. 128-138.

34. Beecham, J. and M. Knapp, *Costing psychiatric interventions*. 2001: Gaskell In Measuring Mental Health Needs. Edited by Thornicroft G. London.

35. Herdman, M., et al., *Development and preliminary testing of the new five-level version of EQ- 5D (EQ-5D-5L).* Quality of life research, 2011. **20**(10): p. 1727-1736.

36. Szmukler, G., et al., *A controlled trial of a counselling intervention for caregivers of relatives with schizophrenia.* Social Psychiatry and Psychiatric Epidemiology, 1996. **31**(3-4): p. 149-155.

37. Barrowclough, C., N. Tarrier, and M. Johnston, *Distress, expressed emotion, and attributions in relatives of schizophrenia patients.* Schizophrenia Bulletin, 1996. **22**(4): p. 691.

38. Birchwood, M. and R. Cochrane, *Families coping with schizophrenia: coping styles, their origins and correlates.* Psychological Medicine, 1990. **20**(04): p. 857-865.

39. Oldridge, M. and I. Hughes, *Psychological well-being in families with a member suffering from schizophrenia. An investigation into long-standing problems.* The British journal of psychiatry, 1992. **161**(2): p. 249-251.

40. Schene AH, Wijngaarden BV, and K. MWJ., *Family caregiving in schizophrenia: Domains and distress. .* Schizophrenia Bulletin, 1998. **24**(4): p. 609-618.

41. Winefield, H.R. and E.J. Harvey, *Determinants of psychological distress in relatives of people with chronic schizophrenia.* Schizophrenia Bulletin, 1993. **19**(3): p. 619.

42. David, M.C. and R.S. Ware, *Meta-analysis of randomized controlled trials supports the use of incentives for inducing response to electronic health surveys.* Journal of clinical epidemiology, 2014.

43. Bailey, J.V., et al., *The Sexunzipped trial: Optimizing the design of online randomized controlled trials.* Journal of medical Internet research, 2013. **15**(12): p. e278.

44. Crutzen, R., et al., *Differential attrition in health behaviour change trials: a systematic review and meta-analysis.* Psychology & Health, 2014: p. 1-29.

45. Crutzen, R., et al., *No differential attrition was found in randomized controlled trials published in general medical journals: a meta-analysis.* Journal of clinical epidemiology, 2013. **66**(9): p. 948-954.

46. Khadjesari, Z., et al., *Health on the Web: randomised controlled trial of online screening and brief alcohol intervention delivered in a workplace setting.* PLOS One, in press.

47. Murray, E., et al., *Attrition revisited: adherence and retention in a web-based alcohol trial.* Journal of medical Internet research, 2013. **15**(8).

48. Addington, J., A. McCleery, and D. Addington, *Three-year outcome of family work in an early psychosis program.* Schizophrenia research, 2005. **79**(1): p. 107-116.

49. Lorig, K.R. and H.R. Holman, *Self-management education: history, definition, outcomes, and mechanisms.* Annals of Behavioral Medicine, 2003. **26**(1): p. 1-7.

50. Barrowclough, C., et al., *Factors Associated With Distress in Relatives of a Family Member Experiencing Recent-Onset Psychosis.* The Journal of nervous and mental disease, 2014. **202**(1): p. 40-46.

51. Brueton, V.C., et al., *Strategies to improve retention in randomised trials.* Cochrane Database Syst Rev, 2013. **12**.

52. Wainwright, L., et al., *The subjective experience of using the Relatives Education And Coping Toolkit.* Journal of Mental Health, submitted- under revision.

53. Lobban, F., et al., *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**(6): p. 567-579.

54. Lobban, F., et al., *Pilot Study to Assess the Feasibility of a Web-based Intervention for Prevention of Relapse in Bipolar Disorder (ERP-Online)*. 2012 –2015, NIHR: Research for Patient Benefit.: Lancaster University.

55. Nicholas, A., et al., *The Sexunzipped Trial: Young People's Views of Participating in an Online Randomized Controlled Trial.* Journal of medical Internet research, 2013. **15**(12): p. e276.

56. Harvey, K., et al., *A review of instruments developed to measure outcomes for carers of people with mental health problems.* Acta Psychiatrica Scandinavica, 2008. **117**(3): p. 164-176.

57. Whittaker, W. and M. Sutton, *Mental health, work incapacity and State transfers: an analysis of the British Household Panel Survey*. 2010, HEDG, c/o Department of Economics, University of York.

58. Whittaker, W., 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.* Journal of Occupational and Environmental Medicine, 2012. **54**(12): p. 1539-1544.

59. Whittaker, W., 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**.

60. Russ, T.C., et al., *Association between psychological distress and mortality: individual participant pooled analysis of 10 prospective cohort studies.* BMJ: British Medical Journal, 2012. **345**.

61. Davidson, L., et al., *Peer support among persons with severe mental illnesses: a review of evidence and experience.* World Psychiatry, 2012. **11**(2): p. 123-128.

62. Repper, J. and T. Carter, *A review of the literature on peer support in mental health services.* Journal of Mental Health, 2011. **20**(4): p. 392-411.

63. McFarlane, W.R., *Multifamily groups in the treatment of severe psychiatric disorders*. 2004: Guilford Press.

64. Barrowclough, C., et al., *Factors associated with distress in relatives experiencing recent onset psychosis in a family member.* Journal of Nervous and Mental Disease, Under Review.

65. Woods, R., et al., *REMCARE: reminiscence groups for people with dementia and their family caregivers - effectiveness and cost-effectiveness pragmatic multicentre randomised trial.* Health Technology Assessment, 2012. **16**(48): p. 121.

66. *Ethics Guidelines for Internet-mediated Research*. 2013, British Psychological Society: Leicester.

67. Andrew A, K.M., McCrone P, Parsonage M, Trachtenberg M. , *Effective interventions in schizophrenia the economic case: A report prepared for the Schizophrenia Commission*. 2012, Rethink Mental Illness: London.

68. Pfammatter, M., U.M. Junghan, and H.D. Brenner, *Efficacy of psychological therapy in schizophrenia: conclusions from meta-analyses.* Schizophrenia Bulletin, 2006. **32**(suppl 1): p. S64-S80.

69. Pharoah, F., et al., *Family intervention for schizophrenia.* Cochrane Database of Systematic Reviews, 2010. **12**.

70. Gleeson, J., Lederman, R.,Wadley, G., Bendall, S., McGorry, P., Alvarez-Jimenez, M. *Safety and privacy outcomes from a moderated online social therapy for young people with first-episode psychosis.* Psychiatric Services, 2014. **65.**