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)

Final Analysis Report

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Date	13/05/2019		
Protocol Version and Date	Protocol version v1.5 Dated 09.01.17		

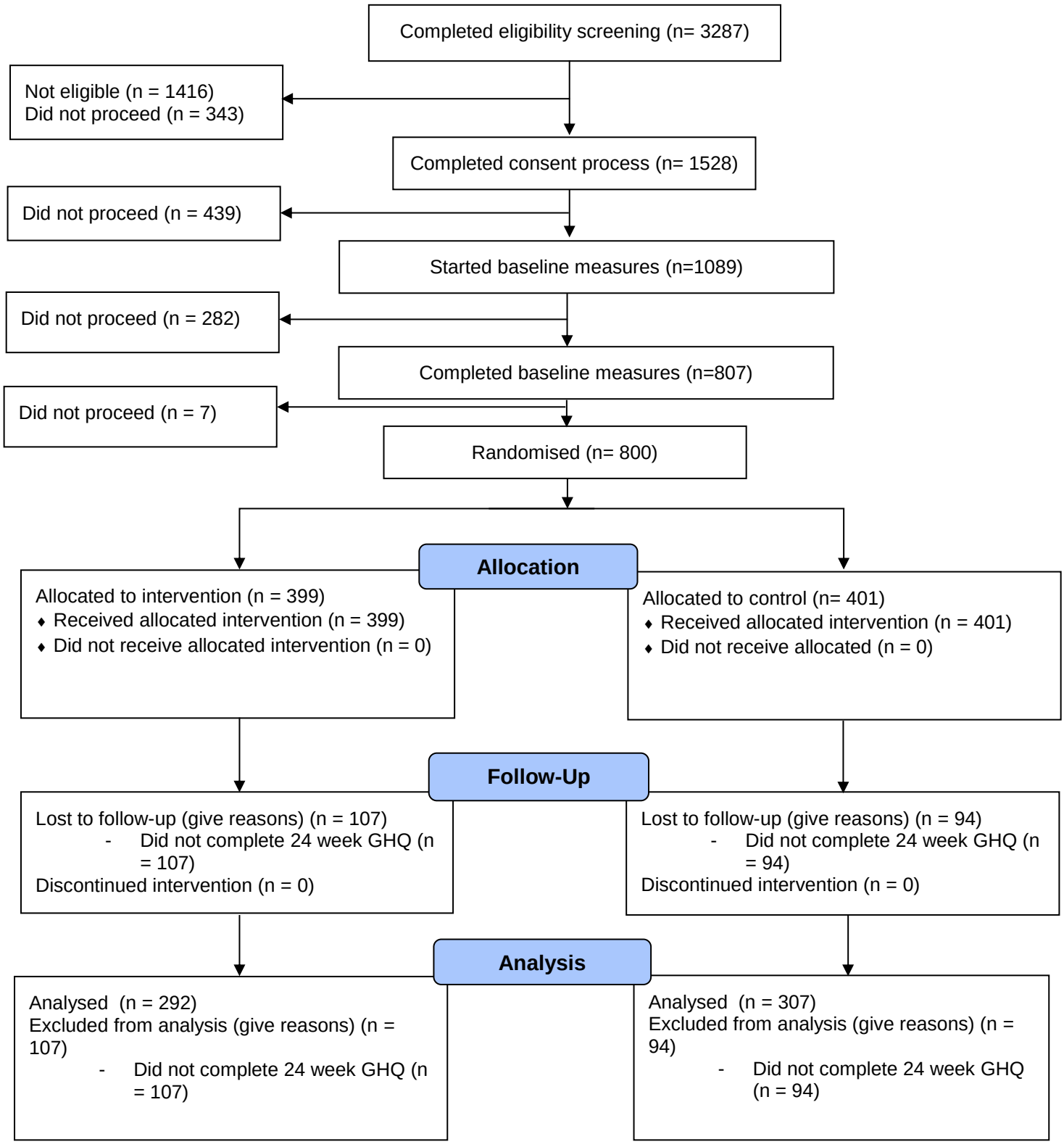
Change Control

Updated shell version no.	Shell section changed	Description of change	Date changed	Initials

1. Table of Contents

2. List of Tables

3. CONSORT diagram shell



3.1 Failed eligibility criteria

Total number failing on eligibility: 1416
Total number failing on more than one criterion: 55

Table 3-1: Eligibility details

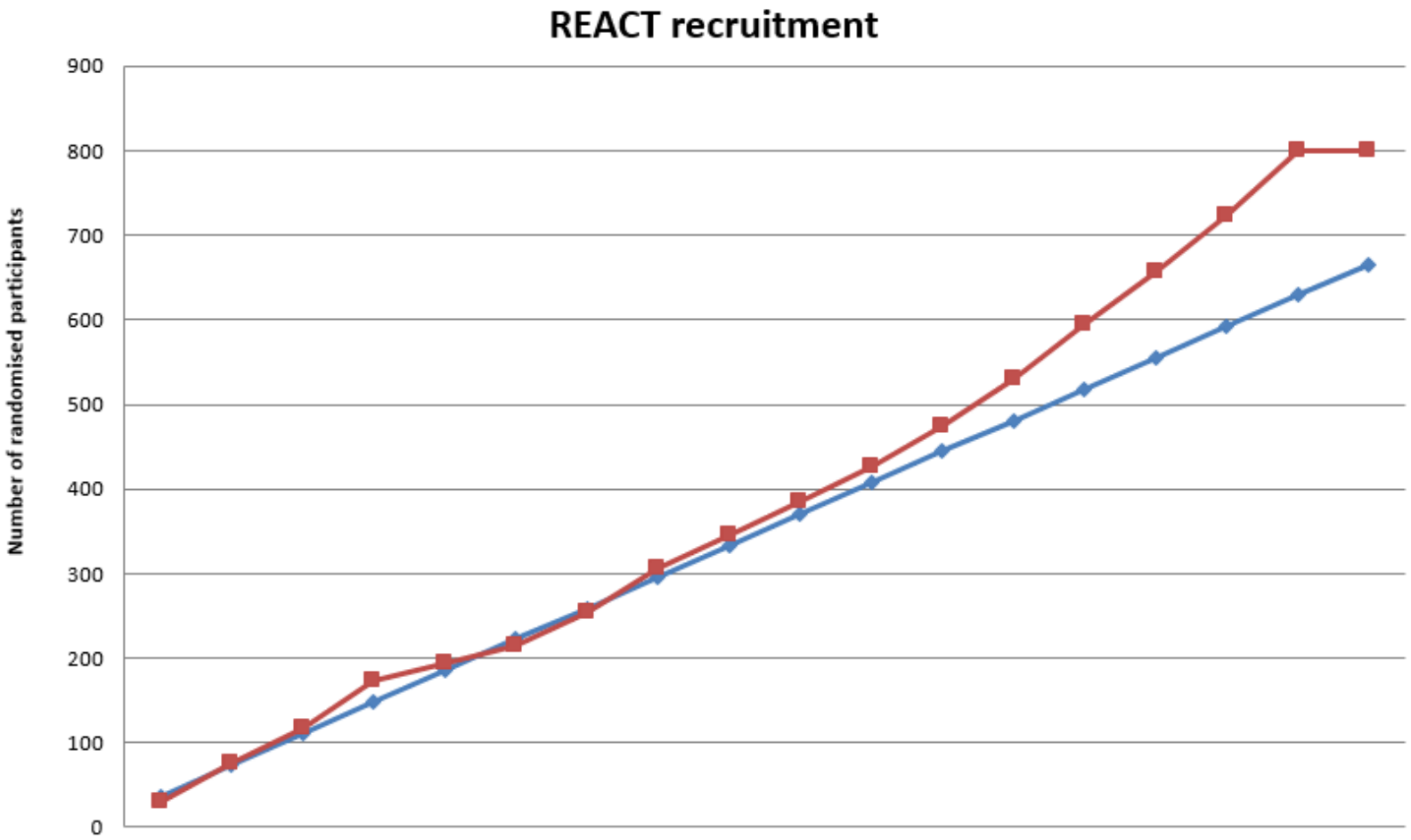
Question	Number failing eligibility on this question (% of total number failing on eligibility)
I am 16 years old or over	10 (0.7%)
I am a relative (or close friend providing regular support) of someone with psychosis or bipolar disorder	88 (6.2%)
Have you recently been feeling nervous and strung-up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

Note: there were also 40 people who failed due to address or mobile already registered
SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\ELIGIBILITY.sas

4. Randomisation checking

All randomisations were sequential. One randomisation was missing (REACT0756) due to a technical issue (see section 6.2.2).

5. Recruitment



	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17
Target	37	74	111	148	185	222	259	296	333	370	407	444	481	518	555	592	629	666
Actual	31	75	117	173	193	215	255	307	346	385	427	474	530	595	657	724	799	800

6. Table Shells

6.1 Baseline characteristics

6.1.1 Demographic details

Table 6-1 Demographic details

	REACT N = 399	RD N = 401	Overall N = 800
Age (years)			
<30	39 (9.77)	36 (8.98)	75 (9.38)
30 – 39	50 (12.53)	73 (18.20)	123 (15.38)
40 – 49	95 (23.81)	104 (25.94)	199 (24.88)
50 – 59	111 (27.82)	112 (27.93)	223 (27.88)
60 – 69	88 (22.06)	61 (15.21)	149 (18.63)
≥70	16 (4.01)	15 (3.74)	31 (3.88)
Mean (SD)	49.4 (13.3)	47.9 (12.7)	48.6 (13.00)
Range (min – max)	16 - 84	18 - 86	16 - 86
Gender			
Male	82 (20.55)	69 (17.21)	151 (18.88)
Female	317 (79.45)	331 (82.54)	648 (81.00)
Missing	0 (0.00)	1 (0.25)	1 (0.13)
How many people do you support			
1	296 (74.19)	295 (73.57)	591 (73.88)
2	68 (17.04)	72 (17.96)	140 (17.50)
3	20 (5.01)	21 (5.24)	41 (5.13)
≥4	15 (3.76)	13 (3.24)	28 (3.50)
Relationship to service user (not mutually exclusive): I am their…			
Mother	187	200	387
Father	17	10	27
Partner	149	143	292
Child	62	63	125
Sibling	41	38	79
Friend	31	26	57
Wider family member	25	19	44
Other	10	12	22
Undefined	38	52	90
Ethnicity			
White			
British	361 (90.48)	366 (91.27)	727 (90.88)
Irish	5 (1.25)	6 (1.50)	11 (1.38)
Any other White background	15 (3.76)	13 (3.24)	28 (3.50)
Mixed	6 (1.50)	6 (1.50)	12 (1.50)
Asian or Asian British	11 (2.76)	3 (0.75)	14 (1.75)
Other Ethnic group	1 (0.25)	5 (1.25)	6 (0.75)
Rather not say	0 (0.00)	2 (0.50)	2 (0.25)
Marital status			
Single	88 (22.06)	77 (19.20)	165 (20.63)

	REACT N = 399	RD N = 401	Overall N = 800
Married	219 (54.89)	239 (59.60)	458 (57.25)
Civil Partnership	14 (3.51)	13 (3.24)	27 (3.38)
Separated	8 (2.01)	15 (3.74)	23 (2.88)
Divorced	47 (11.78)	40 (9.98)	87 (10.88)
Widowed	10 (2.51)	8 (2.00)	18 (2.25)
Rather not say	13 (3.26)	9 (2.24)	22 (2.75)
Living arrangements			
Spouse/Partner	275 (68.92)	289 (72.07)	564 (70.50)
Living Alone	82 (20.55)	80 (19.95)	162 (20.25)
Parent(s)	17 (4.26)	11 (2.74)	28 (3.50)
Other	20 (5.01)	17 (4.24)	37 (4.63)
Rather not say	5 (1.25)	4 (1.00)	9 (1.13)
Dependents			
None	168 (41.90)	175 (43.86)	343 (42.88)
1	99 (24.69)	117 (29.32)	216 (27.00)
2	91 (22.69)	57 (14.29)	148 (18.50)
3	30 (7.48)	28 (7.02)	58 (7.25)
≥4	13 (3.26)	22 (5.49)	35 (3.48)
Highest education level			
School level	65 (16.29)	73 (18.20)	138 (17.25)
Further (College level)	108 (27.07)	117 (29.18)	225 (28.13)
Higher (University level)	226 (56.64)	211 (52.62)	437 (54.63)
Employment status			
Employed full time (35 hrs+ a week)	150 (37.59)	151 (37.66)	301 (37.63)
Employed part time (specify hrs)	92 (23.06)	96 (23.94)	188 (23.50)
Unable to work due to caring responsibilities	33 (8.27)	33 (8.23)	66 (8.25)
Unable to work due to ill health/disability	30 (7.52)	20 (4.99)	50 (6.25)
Unemployed	10 (2.51)	8 (2.00)	18 (2.25)
Student	7 (1.75)	8 (2.00)	15 (1.88)
Retired	53 (13.28)	58 (14.46)	111 (13.88)
Voluntary work	12 (3.01)	11 (2.74)	23 (2.88)
Housewife/House husband	12 (3.01)	16 (3.99)	28 (3.50)
Home internet access			
Yes	395 (99.00)	400 (99.75)	795 (99.38)
No/ Intermittent or poor quality	4 (1.00)	1 (0.25)	5 (0.63)
Characteristics of service user (not mutually exclusive)			
Diagnosis			
Bipolar disorder/Bipolar affective disorder/Manic depression	229	233	462
Schizophrenia	57	51	108
Schizoaffective disorder	17	32	49
Psychosis	61	51	112
Other	115	103	218
Don't know	43	41	84
Undefined	38	52	90
Age (years)			

	REACT N = 399	RD N = 401	Overall N = 800
Under 16	18	18	36
16-20	34	43	77
21-25	67	70	137
26-30	65	58	123
31-35	50	62	112
36-40	46	45	91
41-45	43	38	81
46-50	33	34	67
51-55	36	30	66
56-60	20	21	41
61-65	28	24	52
66-70	19	20	39
71-75	14	7	21
76-80	24	7	31
81-85	9	16	25
≥86	13	18	31
Paid work affected by caring role			
No, I didn't have paid work before	120 (30.08)	125 (31.17)	245 (30.63)
No, I still perform the same amount of paid work	198 (49.62)	195 (48.63)	393 (49.13)
Yes, I stopped work completely	40 (10.03)	33 (8.23)	73 (9.13)
Yes, I reduced my working hours	41 (10.28)	48 (11.97)	89 (11.13)
Please specify:			
Mean (SD)	13.5 (9.3)	11.4 (6.6)	12.4 (8.0)
Min - max	2 – 48	1 – 30	1 - 48

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\ BASELINE_CLOSED.sas

6.1.2 Baseline assessments

Table 6-2 Baseline assessments

	REACT N = 399	RD N = 401	Overall N = 800
General Health Questionnaire (GHQ-28)			
Mean (SD)	40.3 (14.6)	40.0 (14.0)	40.2 (14.3)
Min - max	5 - 83	11 - 81	5 - 83
GHQ-28 subscales			
Somatic symptoms			
Mean (SD)	10.3 (4.4)	10.4 (4.0)	10.3 (4.2)
Min - max	1 - 21	1 - 21	1 – 21
Anxiety/insomnia			
Mean (SD)	13.0 (4.1)	12.9 (4.0)	13.0 (4.1)
Min - max	0 - 21	1 - 21	0 – 21
Social dysfunction			
Median (IQR)	11 (8 – 13)	11 (8 – 14)	11 (8 – 13.5)
Min - max	1 - 21	3 - 21	1 – 21
Severe depression			
Median (IQR)	4 (1 – 9)	4 (1 – 9)	4 (1 – 9)
Min - max	0 - 21	0 - 21	0 – 21
The Carer Well-Being and Support Questionnaire (CWS)			
Well-being			
Mean (SD)	55.9 (25.9)	55.8 (26.4)	55.9 (26.1)
Min - max	0 - 125	0 - 114	0 - 125
Support			
Mean (SD)	19.5 (11.6)	18.8 (11.7)	19.1 (11.7)
Min - max	0 - 51	0 - 51	0 - 51
Brief Illness Perception Questionnaire (IPQ)			
Carer			
Mean (SD)	41.0 (7.4)	41.4 (6.9)	41.2 (7.2)
Min - max	21 - 65	19 - 63	19 - 65
Service user			
Mean (SD)	44.4 (8.5)	44.2 (8.6)	44.3 (8.6)
Min - max	19 - 70	18 - 75	18 - 75
Additional item on coping			
Mean (SD)	5.6 (2.2)	5.6 (2.3)	5.6 (2.2)
Min - max	0 - 10	0 - 10	0 – 10

	REACT N = 399	RD N = 401	Overall N = 800
Brief COPE			
Self-distraction			
Median (IQR)	5 (4 – 6)	5 (4 – 7)	5 (4 – 6)
Min - max	2 - 8	2 - 8	2 - 8
Active coping			
Median (IQR)	5 (4 – 7)	6 (4 – 7)	5 (4 – 7)
Min - max	2 - 8	2 - 8	2 - 8
Denial			
Median (IQR)	2 (2 – 3)	2 (2 – 3)	2 (2 – 3)
Min - max	2 - 8	2 - 8	2 – 8
Substance use			
Median (IQR)	2 (2 – 4)	2 (2 – 4)	2 (2 – 4)
Min - max	2 - 8	2 - 8	2 – 8
Use of emotional support			
Median (IQR)	4 (3 – 5)	4 (3 – 5)	4 (3 – 5)
Min - max	2 - 8	2 - 8	2 – 8
Use of instrumental support			
Median (IQR)	4 (3 – 6)	4 (3 – 6)	4 (3 – 6)
Min - max	2 - 8	2 - 8	2 – 8
Behavioural disengagement			
Median (IQR)	3 (2 – 4)	3 (2 – 4)	3 (2 – 4)
Min - max	2 - 8	2 - 8	2 – 8
Venting			
Median (IQR)	4 (3 – 5)	4 (3 – 5)	4 (3 – 5)
Min - max	2 - 8	2 - 8	2 – 8
Positive reframing			
Median (IQR)	4 (3 – 5)	4 (3 – 5)	4 (3 – 5)
Min - max	2 - 8	2 - 8	2 – 8
Planning			
Median (IQR)	6 (4 – 8)	6 (4 – 7)	6 (4 – 7)
Min - max	2 - 8	2 - 8	2 – 8
Humour			
Median (IQR)	3 (2 – 4)	3 (2 – 4)	3 (2 – 4)
Min - max	2 - 8	2 - 8	2 – 8
Acceptance			
Median (IQR)	6 (5 – 7)	6 (5 – 7)	6 (5 – 7)
Min - max	2 - 8	2 - 8	2 – 8

	REACT N = 399	RD N = 401	Overall N = 800
Religion			
Median (IQR)	2 (2 – 4)	2 (2 – 4)	2 (2 – 4)
Min - max	2 - 8	2 - 8	2 – 8
Self-blame			
Median (IQR)	4 (3 – 6)	4 (3 – 6)	4 (3 – 6)
Min - max	2 - 8	2 - 8	2 – 8
Questions about income			
Personal level of net income over the last 12 weeks from paid work:			
Weekly	25 (6.3%)	37 (9.2%)	62 (7.8%)
Up to £99	7	13	20
£100 and up to £199	9	10	19
£200 and up to £299	4	7	11
£300 and up to £399	3	4	7
£400 and up to £499	2	0	2
£500 and up to £599	0	2	2
£600 and up to £699	0	0	0
£700 and up to £799	0	0	0
£800 and up to £899	0	0	0
£900 and up to £999	0	0	0
£1000 and above	0	1	1
Monthly:	182 (45.6%)	157 (39.2%)	339 (42.4%)
Up to £435*	12	8	20
£436 and up to £867	25	21	46
£868 and up to £1300	55	47	102
£1301 and up to £1733	28	31	59
£1734 and up to £2167	18	19	37
£2168 and up to £2600	17	12	29
£2601 and up to £3033	12	9	21
£3034 and up to £3467	1	3	4
£3468 and up to £3900	2	2	4
£3901 and up to £4333	4	2	6
£4334 and above	8	3	11
Annually	16 (4.0%)	20 (5.0%)	36 (4.5%)
Up to £5,199	0	0	0
£5,200 and up to £10,399	0	1	1
£10,400 and up to £15,599	3	5	8
£15,600 and up to £20,799	4	2	6
£20,800 and up to £25,999	1	2	3
£26,000 and up to £31,199	3	2	5
£31,200 and up to £36,399	1	3	4
£36,400 and up to £41,599	1	3	4
£41,600 and up to £46,799	0	1	1
£46,800 and up to £51,999	1	0	1
£52,000 and above	2	1	3

	REACT N = 399	RD N = 401	Overall N = 800
None	111 (27.8%)	102 (25.4%)	213 (26.6%)
Rather not say	61 (15.3%)	81 (20.2%)	142 (17.8%)
Missing	4 (1.0%)	4 (1.0%)	8 (1.0%)
Received a Carer's allowance during the last 12 weeks			
Yes	40 (10.0%)	34 (8.5%)	74 (9.3%)
No	356 (89.2%)	360 (89.8%)	716 (89.5%)
Rather not say	3 (0.8%)	6 (1.5%)	9 (1.1%)
Missing	0 (0.0%)	1 (0.3%)	1 (0.1%)
Personal level of net income over the last 12 weeks from benefits/pensions:			
Weekly	50 (12.5%)	45 (11.2%)	95 (11.9%)
Up to £99	17	20	37
£100 and up to £199	20	15	35
£200 and up to £299	7	7	14
£300 and up to £399	3	1	4
£400 and up to £499	2	1	3
£500 and up to £599	0	1	1
£600 and up to £699	0	0	0
£700 and up to £799	0	0	0
£800 and up to £899	1	0	1
£900 and up to £999	0	0	0
£1000 and above	0	0	0
Monthly:	129 (32.3%)	115 (28.7%)	244 (30.5%)
Up to £435*	27	24	51
£436 and up to £867	33	25	58
£868 and up to £1300	25	25	50
£1301 and up to £1733	16	20	36
£1734 and up to £2167	11	11	22
£2168 and up to £2600	6	6	12
£2601 and up to £3033	5	3	8
£3034 and up to £3467	0	0	0
£3468 and up to £3900	1	1	2
£3901 and up to £4333	1	0	1
£4334 and above	4	0	4
Annually	11 (2.8%)	11 (2.7%)	22 (2.8%)
Up to £5,199	3	1	4
£5,200 and up to £10,399	2	1	3
£10,400 and up to £15,599	2	2	4
£15,600 and up to £20,799	1	3	4
£20,800 and up to £25,999	0	2	2
£26,000 and up to £31,199	1	1	2
£31,200 and up to £36,399	0	0	0
£36,400 and up to £41,599	1	1	2
£41,600 and up to £46,799	0	0	0

	REACT N = 399	RD N = 401	Overall N = 800
£46,800 and up to £51,999	0	0	0
£52,000 and above	1	0	1
None	130 (32.6%)	138 (34.4%)	268 (33.5%)
Rather not say	77 (19.3%)	89 (22.2%)	166 (20.8%)
Missing	3 (0.8%)	2 (0.5%)	5 (0.6%)

*Participants were shown the category of “Up to £433” rather than “Up to £435”.

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SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\CWS.sas
SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\BIPQ.sas
SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\COPING.sas
SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\INCOME.sas

6.2 Study population

6.2.1 Data sets analysed

Table 6-3 Data sets analysed

Population	REACT	RD	Overall
Randomised	399	401	800
Intention-to-treat	399 (100.0%)	401 (100.0%)	800 (100.0%)
Safety	399 (100.0%)	401 (100.0%)	800 (100.0%)

6.2.2 Protocol deviations and technical issues

Table 6-4 Protocol deviations

Protocol deviations: n (%)	REACT	RD	Overall
n	399	401	800
Any protocol deviation	192 (48.1%)	162 (40.4%)	354 (44.3%)
At least one major:	192 (48.1%)	162 (40.4%)	354 (44.3%)
At least one minor:	0 (0.0%)	0 (0.0%)	0 (0.0%)

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PROTOCOL_DEVIATIONS.sas

Table 6-5 Protocol deviations

Protocol specification	Potential deviation(s)	REACT N = 399	RD N = 401	Total N = 800
Inclusion criteria				
Aged over 16	Recruiting children under the age of 16	0 (0.0%)	0 (0.0%)	0 (0.0%)
A relative/close friend of someone with psychosis or BD	Recruiting participants who do not have a relative/close friend with a mental health problem	0 (0.0%)	0 (0.0%)	0 (0.0%)
Distressed (according to GHQ item score)	Recruiting participants who are not distressed	0 (0.0%)	0 (0.0%)	0 (0.0%)
Help-seeking	Recruiting participants who are not seeking help	0 (0.0%)	0 (0.0%)	0 (0.0%)
Regular access to a computer which is connected to the internet	Recruiting participants who do not have regular access to a computer connected to the internet	0 (0.0%)	0 (0.0%)	0 (0.0%)
A good working knowledge of written and spoken English language	Recruiting participants who do not have a good working knowledge of written and spoken English language	0 (0.0%)	0 (0.0%)	0 (0.0%)
Exclusion criteria				
Living outside the UK	Recruiting participants who live outside of the UK	0 (0.0%)	0 (0.0%)	0 (0.0%)
Living within any of the 6 areas involved in the IMPART study	Recruiting participants who are receiving the REACT intervention as part of the IMPART study	0 (0.0%)	0 (0.0%)	0 (0.0%)
Treatment regime				
Only participants in the REACT arm are permitted to access the REACT toolkit	Participants in the control arm access the REACT toolkit	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study assessments				
Baseline assessment of distress measures	Missing baseline assessments	0 (0.0%)	0 (0.0%)	0 (0.0%)
Baseline demographic information	Missing baseline demographic information	31 (7.8%)	31 (7.7%)	62 (7.8%)
12 week outcome measures	Missing 12 week outcome measures	112 (28.1%)	94 (23.4%)	206 (25.8%)

Protocol specification	Potential deviation(s)	REACT N = 399	RD N = 401	Total N = 800
24 week outcome measures	Missing 24 week outcome measures	107 (26.8%)	94 (23.4%)	201 (25.1%)
Registrations				
Single registration per participant	Multiple registrations by a particular participant	0 (0.0%)	0 (0.0%)	0 (0.0%)
Single relative/friend per service user	Multiple relatives/friends of a single service user	0 (0.0%)	0 (0.0%)	0 (0.0%)
Risk protocol				
Risk protocol to be followed if any participants are identified as being at increased risk	Failure to follow risk protocol (by TM or CI)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Email contact with participants*				
Email contact to participants regarding follow up reminders or secondary randomisation allocation	Any inaccuracies associated with the email contact with participants	26 (6.5%)	20 (5.0%)	46 (5.8%)
Online intervention*				
Downtime of the online intervention (for example, time spent fixing bugs)	Time when the participants are not able to access their assigned online intervention (for example, due to maintenance or bug-fixing)	3 (0.8%)	2 (0.5%)	5 (0.6%)

** Details of these (and other technical issues that were not classed as protocol deviations) are listed in Table 6-6.*

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PROTOCOL_DEVIATIONS.sas

Table 6-6: Technical issues

Issue
12 week reminder emails sent 1-4 days late to 19 participants.
All participants receiving reminder emails to visit the intervention site rather than just the invention arm.
Email reminders not being sent (3 instances throughout trial)
Reminder email sent to participant rather than REACT team
Participant received 2 vouchers for completing 12 week follow-up
15 participants received 24 week follow-up reminder emails without the value of the voucher included
Participant received voucher for 12 week follow-up when completing 24 week follow-up
Participant received reminder emails for follow-up and to visit the site but participant had withdrawn (3 instances throughout trial)
Participant received 5 vouchers
4 participants could not move past question 2 on the baseline questionnaires
System would not allow participant to complete 24 week follow-up
2 participants received 2 “thank you” emails for completing 24 week follow-up
Participant received 2 vouchers for completing 12 week follow-up
2 participants received 2 support emails
6 emails to REACT supporters had participant emails copied in – alerts from the intervention site turned off for 2 days due to this
Activation texts not sent out to 2 participants
1 baseline and 5 12-week “thank you” emails sent with no voucher codes
Multiple usernames allowed (2 with one username, 3 with another). Only the first person with each username could access the intervention site
Participant registered 24 week follow-up as 12 week and received vouchers for both time points
Thank you messages not being sent
Website unavailable to control group
Participant received 4 randomisation emails (but was only randomised once)
Pop-up boxes appearing blank on website
Participant incorrectly completed questionnaire (completed on behalf of partner rather than themselves)
Participant received 5 randomisation emails and vouchers (but was only randomised once)
Participants could leave some baseline questions blank
Participant could not access site due to duplicated username with REACT supporter

Participant not recorded as randomised on database due to the participant pressing the “back” button on the browser before the randomisation process had completed
Text message sent to participant which included another participant’s email address
24 week auto texts not sending
Website went down for 12 hours overnight
Participant was able to provide baseline data before giving contact details, but after consent had taken place
Emails for forgotten username/password not being sent out
URL in message on website was disabled after randomisation but not removed from message
Text message bundle that was purchased for auto reminders had expired, but did not affect any processes

6.3 Compliance with treatment

The first record of a web-page download was on 15-Jun-2017 the following summaries therefore exclude anyone randomised on or before this date.

Table 6-7 Compliance with treatment

	REACT N=348	RD N=352	Overall N=700
Total number of webpage downloads from intervention site[a]			
N	51416	4276	55692
Mean (STD)	149.9 (266)	12.7 (39.1)	82 (202.9)
Median (IQR)	69 (18, 179)	6 (3, 13)	14 (5, 76)
Min - max	1 - 3501	1 - 651	1 - 3501
Total number of times participants logged on to intervention site[a]			
Number of participants who logged in	343	336	679
Total number of logins	2724	681	3405
Mean (STD)	7.9 (13.3)	2 (1.7)	5 (10)
Median (IQR)	4 (2, 9)	1 (1, 2)	2 (1, 5)
Min - max	1 - 159	1 - 12	1 - 159
Total time spent on REACT intervention page per person (mins)[b]			
Number of people who accessed page	343	N/A	N/A
Total time (across all participants)	46531.5	N/A	N/A
Mean time on page per person (STD)	135.7 (296.8)	N/A	N/A
Median time on page per person (IQR)	50.8 (12.4, 172.1)	N/A	N/A
Min – max time spent on page	0.1, 4505.5	N/A	N/A
Number of participants who did not log on to intervention site	5	16	21
Number of participants who did not log on to intervention site after their initial login	75	184	259

[a]Not including randomisation; [b]Including time immediately after randomisation..

Note - inactivity time on a given page is capped at 20 minutes to allow for prolonged periods of inactivity when participants do not actively log off from the intervention. Given that these capped values are not likely to reflect the true time spent on a given page and are likely to skew the data, values including a capped inactivity period of 20 minutes for a given webpage were replaced with the mean total time spent on that webpage for all participants randomised to the REACT intervention (excluding those with capped values for that webpage). Note that the time spent on the final webpage of a given login session for a participant is not available; therefore if there is a video on this webpage, video feedback data will allow calculation of the time spent on this page accurate to within 5 seconds. If there is no video on this page, it was assumed that the time spent on this page is equal to the mean time that they had spent on all previous webpages to date.

6.3.1 Compliance information split by module

The information below will be reproduced for each of the 12 information modules, forum and direct messaging separately **for the REACT group only**, and for the Resource Directory for both groups.

Table 6-8 Resource directory usage

	REACT N=348	RD N=352	Overall N=700
Page hits per person			
Total number of page hits	971	645	1616
Mean page hits per person (STD)	5.1 (5.6)	2.5 (3.9)	3.7 (4.9)
Median page hits per person (IQR)	3 (2, 7)	2 (1, 3)	2 (1, 4)
Min – max page hits per person	1, 37	1, 58	1, 58
Total time spent on page per person (mins)			
Number of people who accessed page	189	253	442
Total time (across all participants)	159.7	189.0	348.7
Mean time on page per person (STD)	4.7 (7.9)	2.2 (5.2)	3.3 (6.6)
Median time n page per person (IQR)	1.4 (0.5, 5.5)	0.5 (0, 1.6)	0.9 (0, 3)
Min – max time spent on page	0, 55.8	0, 42.9	0, 55.8

Table 6-9 REACT module usage

MODULE 1 – What is psychosis	
Page hits per person	
Total number of page hits	1978
Mean page hits per person (STD)	9.6 (9.8)
Median page hits per person (IQR)	7 (3, 13)
Min – max page hits per person	1, 71
Total time spent on page per person (mins)	
Number of people who accessed page	205
Total time (across all participants)	188.4
Mean time on page per person (STD)	11.4 (13.1)
Median time on page per person (IQR)	1.4 (0.5, 5.5)
Min – max time spent on page	0, 55.8
MODULE 2 – What is bipolar disorder	
Page hits per person	
Total number of page hits	2352
Mean page hits per person (STD)	11.6 (11)
Median page hits per person (IQR)	9 (4, 15)
Min – max page hits per person	1, 71
Total time spent on page per person (mins)	
Number of people who accessed page	203
Total time (across all participants)	158.7
Mean time on page per person (STD)	14.6 (17.4)
Median time on page per person (IQR)	8.2 (2.3, 20.4)
Min – max time spent on page	0.1, 97.4
MODULE 3 – Managing positive symptoms	
Page hits per person	
Total number of page hits	1749
Mean page hits per person (STD)	10.7 (8.7)
Median page hits per person (IQR)	9 (4, 14)
Min – max page hits per person	1, 61
Total time spent on page per person (mins)	
Number of people who accessed page	163
Total time (across all participants)	167.1
Mean time on page per person (STD)	13.1 (15.6)
Median time on page per person (IQR)	5.7 (1.8, 20.4)
Min – max time spent on page	0, 75.8
MODULE 4 – Managing negative symptoms	
Page hits per person	
Total number of page hits	1634
Mean page hits per person (STD)	10.7 (13.0)
Median page hits per person (IQR)	8 (3, 12)
Min – max page hits per person	1, 81
Total time spent on page per person (mins)	
Number of people who accessed page	153
Total time (across all participants)	127.5
Mean time on page per person (STD)	14.2 (23.2)
Median time on page per person (IQR)	4.6 (1.2 18.1)
Min – max time spent on page	0.1, 167.3

MODULE 5 – Managing mood swings	
Page hits per person	
Total number of page hits	1173
Mean page hits per person (STD)	8.8 (7.3)
Median page hits per person (IQR)	8 (2, 11)
Min – max page hits per person	1, 37
Total time spent on page per person (mins)	
Number of people who accessed page	134
Total time (across all participants)	64.3
Mean time on page per person (STD)	7.3 (10.4)
Median time on page per person (IQR)	3.4 (0.6, 8.6)
Min – max time spent on page	0.1, 59.1
MODULE 6 – Dealing with difficult situations	
Page hits per person	
Total number of page hits	1392
Mean page hits per person (STD)	9.6 (8.7)
Median page hits per person (IQR)	7 (3, 12)
Min – max page hits per person	1, 48
Total time spent on page per person (mins)	
Number of people who accessed page	145
Total time (across all participants)	117.6
Mean time on page per person (STD)	11.8 (14.5)
Median time on page per person (IQR)	6.3 (1.6, 16.3)
Min – max time spent on page	0.1, 75.3
MODULE 7 – Managing stress – doing this differently	
Page hits per person	
Total number of page hits	1683
Mean page hits per person (STD)	12.7 (14.2)
Median page hits per person (IQR)	10 (2, 17)
Min – max page hits per person	1, 77
Total time spent on page per person (mins)	
Number of people who accessed page	133
Total time (across all participants)	75.2
Mean time on page per person (STD)	14.5 (25.3)
Median time on page per person (IQR)	5 (1.2, 17.4)
Min – max time spent on page	0, 194.8
MODULE 8 – Managing stress – thinking differently	
Page hits per person	
Total number of page hits	747
Mean page hits per person (STD)	6.9 (5.6)
Median page hits per person (IQR)	5.5 (3, 8)
Min – max page hits per person	1, 27
Total time spent on page per person (mins)	
Number of people who accessed page	108
Total time (across all participants)	52.2
Mean time on page per person (STD)	6.5 (7.8)
Median time on page per person (IQR)	3.4 (1.2, 9.3)
Min – max time spent on page	0, 37.5

MODULE 9 – Understanding mental health services	
Page hits per person	
Total number of page hits	1581
Mean page hits per person (STD)	12.5 (17.1)
Median page hits per person (IQR)	6 (3, 16)
Min – max page hits per person	1, 133
Total time spent on page per person (mins)	
Number of people who accessed page	126
Total time (across all participants)	78.9
Mean time on page per person (STD)	11.7 (22.6)
Median time on page per person (IQR)	3.9 (0.4, 14.4)
Min – max time spent on page	0, 136
MODULE 10 – Treatment options	
Page hits per person	
Total number of page hits	1456
Mean page hits per person (STD)	10.4 (13.8)
Median page hits per person (IQR)	7 (2, 13)
Min – max page hits per person	1, 126
Total time spent on page per person (mins)	
Number of people who accessed page	140
Total time (across all participants)	152.3
Mean time on page per person (STD)	12.5 (30.0)
Median time on page per person (IQR)	5.1 (1.2, 14.7)
Min – max time spent on page	0, 329.7
MODULE 11 – Dealing with crises	
Page hits per person	
Total number of page hits	955
Mean page hits per person (STD)	8.5 (10.8)
Median page hits per person (IQR)	6 (2, 10)
Min – max page hits per person	1, 92
Total time spent on page per person (mins)	
Number of people who accessed page	113
Total time (across all participants)	66.5
Mean time on page per person (STD)	9.2 (16.9)
Median time on page per person (IQR)	3.3 (0.8, 9.2)
Min – max time spent on page	0, 129.3
MODULE 12 – Recovery: looking to the future	
Page hits per person	
Total number of page hits	891
Mean page hits per person (STD)	8.3 (6.9)
Median page hits per person (IQR)	7 (3, 10)
Min – max page hits per person	1, 45
Total time spent on page per person (mins)	
Number of people who accessed page	108
Total time (across all participants)	97.6
Mean time on page per person (STD)	10.1 (13.8)
Median time on page per person (IQR)	4.4 (1.3, 15.1)
Min – max time spent on page	0, 77.7

FORUM	
Page hits per person	
Total number of page hits	10733
Mean page hits per person (STD)	51.9 (142)
Median page hits per person (IQR)	13 (4, 48)
Min – max page hits per person	1, 1698
Total time spent on page per person (mins)	
Number of people who accessed page	207
Total time (across all participants)	209.3
Mean time on page per person (STD)	65.0 (201.2)
Median time on page per person (IQR)	12.1 (2.2, 58.4)
Min – max time spent on page	0, 2553.8
DIRECT MESSAGING	
Page hits per person	
Total number of page hits	976
Mean page hits per person (STD)	6.9 (11.4)
Median page hits per person (IQR)	2 (1, 8)
Min – max page hits per person	1, 71
Total time spent on page per person (mins)	
Number of people who accessed page	141
Total time (across all participants)	72.3
Mean time on page per person (STD)	15.8 (40.1)
Median time on page per person (IQR)	0.7 (0.2, 7.2)
Min – max time spent on page	0, 260.7

6.3.2 Reminders

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

Table 6-10: Intervention use (REACT group only) within 1 day, 3 days and 7 days of first reminder to access intervention compared to period prior to first reminder

	Daily rate within 1 day of first reminder	Daily rate within 3 days of first reminder[1]	Daily rate within 7 days of first reminder[2]	Daily rate prior to first reminder[3]
Page hits (average per person per day)				
Mean (STD)	2.9 (10.2)	2.0 (5.3)	1.3 (2.8)	3.0 (4.4)
Median (IQR)	0 (0, 0)	0 (0, 0.7)	0 (0, 1.6)	1.6 (0.5, 4.0)
Min – max	0, 94	0, 38.7	0, 24.6	0, 49.4
Total time spent on intervention (average per person per day in minutes)				
Mean (STD)	0.1 (0.4)	0.1 (0.3)	0.04 (0.1)	2.6 (3.6)
Median (IQR)	0 (0, 0)	0 (0, 0.02)	0 (0, 0. 1)	1.0 (0.2, 4.1)
Min – max	0, 4.8	0, 4.5	0, 0.7	0, 30.3

[1] Based on each participant's daily average over the 3 days following the first reminder
[2] Based on each participant's daily average over the 7 days following the first reminder
[3] Based on each participant's daily average over the period prior to the first reminder

SAS file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – Reminders v2.0.sas

6.3.3 Out of hours access

Table 6-11 Out of hours access

	Working week access[1]			Out of hours access[1]		
	REACT N=343	**RD N=336**	**Overall N=679**	**REACT N=343**	**RD N=336**	**Overall N=679**
Total number of webpage downloads from intervention site						
Mean (STD)	49.3 (99.0)	4.9 (12.2)	27.3 (74.2)	100.6 (193.3)	7.9 (30.3)	54.7 (146.4)
Median (IQR)	14 (0, 57)	0 (0, 5)	3 (0, 19)	44 (9, 124)	3 (1, 8)	8 (2, 48)
Min - max	0, 890	0, 128	0, 890	0, 2611	0, 523	0, 2611
Total number of times participants logged on to intervention site[a]						
Mean (STD)	2.8 (5.7)	0.8 (1.1)	1.8 (4.2)	5.1 (8.8)	1.3 (1.3)	3.2 (6.6)
Median (IQR)	1 (0, 3)	0 (0, 1)	1 (0, 2)	3 (1, 6)	1 (1, 2)	1 (1, 3)
Min - max	0, 54	0, 6	0, 54	0, 105	0, 9	0, 105
Total time spent on REACT intervention page per person (mins)[b]						
Mean time on page per person (STD)	58.9 (109.6)	6.6 (11.7)	37.4 (88.2)	97.3 (231.6)	6.2 (8.9)	56.3 (177.5)
Median time on page per person (IQR)	24.5 (4.8, 64.9)	3 (0.9, 6.7)	7.1 (2.2, 35.6)	33.6 (7.2, 110.2)	2.7 (1.1, 7.0)	8 (1.8, 45.4)
Min – max time spent on page	0.1, 1054.3	0, 97.3	0, 1054.3	0, 3445.8	0, 61	0, 3445.8

[1]The working week is defined as defined as 9am to 5pm Monday to Friday (excluding Bank Holidays) UK time; out of hours access is any other time.

SAS file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – Timing of Intervention.sas

6.4 Unblinding

Table 6-12: Unblinding reasons

Reason	REACT N = 399	RD N = 401	Overall N = 800
Participants complained about a forum message when calling/texting for follow-up			
Total	2 (0.5%)	0 (0.0%)	2 (0.3%)
Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
12 weeks	2 (0.5%)	0 (0.0%)	2 (0.3%)
24 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)
Participant emailed the team to change his username to maintain anonymity on forum			
Total	1 (0.3%)	0 (0.0%)	1 (0.1%)
Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
12 weeks	1 (0.3%)	0 (0.0%)	1 (0.1%)
24 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)
Participant emailed the team to say that she was disappointed for being in control arm			
Total	0 (0.0%)	1 (0.2%)	1 (0.1%)
Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
12 weeks	0 (0.0%)	1 (0.2%)	1 (0.1%)
24 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unblinded via enquiries from the REACT supporters			
Total	2 (0.5%)	0 (0.0%)	2 (0.3%)
Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
12 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)
24 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)
After all follow-up completed	2 (0.5%)	0 (0.0%)	2 (0.3%)
While helping participants to access measures, participant explained the screen and described the toolkit (over the phone).			
Total	2 (0.5%)	0 (0.0%)	2 (0.3%)
Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
12 weeks	2 (0.5%)	0 (0.0%)	2 (0.3%)
24 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)
Participant lost interest in REACT due to being in control arm- disclosed over the follow-up reminder phone call			
Total	0 (0.0%)	1 (0.2%)	1 (0.1%)

Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
12 weeks	0 (0.0%)	1 (0.2%)	1 (0.1%)
24 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)
Participant replied to FU reminder text saying gone through modules			
Total	1 (0.3%)	0 (0.0%)	1 (0.1%)
Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
12 weeks	1 (0.3%)	0 (0.0%)	1 (0.1%)
24 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)
Participant had forgotten login to toolkit (discussed over a follow-up reminder phone call)			
Total	1 (0.3%)	0 (0.0%)	1 (0.1%)
Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
12 weeks	1 (0.3%)	0 (0.0%)	1 (0.1%)
24 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)
Participant emailed REACT with access issues to the toolkit			
Total	1 (0.3%)	0 (0.0%)	1 (0.1%)
Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
12 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)
24 weeks	1 (0.3%)	0 (0.0%)	1 (0.1%)
Participant emailed to thank us for toolkit allocation			
Total	1 (0.3%)	0 (0.0%)	1 (0.1%)
Baseline	1 (0.3%)	0 (0.0%)	1 (0.1%)
12 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)
24 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)
Participant gave feedback on toolkit (follow-up reminder phone call)			
Total	1 (0.3%)	0 (0.0%)	1 (0.1%)
Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
12 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)
24 weeks	1 (0.3%)	0 (0.0%)	1 (0.1%)
Total Unblinding events	12 (3.0%)	2 (0.5%)	14 (1.8%)
Baseline	1 (0.3%)	0 (0.0%)	1 (0.1%)
12 weeks	7 (1.8%)	2 (0.5%)	9 (1.1%)
24 weeks	2 (0.5%)	0 (0.0%)	2 (0.3%)
After all follow-up completed	2 (0.5%)	0 (0.0%)	2 (0.3%)

Note: There was also one unblinding event of the voucher value

6.5 Safety data

6.5.1 Adverse events and Serious adverse events (in terms of number of times the risk protocol was triggered)

6.5.1.1 Adverse events (AEs) and Serious adverse events (SAEs) (in terms of number of times the risk protocol was triggered)

Table 6-13 Adverse events (AEs) and Serious adverse events (SAEs) (in terms of number of times the risk protocol was triggered)

Risk protocol triggered	REACT N = 399		RD N = 401		Overall N = 800	
	Events: n	Participants: n(%)	Events: n	Participants: n(%)	Events: n	Participants: n(%)
Low risk events (AE)	16	10 (2.5%)	3	2 (0.5%)	19	12 (1.5%)
High risk events (SAE)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\RISK_STATUS.sas

Low risk events are classified as Adverse Events, and high risk events are classified as Serious Adverse Events.

- From a total of 800 patients, 19 low risk protocol events have been reported from 12 (1.5 %) patients.
  - From a total of 399 patients on the REACT arm, 16 low risk events have been identified from 10 (2.5%) patients.
  - From a total of 401 patients on the RD arm, 3 low risk events have been identified from 2 (0.5%) patients.
- From a total of 800 patients, 0 high risk protocol events have been reported from 0 (0.0 %) patients.

Table 6-14 Risk protocol triggers

Low risk events (AE)

	Number of events (number of people)		
Identification source	REACT N = 399	RD N = 401	Total N = 800
TM	0 (0)	3 (2)	3 (2)
Phone call	0 (0)	3 (2)	3 (2)
REACT supporter	16 (10)	0 (0)	16 (10)
Forum	8 (5)	0 (0)	8 (5)
Direct messaging	5 (4)	0 (0)	5 (4)
Email	3 (2)	0 (0)	3 (2)

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\RISK_STATUS.sas

Table 6-15 Red flag items

Number of randomised participants with red flag answers: 363
Number of randomised participants with more than one red flag answer: 185

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

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\RED_FLAG.sas

6.6 Efficacy data

6.6.1 Primary efficacy assessment – General Health Questionnaire (GHQ-28) at 24 weeks

6.6.1.1 Primary efficacy assessment – ITT analysis

Table 6-16: Primary efficacy results

	REACT	RD	Overall
General Health Questionnaire (GHQ-28)			
n	292	307	599
Mean (SD)	29.6 (15.9)	31.3 (15.2)	30.5 (15.6)
Min - max	2 - 79	3 - 81	2 - 81

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PRIMARY_OUTCOME.sas

Table 6-17: Analysis of covariance, adjusting for baseline GHQ-28

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

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PRIMARY_OUTCOME.sas

Table 6-18 GHQ-28 subscales

	REACT N = 292	RD N = 307	Overall N = 599
Somatic symptoms			
Mean (SD)	7.9 (4.7)	8.3 (4.5)	8.1 (4.6)
Min - max	0 - 21	0 - 21	0 - 21
Anxiety/insomnia			
Mean (SD)	9.2 (4.9)	9.9 (4.9)	9.6 (4.9)
Min - max	0 - 21	0 – 21	0 - 21
Social dysfunction			
Median (IQR)	8 (7 – 11)	8 (7 – 11)	8 (7 – 11)
Min - max	0 - 21	0 - 20	0 - 21
Severe depression			
Median (IQR)	2 (0 – 6)	2 (0 – 7)	2 (0 – 7)
Min - max	0 - 21	0 - 21	0 - 21

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PRIMARY_OUTCOME.sas

Table 6-19: Analysis of covariance for Somatic symptoms, adjusting for baseline Somatic symptoms

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline Somatic symptoms	0.44 (0.36, 0.53)	116.62	<.0001
Treatment (REACT versus control)	-0.29 (-0.97, 0.38)	0.74	0.3914

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PRIMARY_OUTCOME.sas

Table 6-20: Analysis of covariance for Anxiety/insomnia, adjusting for baseline Anxiety/insomnia

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline Anxiety/insomnia	0.49 (0.40, 0.58)	107.56	<.0001
Treatment (REACT versus control)	-0.64 (-1.37, 0.08)	3.07	0.0805

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PRIMARY_OUTCOME.sas

Table 6-21: Mann Whitney U test for Social dysfunction

Covariate	p-value
Treatment (REACT versus control)	0.3090

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PRIMARY_OUTCOME.sas

Table 6-22: Mann Whitney U test for Severe depression

Covariate	p-value
Treatment (REACT versus control)	0.3110

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PRIMARY_OUTCOME.sas

Table 6-23: MANOVA GHQ-28 subscales - 24 Weeks

Source	Statistic	F statistic	p-value
Model			
Wilks' lambda	0.4	2.2	<0.0001
Pillai's trace	0.8	2.1	<0.0001
Lawley-Hotelling trace	1.1	2.3	<0.0001
Roy's largest root	0.6	4.7	<0.0001
Treatment group			
Wilks' lambda	1.0	1.0	0.4083
Pillai's trace	0.01	1.0	0.4083
Lawley-Hotelling trace	0.01	1.0	0.4083
Roy's largest root	0.01	1.0	0.4083
Baseline GHQ-28 score			
Wilks' lambda	0.4	2.2	<0.0001
Pillai's trace	0.8	2.1	<0.0001
Lawley-Hotelling trace	1.1	2.3	<0.0001
Roy's largest root	0.6	4.8	<0.0001

Number included in analysis - REACT: N=292; RD: N=307.

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – MANOVA.do

Table 6-23 shows the results from a multivariate analysis of covariance model where the outcome variables are the GHQ-28 subscales at 24 weeks: somatic symptoms, anxiety/insomnia, social dysfunction and severe depression. The model was adjusted for baseline overall GHQ-28 score. The p-values for the tests associated with the overall model

are all <0.0001, but this effect is due to the baseline GHQ-28 score adjustment (p<0.0001), rather than because of a difference between randomised groups (p=0.4083).

6.6.2 Primary efficacy assessment – General Health Questionnaire (GHQ-28) at 24 weeks (Caseness)

6.6.2.1 Primary efficacy assessment – ITT analysis (Caseness)

Table 6-24: Primary efficacy results

	REACT	RD	Overall
General Health Questionnaire (GHQ-28)			
n	292	307	599
Mean (SD)	8.2 (7.8)	9.0 (7.6)	8.6 (7.7)
Min - max	0 - 28	0 - 28	0 - 28

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PO_CASENESS.sas

Table 6-25: Analysis of covariance, adjusting for baseline GHQ-28

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline GHQ-28	0.42 (0.34, 0.51)	91.87	<.0001
Treatment (REACT versus control)	-0.70 (-1.85, 0.45)	1.44	0.2304

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\ PO_CASENESS.sas
Number included in analysis - REACT: N=292; RD: N=307.

Table 6-26 GHQ-28 subscales

	REACT N = 292	RD N = 307	Overall N = 599
Somatic symptoms			
Mean (SD)	2.4 (2.3)	2.5 (2.3)	2.4 (2.3)
Min - max	0 - 7	0 - 7	0 - 7
Anxiety/insomnia			
Mean (SD)	2.8 (2.5)	3.1 (2.6)	3.0 (2.6)
Min - max	0 - 7	0 – 7	0 - 7
Social dysfunction			
Median (IQR)	1 (0 - 4)	1 (0 - 4)	1 (0 – 4)
Min - max	0 - 7	0 - 7	0 - 7
Severe depression			
Median (IQR)	0 (0 – 1)	0 (0 – 2)	0 (0 – 1)
Min - max	0 - 7	0 - 7	0 - 7

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PRIMARY_OUTCOME.sas

Table 6-27: Analysis of covariance for Somatic symptoms, adjusting for baseline Somatic symptoms

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline Somatic symptoms	0.33 (0.25, 0.41)	60.00	<.0001
Treatment (REACT versus control)	-0.07 (-0.43, 0.28)	0.16	0.6850

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\ PO_CASENESS.sas
Number included in analysis - REACT: N=292; RD: N=307.

Table 6-28: Analysis of covariance for Anxiety/insomnia, adjusting for baseline Anxiety/insomnia

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline Anxiety/insomnia	0.35 (0.25, 0.46)	46.20	<.0001
Treatment (REACT versus control)	-0.31 (-0.71, 0.08)	2.39	0.1225

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\ PO_CASENESS.sas
Number included in analysis - REACT: N=292; RD: N=307.

Table 6-29: Mann Whitney U test for Social dysfunction

Covariate	p-value
Treatment (REACT versus control)	0.4031

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\ PO_CASENESS.sas
Number included in analysis - REACT: N=292; RD: N=307.

Table 6-30: Mann Whitney U test for Severe depression

Covariate	p-value
Treatment (REACT versus control)	0.1106

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\ PO_CASENESS.sas
Number included in analysis - REACT: N=292; RD: N=307.

Table 6-31: MANOVA GHQ-28 case subscales - 24 Weeks

Source	Statistic	F statistic	p-value
Model			
Wilks' lambda	0.7	2.1	<0.0001
Pillai's trace	0.4	2.1	<0.0001
Lawley-Hotelling trace	0.5	2.2	<0.0001
Roy's largest root	0.3	5.8	<0.0001
Treatment group			
Wilks' lambda	1.0	0.7	0.5844
Pillai's trace	0.01	0.7	0.5844
Lawley-Hotelling trace	0.01	0.7	0.5844
Roy's largest root	0.01	0.7	0.5844
Baseline GHQ-28 score			
Wilks' lambda	0.7	2.2	<0.0001
Pillai's trace	0.4	2.1	<0.0001
Lawley-Hotelling trace	0.4	2.3	<0.0001
Roy's largest root	0.3	5.9	<0.0001

Number included in analysis - REACT: N=292; RD: N=307.

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – MANOVA.do

Number included in analysis - REACT: N=292; RD: N=307.

Table 6-31 shows the results from a multivariate analysis of covariance model where the outcome variables are the GHQ-28 subscales at 24 weeks: somatic symptoms, anxiety/insomnia, social dysfunction and severe depression. The model was adjusted for baseline overall GHQ-28 score. The p-values for the tests associated with the overall model are all <0.0001, but this effect is due to the baseline GHQ-28 score adjustment (p<0.0001), rather than because of a difference between randomised groups (p=0.5844).

6.6.3 Secondary efficacy endpoint - General Health Questionnaire (GHQ-28) at 12 weeks

6.6.3.1 Secondary efficacy assessment – ITT analysis

Table 6-32: GHQ at 12 weeks

	REACT N = 287	RD N = 307	Overall N = 594
General Health Questionnaire (GHQ-28)			
Mean (SD)	30.6 (15.2)	32.9 (15.4)	31.8 (15.3)
Min - max	3 - 80	1 - 77	1 - 80
Subscales			
Somatic symptoms			
Mean (SD)	8.1 (4.3)	8.7 (4.4)	8.4 (4.4)
Min - max	0 - 21	0 - 21	0 - 21
Anxiety/insomnia			
Mean (SD)	9.5 (4.7)	10.1 (4.8)	9.8 (4.7)
Min - max	0 - 21	0 – 21	0 - 21
Social dysfunction			
Median (IQR)	8 (7 – 11)	9 (7 – 13)	9 (7 – 12)
Min - max	0 - 21	0 – 21	0 - 21
Severe depression			
Median (IQR)	2 (0 – 7)	3 (0 – 7)	2 (0 – 7)
Min - max	0 - 21	0 - 21	0 – 21

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\SECONDARY_OUTCOME_1.sas

Table 6-33: Analysis of covariance, adjusting for baseline GHQ-28 (12 weeks)

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline GHQ-28	0.61 (0.53, 0.68)	265.18	<.0001
Treatment (REACT versus control)	-2.08 (-4.14, -0.03)	4.91	0.0271

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\SECONDARY_OUTCOME_1.sas
Number included in analysis - REACT: N=287; RD: N=307.

Table 6-34: Analysis of covariance for Somatic symptoms, adjusting for baseline Somatic symptoms (12 weeks)

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline Somatic symptoms	0.48 (0.41, 0.55)	161.51	<.0001
Treatment (REACT versus control)	-0.48 (-1.11, 0.14)	2.33	0.1275

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\SECONDARY_OUTCOME_1.sas
Number included in analysis - REACT: N=287; RD: N=307.

Table 6-35: Analysis of covariance for Anxiety/insomnia, adjusting for baseline Anxiety/insomnia (12 weeks)

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline Anxiety/insomnia	0.53 (0.45, 0.62)	151.56	<.0001
Treatment (REACT versus control)	-0.61 (-1.30, 0.07)	3.13	0.0774

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\SECONDARY_OUTCOME_1.sas
Number included in analysis - REACT: N=287; RD: N=307.

Table 6-36: Mann Whitney U test for Social dysfunction (12 weeks)

Covariate	p-value
Treatment (REACT versus control)	0.0685

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\SECONDARY_OUTCOME_1.sas
Number included in analysis - REACT: N=287; RD: N=307.

Table 6-37: Mann Whitney U test for Severe depression (12 weeks)

Covariate	p-value
Treatment (REACT versus control)	0.1888

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\SECONDARY_OUTCOME_1.sas
Number included in analysis - REACT: N=287; RD: N=307.

Table 6-38: MANOVA GHQ-28 subscales - 12 Weeks

Source	Statistic	F statistic	p-value
Model			
Wilks' lambda	0.4	2.1	<0.0001
Pillai's trace	0.8	1.9	<0.0001
Lawley-Hotelling trace	1.2	2.3	<0.0001
Roy's largest root	0.8	6.4	<0.0001
Treatment (REACT versus control)			
Wilks' lambda	1.0	1.4	0.2481
Pillai's trace	0.01	1.4	0.2481
Lawley-Hotelling trace	0.01	1.4	0.2481
Roy's largest root	0.01	1.4	0.2481
Baseline GHQ-28 score			
Wilks' lambda	0.4	2.1	<0.0001
Pillai's trace	0.8	1.9	<0.0001
Lawley-Hotelling trace	1.2	2.4	<0.0001
Roy's largest root	0.8	6.5	<0.0001

Number included in analysis - REACT: N=287; RD: N=307.

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – MANOVA.do

Table **6-38** shows the results from a multivariate analysis of covariance model where the outcome variables are the GHQ-28 subscales at 12 weeks: somatic symptoms, anxiety/insomnia, social dysfunction and severe depression. The model was adjusted for baseline overall GHQ-28 score. The p-values for the tests associated with the overall model are all <0.0001, but this effect is due to the baseline GHQ-28 score adjustment (p<0.0001), rather than because of a difference between randomised groups (p=0.2481).

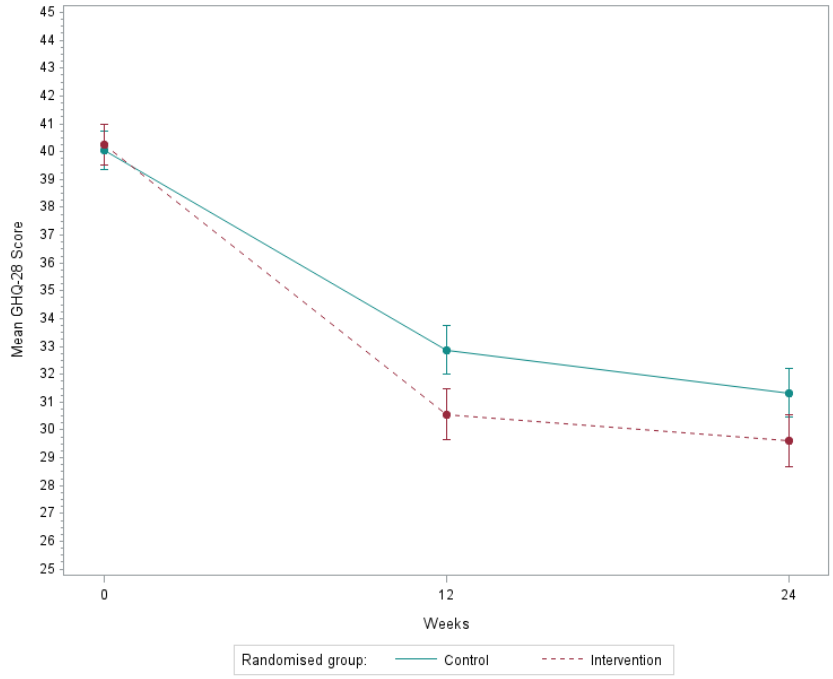
6.6.4 Joint modelling analysis – GHQ-28 score

The longitudinal process was modelled using a linear submodel with a random intercept and slope; the covariates were randomised group and time of assessment as a continuous variable.

The survival process was modelled using a Weibull proportional hazards submodel including a covariate for randomised group.

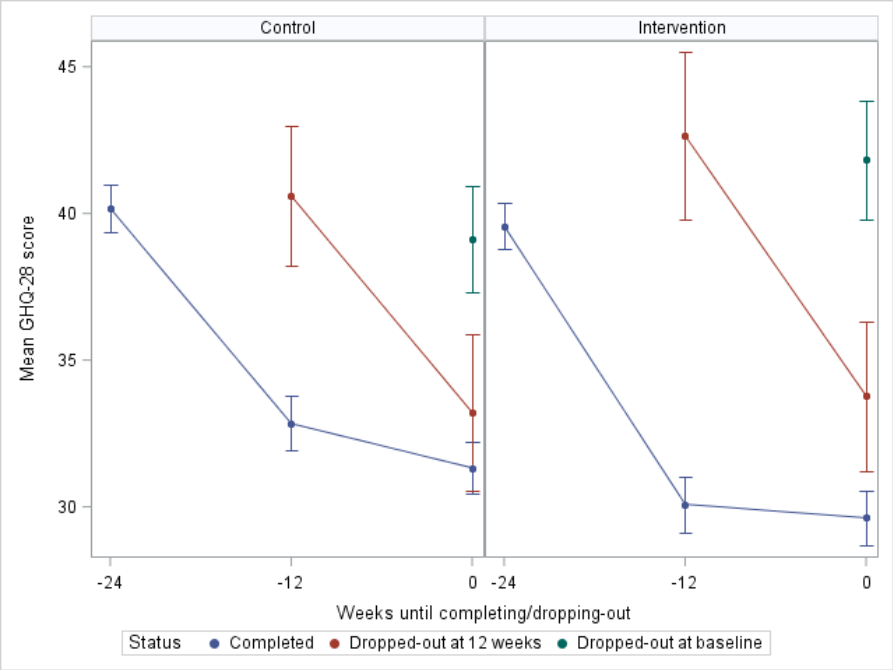
Figure 6-1 shows the raw mean GHQ-28 scores over time by randomised group with no adjustments for drop-out. Figure 6-2 shows the trajectory of GHQ-28 scores in the time before drop-out/censoring split by those who were censored and those who completed the 24 week GHQ-28 assessment.

Figure 6-1 Mean (SE) GHQ-28 scores over time by randomised group with no adjustment for drop-out



SAS file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis - GHQ-28 Mean Profile Plot.sas

Figure 6-2 Mean (SE) profile plots of GHQ-28 scores in the time to completing 24 weeks or dropping out in those who completed the 24 week GHQ-28 and those who dropped out at baseline or 12 weeks



SAS file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis - GHQ-28 Mean Profile Plot.sas

Table 6-39: Joint model results – GHQ-28

Covariate	Coefficient (95% CI)	Z statistic	p-value
Longitudinal *(GHQ-28 score)*			
Time	-0.06 (-0.06, -0.05)	-15.8	<0.001
Treatment effect (REACT versus control)	-0.56 (-2.34, 1.22)	-0.5	0.538
Survival *(Time in days to drop out)*			
Treatment effect (REACT versus control)	0.17 (-0.10, 0.45)	1.2	0.225
Overall *(Time in days to drop out)*			
Treatment effect (REACT versus control)	0.16 (-0.12, 0.44)	1.1	0.256
Association parameter	0.02 (0.01, 0.04)	2.8	0.006

Number included in analysis - REACT: N=399; RD: N=401.

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – Joint modelling.do

The survival submodel gives a log hazard ratio estimate of the direct effect of treatment on drop out equal to 0.17 (95% CI -0.10, 0.45) which indicates that participants in the intervention group were 1.19 times (HR=1.19, 95% CI: 0.90, 1.57) more likely to drop-out compared to participants in the control group; however there was no statistically significant evidence of a difference (p=0.225).

The overall effect of randomised group on risk of drop-out, accounting for the longitudinal GHQ-28 score, equals a log-hazard ratio of 0.16 (95% CI: -0.12, 0.44) which equates to a hazard ratio of 1.17 (95% CI: 0.89, 1.55; p=0.256).

The association estimate of 0.02 (95% CI: 0.01, 0.04) equates to a hazard ratio of 1.02 (95% CI: 1.01, 1.04), which indicates that chance of drop out increases significantly as GHQ-28 score increases (p=0.006).

Difference between randomised groups in GHQ-28 score over time is estimated by the longitudinal submodel which shows participants in the intervention group had a lower overall GHQ-28 score (difference of -0.56, 95% CI: -2.34, 1.22) compared to the control group; however there was no statistically significant evidence of a difference (p=0.538).

An interaction between time and treatment effect was added to see whether the effect of treatment varied over time; however there was no evidence of a significant difference (p=0.240) and therefore the interaction was not included in the final model.

6.6.5 Joint modelling analysis – GHQ-28 (Caseness) score

The longitudinal process was modelled using a linear submodel with a random intercept and slope; the covariates were randomised group and time of assessment as a continuous variable.

The survival process was modelled using a Weibull proportional hazards submodel including a covariate for randomised group.

Figure 6-1 shows the raw mean GHQ-28 (Caseness) scores over time by randomised group with no adjustments for drop-out. Figure 6-2 shows the trajectory of GHQ-28 (Caseness) scores in the time before drop-out/censoring split by those who were censored and those who completed the 24 week GHQ-28 assessment.

Figure 6-3 Mean (SE) GHQ-28 (Caseness) scores over time by randomised group with no adjustment for drop-out

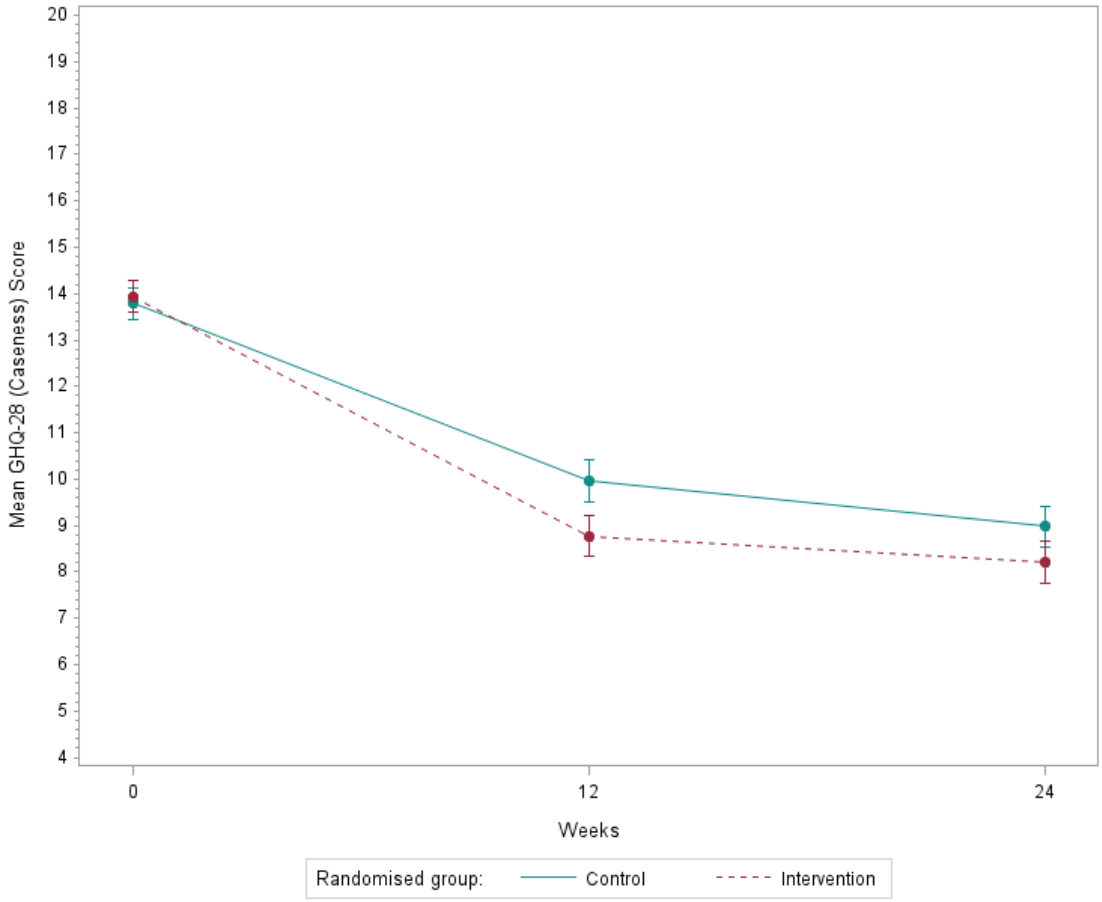
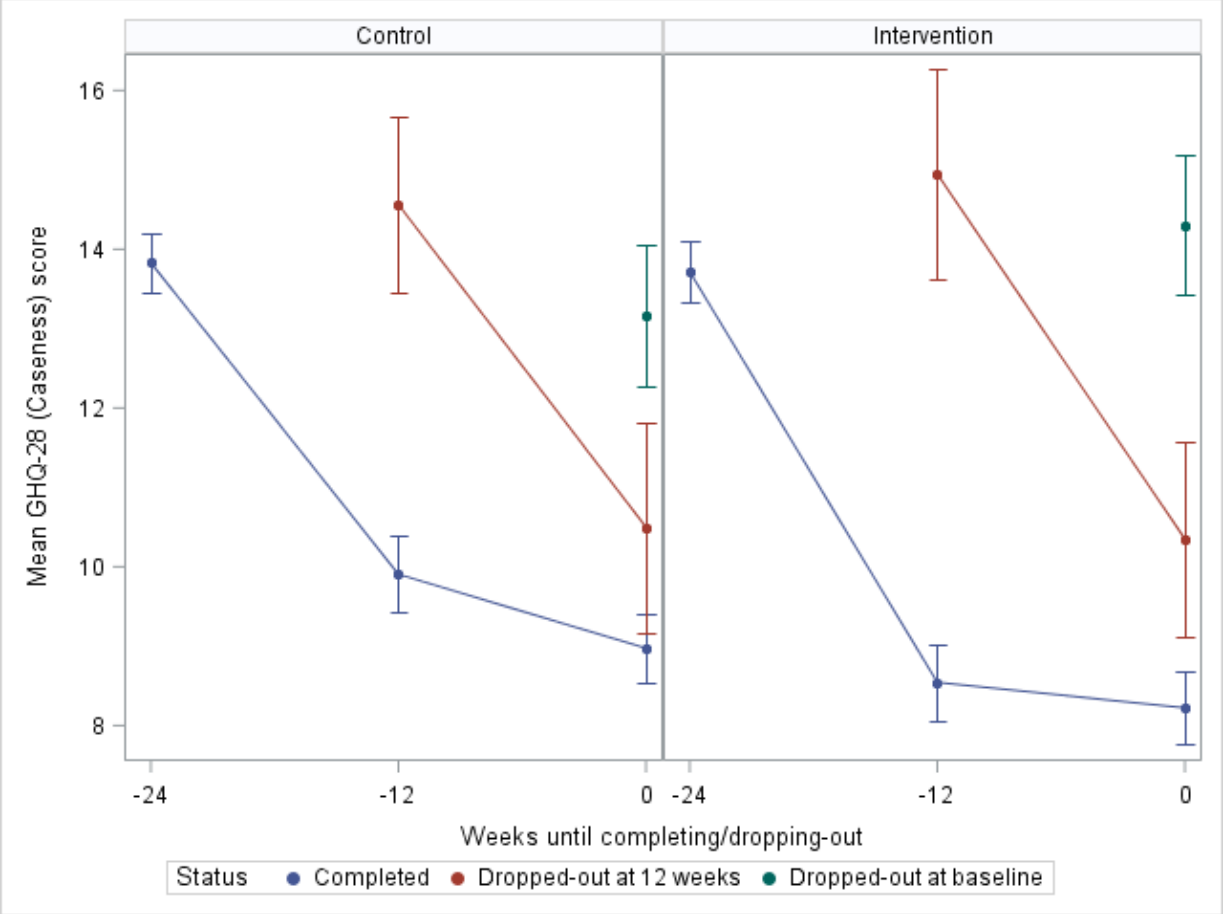


Figure 6-4 Mean (SE) profile plots of GHQ-28 (Caseness) scores in the time to completing 24 weeks or dropping out in those who completed the 24 week GHQ-28 (Caseness) scores and those who dropped out at baseline or 12 weeks



SAS file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis - GHQ-28 (Caseness) Mean Profile Plot.sas

Table 6-40: Joint model results – GHQ-28 (Caseness) scores

Covariate	Coefficient (95% CI)	Z statistic	p-value
Longitudinal *(GHQ-28 case score)*			
Time	-0.03 (-0.03, -0.03)	-16.1	<0.001
Treatment effect (REACT versus control)	-0.28 (-1.11, 0.55)	-0.7	0.505
Survival *(Time in days to drop out)*			
Treatment effect (REACT versus control)	0.18 (-0.10, 0.46)	1.2	0.225
Overall *(Time in days to drop out)*			
Treatment effect (REACT versus control)	0.16 (-0.12, 0.44)	1.2	0.241
Association parameter	0.06 (0.02, 0.10)	3.0	0.002

Number included in analysis - REACT: N=399; RD: N=401.

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – Joint modelling.do

The survival submodel gives a log hazard ratio estimate of the direct effect of treatment on drop out equal to 0.18 (95% CI -0.10, 0.46) which indicates that participants in the intervention

group were 1.20 times (HR=1.20, 95% CI: 0.91, 1.58) more likely to drop-out compared to participants in the control group; however there was no statistically significant evidence of a difference (p=0.225).

The overall effect of randomised group on risk of drop-out, accounting for the longitudinal GHQ-28 case score, equals a log-hazard ratio of 0.16 (95% CI: -0.12, 0.44) which equates to a hazard ratio of 1.18 (95% CI: 0.89, 1.56; p=0.241).

The association estimate of 0.06 (95% CI: 0.02, 0.10) equates to a hazard ratio of 1.06 (95% CI: 1.02, 1.11), which indicates that chance of drop out increases significantly as GHQ-28 case score increases (p=0.002).

Difference between randomised groups in GHQ-28 score over time is estimated by the longitudinal submodel which shows participants in the intervention group had a lower overall GHQ-28 score (difference of -0.28, 95% CI: -1.11, 0.55) compared to the control group; however there was no statistically significant evidence of a difference (p=0.505).

An interaction between time and treatment effect was added to see whether the effect of treatment varied over time; however there was no evidence of a significant difference (p=0.233) and therefore the interaction was not included in the final model.

6.6.6 Secondary efficacy endpoint - Carer Well-Being and Support Questionnaire at 12 and 24 weeks

6.6.6.1 Secondary efficacy assessment – ITT analysis

Table 6-41: CWS at 12 weeks

The Carer Well-Being and Support Questionnaire (CWS) at 12 weeks	REACT N = 233	RD N = 271	Total N = 504
Well-being			
Mean (SD)	72.0 (27.0)	68.9 (27.7)	70.3 (27.4)
Min - max	15 - 127	0 - 128	0 - 128
Support			
Mean (SD)	26.0 (12.0)	22.6 (12.0)	24.2 (12.1)
Min - max	0 - 51	0 - 50	0 - 51

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\SECONDARY_OUTCOME_2.sas

Table 6-42: Analysis of covariance, adjusting for baseline Well-being (12 weeks)

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline Well-being	0.66 (0.59, 0.74)	326.79	<.0001
Treatment (REACT versus control)	1.53 (-2.21, 5.27)	0.64	0.4225

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\SECONDARY_OUTCOME_2.sas
Number included in analysis - REACT: N=233; RD: N=271.

Table 6-43: Analysis of covariance, adjusting for baseline Support (12 weeks)

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline Support	0.68 (0.61, 0.76)	351.15	<.0001
Treatment (REACT versus control)	2.50 (0.87, 4.12)	16.83	<.0001

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\SECONDARY_OUTCOME_2.sas
Number included in analysis - REACT: N=233; RD: N=271.

Table 6-44: CWS at 24 weeks

The Carer Well-Being and Support Questionnaire (CWS) at 24 weeks	REACT N = 249	RD N = 275	Total N = 524
Well-being			
Mean (SD)	77.0 (26.6)	72.6 (30.5)	74.7 (28.8)
Min - max	8 - 124	0 - 127	0 - 127
Support			
Mean (SD)	25.7 (11.7)	23.2 (12.2)	24.4 (12.0)
Min - max	0 - 51	0 - 51	0 – 51

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\SECONDARY_OUTCOME_2.sas

Table 6-45: Analysis of covariance, adjusting for baseline Well-being (24 weeks)

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline Well-being	0.61 (0.53, 0.69)	219.13	<.0001
Treatment (REACT versus control)	2.39 (-1.76, 6.54)	1.28	0.2582

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\SECONDARY_OUTCOME_2.sas
Number included in analysis - REACT: N=249; RD: N=275.

Table 6-46: Analysis of covariance, adjusting for baseline Support (24 weeks)

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline Support	0.64 (0.57, 0.71)	321.52	<.0001
Treatment (REACT versus control)	1.65 (0.04, 3.27)	4.03	0.0451

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\SECONDARY_OUTCOME_2.sas
Number included in analysis - REACT: N=249; RD: N=275.

6.6.7 Joint modelling analysis – CWS score

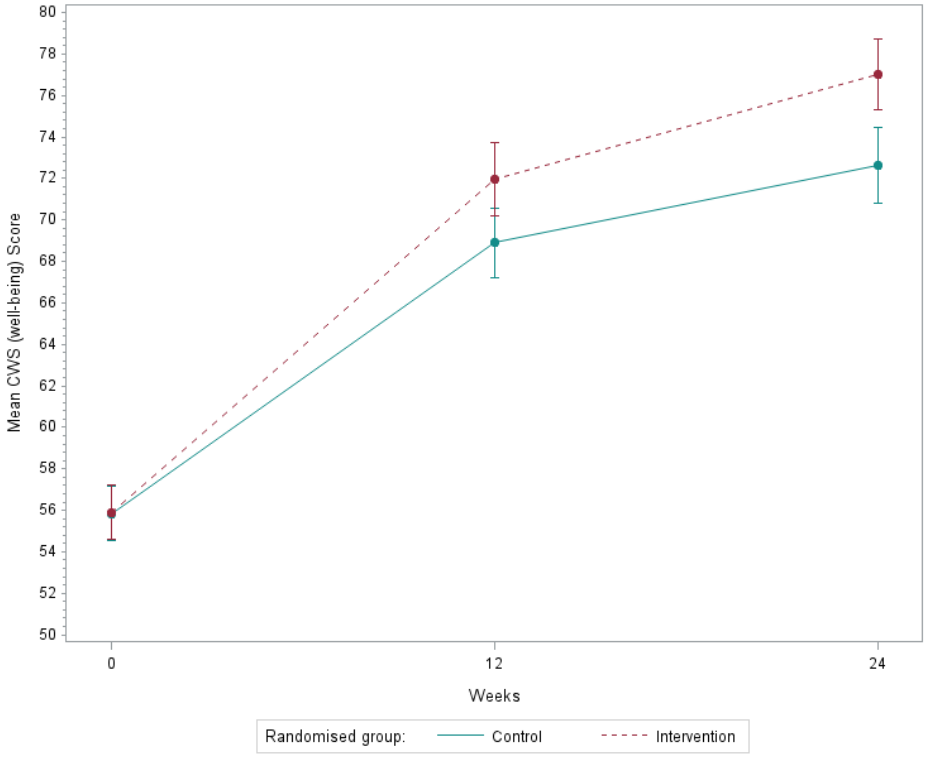
CWS well-being scores and CWS support scores were modelled separately.

The longitudinal processes were modelled using a linear submodel with a random intercept and slope; the covariates were randomised group and time of assessment as a continuous variable.

The survival processes were modelled using a Weibull proportional hazards submodel including a covariate for randomised group.

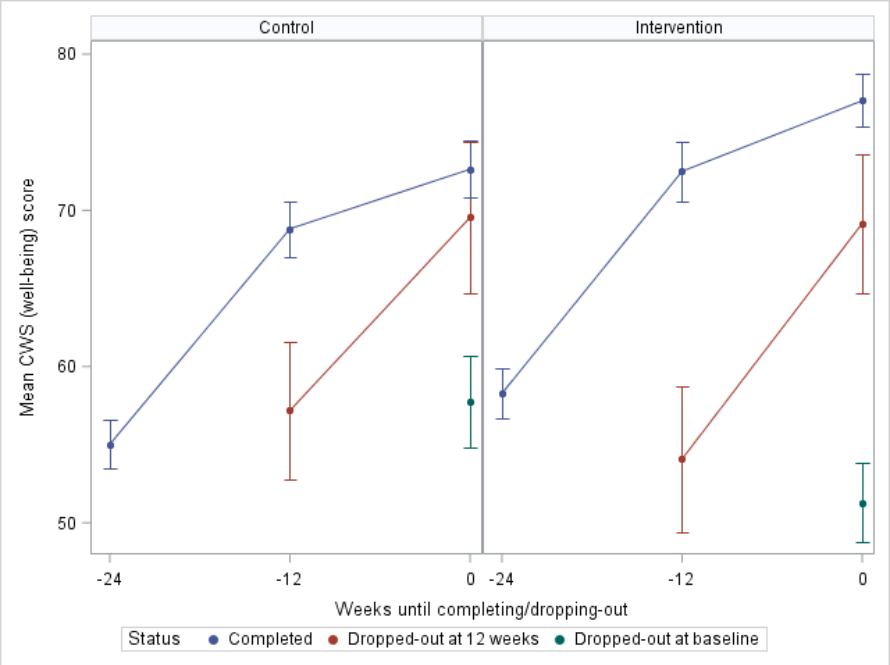
Figure 6-5 shows the raw mean CWS well-being scores over time by randomised group with no adjustments for drop-out. Figure 6-6 shows the trajectory of CWS well-being scores in the time before drop-out/censoring split by those who were censored and those who completed the 24 week CWS well-being assessment.

Figure 6-5 Mean (SE) CWS well-being scores over time by randomised group with no adjustment for drop-out



SAS file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis - CWS (Well-being) Mean Profile Plot.sas

Figure 6-6 Mean (SE) profile plots of CWS well-being scores in the time to completing 24 weeks or dropping out in those who completed the 24 week CWS well-being and those who dropped out at baseline or 12 weeks



SAS file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis - CWS (Well-being) Mean Profile Plot.sas

Table 6-47: Joint model results – CWS well-being

Covariate	Coefficient (95% CI)	Z statistic	p-value
Longitudinal *(CWS well-being score)*			
Time	0.11 (0.09, 0.12)	16.7	<0.001
Treatment effect (REACT versus control)	0.61 (-2.75, 3.98)	0.4	0.722
Survival *(Time in days to drop out)*			
Treatment effect (REACT versus control)	0.26 (0.02, 0.50)	2.1	0.032
Overall *(Time to drop out)*			
Treatment effect (REACT versus control)	0.25 (0.01, 0.49)	2.1	0.039
Association parameter	-0.01 (-0.02, -0.01)	-3.4	0.001

Number included in analysis - REACT: N=399; RD: N=401.

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – Joint modelling.do

The survival submodel gives a log hazard ratio estimate of the direct effect of treatment on drop out equal to 0.26 (95% CI: 0.02, 0.50) which indicates that participants in the intervention group were 1.30 times (HR=1.30, 95% CI: 1.02, 1.65) more likely to drop-out compared to participants in the control group (p=0.032).

The overall effect of randomised group on risk of drop-out equals a log-hazard ratio of 0.25 (95% CI: 0.01, 0.49) which equates to a hazard ratio of 1.29 (95% CI: 1.01, 1.63; p=0.039).

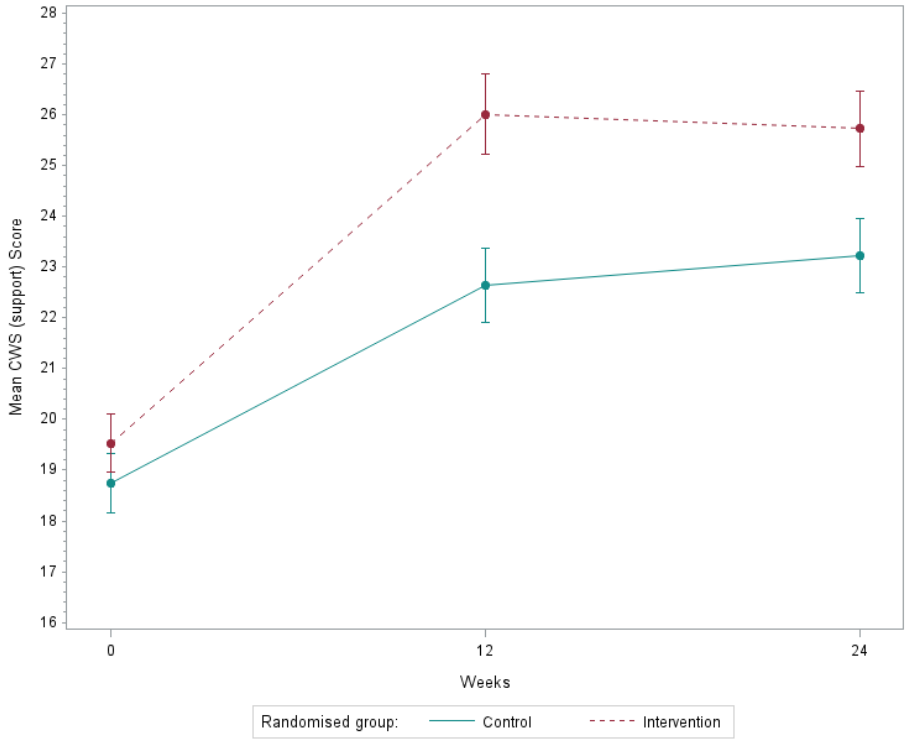
The association estimate of -0.01 (95% CI: -0.02, -0.01) equates to a hazard ratio of 0.99 (95% CI: 0.98, 0.99), which indicates that chance of drop out decreases significantly as CWS well-being score increases (p=0.001).

Difference between randomised groups in CWS well-being score is estimated by the longitudinal submodel which shows participants in the intervention group had a higher CWS well-being score by 0.61 (95% CI: -2.75, 3.98) compared to the control group; however there was no statistically significant evidence of a difference (p=0.722).

An interaction between time and treatment effect was added to see whether the effect of treatment varied over time; however there was no evidence of a significant difference (p=0.323) and therefore the interaction was not included in the final model.

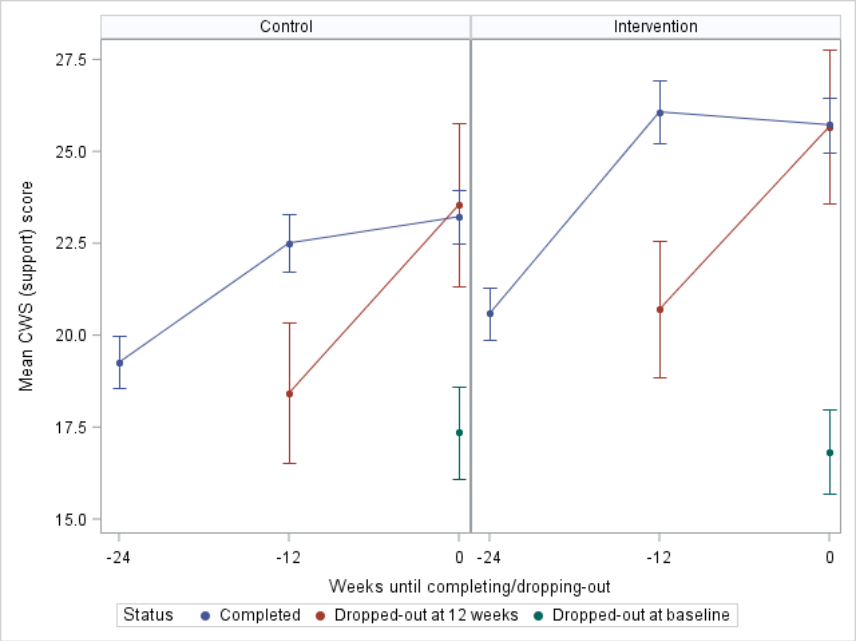
Figure 6-7 shows the raw mean CWS support scores over time by randomised group with no adjustments for drop-out. Figure 6-8 shows the trajectory of CWS support scores in the time before drop-out/censoring split by those who were censored and those who completed the 24 week CWS support assessment.

Figure 6-7 Mean (SE) CWS support scores over time by randomised group with no adjustment for drop-out



SAS file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis - CWS (Support) Mean Profile Plot.sas

Figure 6-8 Mean (SE) profile plots of CWS support scores in the time to completing 24 weeks or dropping out in those who completed the 24 week CWS support and those who dropped out at baseline or 12 weeks



SAS file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis - CWS (Support) Mean Profile Plot.sas

Table 6-48: Joint model results

Covariate	Coefficient (95% CI)	Z statistic	p-value
Longitudinal *(CWS support score)*			
Time	0.03 (0.02, 0.03)	10.8	<0.001
Treatment effect (REACT versus control)	1.51 (-0.005, 3.01)	2.0	0.051
Survival *(Time in days to drop out)*			
Treatment effect (REACT versus control)	0.30 (0.06, 0.54)	2.5	0.014
Overall *(Time in days to drop out)*			
Treatment effect (REACT versus control)	0.25 (0.01, 0.49)	2.0	0.041
Association parameter	-0.03 (-0.05, -0.02)	-4.14	<0.001

Number included in analysis - REACT: N=399; RD: N=401.

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – Joint modelling.do

The survival submodel gives a log hazard ratio estimate of 0.30 (95% CI: 0.06, 0.54) which indicates that participants in the intervention group were 1.35 times (HR=1.35, 95% CI: 1.06, 1.72) more likely to drop-out compared to participants in the control group (p=0.014).

The overall effect of randomised group on risk of drop-out equals a log-hazard ratio of 0.25 (95% CI: 0.01, 0.49) which equates to a hazard ratio of 1.3 (95% CI: 1.01, 1.6; p=0.041).

An association estimate of -0.03 (95% CI: -0.05, -0.02) equates to a hazard ratio of 0.97 (95% CI: 0.95, 0.98), which indicates that chance of drop out decreases significantly as CWS support score increases ($p<0.001$).

Difference between randomised groups in CWS support score is estimated by the longitudinal submodel which shows that participants in the intervention group had a greater mean CWS support score of 1.51 (95% CI: -0.005, 3.01) compared to the control group; however there was no statistically significant evidence of a difference ($p=0.051$).

An interaction between time and treatment effect was added to see whether the effect of treatment varied over time; however there was no evidence of a significant difference ($p=0.107$) and therefore the interaction was not included in the final model.

6.6.8 Causal analysis

Causal methods to estimate efficacy of actual website use on the primary outcome (GHQ-28 at 24 weeks)

6.6.8.1 Instrumental variable (IV) regression

IV regression was used to estimate the association between intervention use and GHQ-28 score at 24 weeks. Intervention use was summarised as the number of web-page downloads during the 24 weeks of follow-up; this was 0 for those in the control arm since they were not granted access to the intervention.

Randomised group was chosen as the instrumental variable as it was assumed to satisfy the following criteria:

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

A two-stage least squares estimator (2SLS) was used: the first stage was to fit a model regressing web-page downloads on randomisation and the second stage was to regress GHQ-28 at 24 weeks on the fitted values of web-page downloads predicted in the previous step. The model was adjusted for baseline GHQ-28 score.

Table 6-49 IV regression of GHQ-28 at 24 weeks on web-page downloads in 24 weeks of follow-up, adjusted for baseline GHQ-28 score

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

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

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – IV Regression.do

For each additional web-page download there is a mean reduction in GHQ-28 at 24 weeks of 0.01 (95% CI: -0.02, 0.01); however, this effect was not statistically significant (p=0.295). It would have taken 300 web-page downloads to achieve the prespecified clinically significant reduction of 3 in GHQ score at 24 weeks, and 500 web-page downloads to achieve the prespecified required mean difference of 5 to show a positive effect of REACT in the trial .

Table 6-50 Tests of exogeneity – web-page downloads

Test *(H0: Variables are exogenous)*	**p-value**
Durbin (score)	0.6634
Wu-Hausman	0.6648

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – IV Regression.do

The Durbin and Wu-Hausman tests give no evidence to reject the null hypothesis that web-page downloads is an exogenous variable, which suggests that an ordinary least squares regression may be appropriate.

Table 6-51: Tests for redundancy – web-page downloads

Test *(H0: Instruments are weak)*	**First stage regression F-statistic**	**Critical Values**			
		5%	**15%**	**20%**	**25%**
2SLS Size of nominal 5% Wald test	104.6	16.4	9.0	6.7	5.5

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – IV Regression.do

The F-statistic from the first-stage regression, also the minimum eigenvalue statistic, of 106.4 is larger than the critical values which indicates that there is evidence to reject the null hypothesis that randomisation is a weak instrument.

Since the number of instruments was equal to the number of endogenous regressors there were no over identifying restrictions.

6.6.8.1.1 Exploratory analysis using participants' total number of logins over 24 weeks of follow-up

Table 6-52: IV regression of GHQ-28 at 24 weeks on total number of logins in 24 weeks of follow-up, adjusted for baseline GHQ-28 score.

Covariate	**Coefficient (95% CI)**	**Z statistic**	**p-value**
Baseline GHQ-28	0.53 (0.43, 0.61)	11.9	<0.001
Total number of logins	-0.17 (-0.48, 0.15)	-1.0	0.296

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

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – IV Regression.do

For each additional login to the intervention site there is a mean reduction in GHQ-28 at 24 weeks of 0.17 (95% CI: -0.48, 0.15); however, this effect was not statistically significant (p=0.296). It would have taken 30 logins to achieve the prespecified clinically significant reduction of 5 in GHQ-28 score at 24 weeks.

Table 6-53: Tests of exogeneity – total number of logins

Test *(H0: Variables are exogenous)*	**p-value**
Durbin (score)	0.5587
Wu-Hausman	0.5604

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – IV Regression.do

The Durbin and Wu-Hausman tests give no evidence to reject the null hypothesis that web-page downloads is an exogenous variable, which suggests that an ordinary least squares regression may be appropriate.

Table 6-54: Tests for redundancy – total number of logins

Test *(H0: Instruments are weak)*	**First stage regression F-statistic**	**Critical Values**			
		5%	**15%**	**20%**	**25%**
2SLS Size of nominal 5% Wald test	68.8	16.4	9.0	6.7	5.5

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – IV Regression.do

The F-statistic from the first-stage regression, also the minimum eigenvalue statistic, of 114.0 is larger than the critical values which indicates that there is evidence to reject the null hypothesis that randomisation is a weak instrument.

Since the number of instruments was equal to the number of endogenous regressors there were no over identifying restrictions.

6.6.8.1.2 Exploratory analysis using total time spent on the intervention site over 24 weeks of follow-up

Table 6-55: IV regression of GHQ-28 at 24 weeks on total time spent on intervention site in 24 weeks of follow-up, adjusted for baseline GHQ-28 score

Covariate	**Coefficient (95% CI)**	**Z statistic**	**p-value**
Baseline GHQ-28	0.5 (0.4, 0.6)	12.0	<0.001
Total time spent (minutes)	-0.01 (-0.02, 0.01)	-1.1	0.296

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

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – IV Regression.do

For each additional login to the intervention site there is a mean reduction in GHQ-28 at 24 weeks of 0.01 (95% CI: -0.02, 0.01); however, this effect was not statistically significant (p=0.296). It would have taken 500 minutes on the intervention site to achieve the prespecified clinically significant reduction of 5 in GHQ-28 score at 24 weeks.

Table 6-56 Tests of the exogeneity – total time spent

Test *(H0: Variables are exogenous)*	**p-value**
Durbin (score)	0.6194
Wu-Hausman	0.6209

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – IV Regression.do

The Durbin and Wu-Hausman tests give no evidence to reject the null hypothesis that web-page downloads is an exogenous variable, which suggests that an ordinary least squares regression may be appropriate.

Table 6-57 Tests for redundancy – total time spent

Test *(H0: Instruments are weak)*	First stage regression F-statistic	Critical Values			
		5%	15%	20%	25%
2SLS Size of nominal 5% Wald test	65.2	16.4	9.0	6.7	5.5

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – IV Regression.do

The F-statistic from the first-stage regression, also the minimum eigenvalue statistic, of 65.2 is larger than the critical values which indicates that there is evidence to reject the null hypothesis that randomisation is a weak instrument.

Since the number of instruments was equal to the number of endogenous regressors there were no over identifying restrictions.

6.6.8.1.3 Exploratory Analysis - Lurkers

Users were defined as participants who left at least one comment on the forum in the 24 weeks of followup, lurkers accessed the forum but left no comments and non-users did not access the forum. Those in the RD arm were all classed as non-users. Table 6-58 gives the proportion of participants in each category.

Table 6-58 Proportion of lurkers

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

In the absence of a second instrument to facilitate the three-way comparison of non-users versus lurkers versus users in relation to the GHQ-28 score at 24 weeks, an ordinary least squares (OLS) regression was used, adjusting for baseline covariates that are likely to confound the relationship between use of social forums and outcome. The validity of this model was then assessed by repeating the model (including the same baseline covariates) for the binary comparison of users versus non-users (with lurkers included as users) and comparing the OLS group effect to that obtained by IV regression for the users vs non-users comparison.

Table 6-59 shows the results for the three-way (non-users versus lurkers versus users) OLS regression model. Users were estimated to have lower GHQ-28 scores at 24 weeks compared to non-users (-2.0, 95% CI: -5.9, 1.9) and lurkers have a similar effect size to non-users (-0.1, 95% CI: -3.2, 2.9); however there was no evidence of a significant difference for this covariate (p=0.5949).

Comparing the IV regression results (

Table 6-60) to those of the OLS binary-user model (

Table 6-63), the effect sizes and significance levels are very similar for all baseline covariates except for the binary-user indicator, for which the effect estimate in the IV regression is larger in magnitude and the p-value smaller than in the OLS regression. This suggests that the effect size estimated in the three-way OLS model for the forum use variable may also be conservative and the true effect may be larger than estimated.

Table 6-59 Ordinary least squares (OLS) regression (non-users vs lurkers vs users)

Covariate	Coefficient (95% CI)	Z statistic	p-value
Baseline GHQ-28	0.5 (0.4, 0.6)	11.2	<0.001
Forum use (reference category: Non-users)			0.595
Lurkers	-0.1 (-3.2, 2.9)	-0.1	
Users	-2.0 (-5.9, 1.9)	-1.0	
Gender (Male vs reference category: Female)	3.1 (-0.2, 6.4)	1.9	0.064
Marital status (Married/civil partnership vs reference category: Single/divorced/separated/widowed)	-4.3 (-6.9, -1.7)	-3.3	0.001
Education (reference category: School)			0.020
College	4.4 (0.6, 8.2)	2.3	
University level	0.7 (-2.8, 4.3)	0.4	
Employment (reference category: None/unpaid)			0.008
Part-time	-2.4 (-5.6, 0.7)	-1.5	
Full-time	-4.6 (-7.4, -1.7)	-3.1	

Number included in analysis - REACT: N=245; RD: N=261.

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – Lurkers.do

IV regression was used to assess whether users of the forum (including lurkers) compared to non-users had an improved GHQ-28 score at 24 weeks. There was no evidence of a difference in users versus non-users (

Table **6-60**).

Table 6-60 IV regression of GHQ-28 at 24 weeks on users vs non-users in 24 weeks of follow-up

Covariate	Coefficient (95% CI)	Z statistic	p-value
Baseline GHQ-28	0.5 (0.4, 0.6)	11.2	<0.001
Forum use (Users vs reference category: Non-users)	-2.6 (-6.2, 1.0)	-1.4	0.156
Gender (Male vs reference category: Female)	3.0 (-0.2, 6.3)	1.8	0.067
Marital status (Married/civil partnership vs reference category: Single/divorced/separated/widowed)	-4.4 (-6.9, -1.8)	-3.3	0.001
Education (reference category: School)			0.017
College	4.5 (0.7, 8.2)	2.3	
University level	0.8 (-2.7, 4.3)	0.5	
Employment (reference category: None/unpaid)			0.007
Part-time	-2.4 (-5.6, 0.7)	-1.5	
Full-time	-4.6 (-7.4, 1.7)	-3.2	

Number included in analysis - REACT: N=245; RD: N=261.

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – Lurkers.do

Table 6-61 Tests of the exogeneity – total time spent

Test *(H0: Variables are exogenous)*	**p-value**
Durbin (score)	0.1562
Wu-Hausman	0.1602

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – Lurkers.do

The Durbin and Wu-Hausman tests give no evidence to reject the null hypothesis that web-page downloads is an exogenous variable, which suggests that an ordinary least squares regression may be appropriate.

Table 6-62 Tests for redundancy – total time spent

Test *(H0: Instruments are weak)*	**First stage regression F-statistic**	**Critical Values**			
		10%	**15%**	**20%**	**25%**
2SLS Size of nominal 5% Wald test	536.3	16.4	9.0	6.7	5.5

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – Lurkers.do

The F-statistic from the first-stage regression, also the minimum eigenvalue statistic, of 536.3 is larger than the critical values which indicates that there is evidence to reject the null hypothesis that randomisation is a weak instrument.

Table 6-63 Ordinary least squares (OLS) regression (users vs non-users)

Covariate	Coefficient (95% CI)	Z statistic	p-value
Baseline GHQ-28	0.5 (0.4, 0.6)	11.2	<0.001
Forum use (Users vs reference category: Non-users)	-0.8 (-3,4, 1.8)	-0.6	0.547
Gender (Male vs reference category: Female)	3.1 (-0.2, 6.4)	1.9	0.064
Marital status (Married/civil partnership vs reference category: Single/divorced/separated/widowed)	-4.3 (-6.9, -1.7)	-3.3	0.001
Education (reference category: School)			0.019
College	4.4 (0.5, 8.2)	2.2	
University level	0.7 (-2.8, 4.2)	0.4	
Employment (reference category: None/unpaid)			0.008
Part-time	-2.4 (-5.6, 0.7)	-1.5	
Full-time	-4.6 (-7.4, -1.7)	-3.1	

Number included in analysis - REACT: N=245; RD: N=261.

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – Lurkers.do

6.6.9 Mediation analyses

6.6.9.1 Brief Illness Perception Questionnaire (IPQ)

Table 6-64: BIPQ at 12 weeks

Brief Illness Perception Questionnaire (IPQ)	REACT N = 228	RD N = 263	Total N = 491
Carer			
Mean (SD)	38.7 (7.5)	39.2 (7.0)	39.0 (7.2)
Min - max	16 - 59	16 – 55	16 - 59
Service user			
Mean (SD)	42.6 (8.5)	42.6 (8.1)	42.6 (8.3)
Min - max	18 - 66	20 - 69	18 - 69
Additional item on coping			
Mean (SD)	5.0 (2.3)	5.0 (2.2)	5.0 (2.2)
Min - max	0 - 10	0 - 10	0 - 10

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\BIPQ_ANALYSIS.sas

Table 6-65: Analysis of covariance, adjusting for baseline Carer (12 weeks)

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline Carer score	0.71 (0.64, 0.78)	407.90	<.0001
Treatment (REACT versus control)	-0.18 (-1.13, 0.77)	0.14	0.7091

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\BIPQ_ANALYSIS.sas
Number included in analysis - REACT: N=228; RD: N=263.

Table 6-66: Analysis of covariance, adjusting for baseline Service user (12 weeks)

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline Service user score	0.64 (0.57, 0.71)	334.10	<.0001
Treatment (REACT versus control)	-0.05 (-1.19, 1.08)	0.01	0.9274

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\BIPQ_ANALYSIS.sas
Number included in analysis - REACT: N=228; RD: N=263.

Table 6-67: Analysis of covariance, adjusting for baseline Additional (12 weeks)

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline Additional item on coping score	0.50 (0.42, 0.58)	163.36	<.0001
Treatment (REACT versus control)	0.06 (-0.29, 0.40)	0.10	0.7497

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\BIPQ_ANALYSIS.sas
Number included in analysis - REACT: N=228; RD: N=263.

Table 6-68: MANOVA BIPQ subscales - 12 Weeks

Source	Statistic	F statistic	p-value
Treatment (REACT versus control)			
Wilks' lambda	1.0	0.6	0.6420
Pillai's trace	0.003	0.6	0.6420
Lawley-Hotelling trace	0.003	0.6	0.6420
Roy's largest root	0.003	0.6	0.6420

Number included in analysis - REACT: N=228; RD: N=263.

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – MANOVA.do

Table **6-68** shows the results from a multivariate analysis of covariance model where the outcome variables are the service user score, carer score and the additional item score at 12 weeks. The p-values for the tests are non-significant indicating no evidence of a difference between randomised groups for one or more of the outcomes.

Table 6-69: BIPQ at 24 weeks

Brief Illness Perception Questionnaire (IPQ)	REACT N = 244	RD N = 268	Total N = 512
Carer			
Mean (SD)	37.5 (7.7)	38.0 (7.7)	37.8 (7.7)
Min - max	10 - 61	10 - 62	10 - 62
Service user			
Mean (SD)	41.5 (8.7)	41.8 (8.4)	41.6 (8.5)
Min - max	15 - 65	13 - 66	13 – 66
Additional item on coping			
Mean (SD)	4.5 (2.1)	4.9 (2.2)	4.7 (2.2)
Min - max	0 - 10	0 - 10	0 – 10

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\BIPQ_ANALYSIS.sas

Table 6-70: Analysis of covariance, adjusting for baseline Carer (24 weeks)

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline Carer score	0.66 (0.58, 0.73)	284.14	<.0001
Treatment (REACT versus control)	0.37 (-0.71, 1.44)	0.44	0.5058

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\BIPQ_ANALYSIS.sas
Number included in analysis - REACT: N=244; RD: N=268.

Table 6-71: Analysis of covariance, adjusting for baseline Service user (24 weeks)

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline Service user score	0.60 (0.53, 0.67)	261.70	<.0001
Treatment (REACT versus control)	-0.16 (-1.36, 1.05)	0.07	0.7965

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\BIPQ_ANALYSIS.sas
Number included in analysis - REACT: N=244; RD: N=268.

Table 6-72: Analysis of covariance, adjusting for baseline Additional (24 weeks)

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline Additional item on coping score	0.48 (0.40, 0.55)	165.55	<.0001
Treatment (REACT versus control)	-0.39 (-0.72, -0.06)	5.53	0.0191

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\BIPQ_ANALYSIS.sas
Number included in analysis - REACT: N=244; RD: N=268.

Table 6-73: MANOVA BIPQ subscales at 24 Weeks

Source	Statistic	F statistic	p-value
Treatment (REACT versus control)			

Wilks' lambda	1.0	2.1	0.1044
Pillai's trace	0.01	2.1	0.1044
Lawley-Hotelling trace	0.01	2.1	0.1044
Roy's largest root	0.01	2.1	0.1044

Number included in analysis - REACT: N=244; RD: N=268.

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – MANOVA.do

Table 6-73 shows the results from a multivariate analysis of covariance model where the outcome variables are the carer score, service user score and the additional item score at 24 weeks. The p-values for the tests are non-significant indicating no evidence of a difference between randomised groups for one or more of the outcomes.

Instrumental variable (IV) regression

IV regression, with the interaction between randomised group and baseline score of the mediator as the instrument, was performed in order to assess whether the 24 week mediator score was a predictor of the 24 week GHQ-28 score. Tests of redundancy were used to assess whether the choice of instrument was appropriate. Results from the tests are displayed in Table 6-74 and Table 6-76.

Table 6-74 shows the summary statistics from the first-stage regressions. The partial R^2 refers to the correlation between the instrument and the endogenous variable (i.e. between the interaction of randomised group and baseline score of the mediator, and the mediator at 24 weeks). In each instance the correlation is very low, which suggests the instruments are weak.

Further confirmation of weak instruments comes from inspection of the F-statistic. An F-statistic greater than 10 is generally accepted as indication of a strong instrument whereas the F-statistics displayed in Table 6-74 range from 0.1 to 4.0.

Finally, the Stock and Yogo tests for a weak instrument are predicated on the premise that an instrument is weak if a Wald test at the 5% level can have an actual rejection rate (the probability of correctly rejecting the null hypothesis) of no more than a certain threshold (10%, 15%, 20% or 25%) for all possible configurations of the IV regression model. In each case, the minimum eigenvalue statistic is lower than all the critical values displayed in Table 6-75 giving further evidence of weak instruments.

Table 6-74: Tests of redundancy – First-stage regression summary statistics - BIPQ

Item	Partial R^2	F-statistic/ Minimum eigenvalue statistic
BIPQ		
User	0.0003	0.1
Carer	0.008	4.0
Additional item on coping	0.003	1.6

Table 6-75: Critical values for the 2SLS size of a nominal 5% Wald test

Critical Values 2SLS size of nominal 5% Wald test			
10%	**15%**	**20%**	**30%**
16.4	9.0	6.7	5.5

Tests of exogeneity were also performed to assess whether IV regression was appropriate or whether ordinary least squares (OLS) regression would have been more appropriate. Results displayed in Table 6-76 show that in most cases OLS regression would have been appropriate, however, the BIPQ carer score p-value of <0.05 gives evidence that this variable should be treated as endogenous.

Table 6-76: Tests of exogeneity - BIPQ

	Tests of exogeneity *H0: Variables are exogenous*	
	Durbin score p-value	**Wu-Hausman p-value**
BIPQ		
User	0.0946	0.0937
Carer	0.0034	0.0034
Additional item on coping	0.1267	0.1283

Causal mediation methods were used to estimate the average causal mediated effect (ACME) of GHQ-28 score at 24 weeks. These methods rely on the sequential ignorability assumption which stipulates that assignment to each treatment group is random (satisfied by randomisation) and that there are no unmeasured confounders. Sensitivity analyses, to assess the impact of any unmeasured confounders, were conducted.

The results displayed in Table 6-77 indicate that none of the putative mediators have a significant mediation effect on outcome (as the 95% CIs for the ACME include 0 for each mediator). Thus, the sensitivity analyses investigating the potential impact of any unmeasured confounders on the true ACME are less crucial. However, the interpretation of the sensitivity analysis results are as follows:

- “Rho at which ACME = 0” indicates the magnitude of the correlation between the error terms from the model predicting the effect of treatment on mediator and the error terms from the model predicting the effect of treatment on outcome that would be required to reduce the ACME to 0

- “R2_M*R2_Y* at which ACME = 0” indicates the product of the proportion of the remaining variance explained by the unmeasured confounder on mediator by the proportion of the remaining variance explained by the unmeasured confounder on outcome that would be required to reduce the ACME to 0. For example, if there was an unmeasured confounder that explained 20% of the remaining variation in User score and 25% of the remaining variation in GHQ-28 score (giving a product of

0.2*0.25 = 0.05), this confounder would reduce the ACME of User score on GHQ-28 to 0.

- R2_M~R2_Y~ at which ACME = 0 at which ACME = 0" indicates the product of the proportion of the total variance of the mediator explained by the unmeasured confounder by the proportion of the total variance of the outcome explained by the unmeasured confounder that would be required to reduce the ACME to 0. For example, if there was an unmeasured confounder that explained 20% of the total variation in User score and 10% of the total variation in GHQ-28 score (giving a product of 0.2*0.1 = 0.02), this confounder would reduce the ACME of User score on GHQ-28 to 0.

Table 6-77: Mediation results - BIPQ

Mediator at 24 weeks	Mean average direct effect, ADE (95% CI)	Average causal mediated effect, ACME (95% CI)	Total effect (95% CI)	Proportion of effect mediated, % (95% CI)	Rho at which ACME = 0	R^2_M*R^2_Y* at which ACME = 0	R^2_M~R^2_Y~ at which ACME = 0
User score	-0.8 (-3.2, 1.4)	-0.05 (-0.5, 0.5)	-0.9 (-3.3, 1.5)	0.03 (-0.5, 0.4)	0.2	0.05	0.02
Carer score	-1.0 (-3.4, 1.2)	0.3 (-0.4, 1.1)	-0.7 (3.2, 1.7)	-0.2 (-4.8, 3.0)	0.3	0.1	0.05
Additional item on coping	0.04 (-2.3, 2.2)	-0.9 (-1.7, -0.2)	-0.9 (-3.3, 1.5)	0.5 (-10.3, 7.8)	0.3	0.1	0.1

Number included in analysis - REACT: N=244; RD: N=267.

6.6.9.2 Brief COPE

Table 6-78: Brief COPE at 12 weeks

Brief COPE	REACT N = 228	RD N = 263	Total N = 491
Self-distraction			
Median (IQR)	5 (4 – 6)	5 (4 – 6)	5 (4 – 6)
Min - max	2 - 8	2 - 8	2 – 8
Mann Whitney U p-value	0.3654		
Active coping			
Median (IQR)	6 (4 – 7)	5 (4 – 7)	5 (4 – 7)
Min - max	2 - 8	2 - 8	2 - 8
Mann Whitney U p-value	0.6969		
Denial			
Median (IQR)	2 (2 – 3)	2 (2 -2)	2 (2 – 3)
Min - max	2 - 8	2 - 8	2 – 8
Mann Whitney U p-value	0.2837		
Substance use			
Median (IQR)	2 (2 – 4)	2 (2 – 4)	2 (2 – 4)
Min - max	2 - 8	2 - 8	2 – 8
Mann Whitney U p-value	0.8157		
Use of emotional support			
Median (IQR)	4 (3 – 6)	4 (3 – 5)	4 (3 – 5)
Min - max	2 - 8	2 - 8	2 – 8
Mann Whitney U p-value	0.0028		
Use of instrumental support			
Median (IQR)	4 (3.5 – 6)	4 (3 – 5)	4 (3 – 6)
Min - max	2 - 8	2 - 8	2 – 8
Mann Whitney U p-value	0.0559		
Behavioural disengagement			
Median (IQR)	2 (2 – 4)	3 (2 – 4)	3 (2 – 4)
Min - max	2 - 8	2 - 8	2 – 8
Mann Whitney U p-value	0.3561		
Venting			
Median (IQR)	3.5 (3 – 4)	3 (3 – 5)	3 (3 – 4)
Min - max	2 - 8	2 - 8	2 – 8
Mann Whitney U p-value	0.5816		
Positive reframing			
Median (IQR)	4 (3 – 5)	4 (3 – 5)	4 (3 – 5)
Min - max	2 - 8	2 - 8	2 – 8
Mann Whitney U p-value	0.5805		

Planning			
Median (IQR)	6 (4 – 7)	6 (4 – 7)	6 (4 – 7)
Min - max	2 - 8	2 - 8	2 – 8
Mann Whitney U p-value	0.6936		
Humour			
Median (IQR)	2 (2 – 4)	3 (2 – 4)	3 (2 – 4)
Min - max	2 - 8	2 - 8	2 – 8
Mann Whitney U p-value	0.1743		
Acceptance			
Median (IQR)	6 (5 – 7)	6 (5 – 8)	6 (5 – 7)
Min - max	2 - 8	2 - 8	2 – 8
Mann Whitney U p-value	0.4409		
Religion			
Median (IQR)	2 (2 – 4)	2 (2 – 4)	2 (2 – 4)
Min - max	2 - 8	2 - 8	2 – 8
Mann Whitney U p-value	0.4568		
Self-blame			
Median (IQR)	4 (3 – 5)	4 (3 – 5)	4 (3 – 5)
Min - max	2 - 8	2 - 8	2 – 8
Mann Whitney U p-value	0.3386		

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\COPING.sas

Table 6-79: MANOVA COPE subscales - 12 Weeks

Source	Statistic	F statistic	p-value
Treatment (REACT versus control)			
Wilks' lambda	1.0	1.6	0.0691
Pillai's trace	0.05	1.6	0.0691
Lawley-Hotelling trace	0.05	1.6	0.0691
Roy's largest root	0.05	1.6	0.0691

Number included in analysis - REACT: N=228; RD: N=263.

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – MANOVA.do

Table 6-79 shows the results from a multivariate analysis of covariance model where the outcome variables are the subscales for the COPE at 12 weeks: Self-distraction; Active coping; Denial; Substance use; Use of emotional support; Use of instrumental support; Behavioural disengagement; Venting; Positive reframing; Planning; Humour; Acceptance; Religion; Self-blame. The p-values for the tests are non-significant indicating no evidence of a difference between randomised groups for one or more of the outcomes.

Table 6-80: Brief COPE at 24 weeks

Brief COPE	REACT N = 243	RD N = 265	Total N = 508
Self-distraction			
Median (IQR)	5 (4 – 6)	5 (4 – 6)	5 (4 – 6)
Min - max	2 - 8	2 - 8	2 - 8
Mann Whitney U p-value	0.9350		
Active coping			
Median (IQR)	5 (4 – 6)	5 (4 - 6)	5 (4 – 6)
Min - max	2 - 8	2 - 8	2 - 8
Mann Whitney U p-value	0.8700		
Denial			
Median (IQR)	2 (2 – 2)	2 (2 – 2)	2 (2 – 2)
Min - max	2 - 8	2 - 7	2 - 8
Mann Whitney U p-value	0.7378		
Substance use			
Median (IQR)	2 (2 – 4)	2 (2 – 4)	2 (2 – 4)
Min - max	2 - 8	2 - 8	2 - 8
Mann Whitney U p-value	0.4303		
Use of emotional support			
Median (IQR)	4 (3 – 6)	4 (3 – 5)	4 (3 – 5)
Min - max	2 - 8	2 - 8	2 - 8
Mann Whitney U p-value	0.3877		
Use of instrumental support			
Median (IQR)	4 (3 – 5)	4 (3 – 5)	4 (3 – 5)
Min - max	2 - 8	2 - 8	2 - 8
Mann Whitney U p-value	0.9637		
Behavioural disengagement			
Median (IQR)	2 (2 – 4)	3 (2 – 4)	2 (2 – 4)
Min - max	2 - 8	2 - 8	2 - 8
Mann Whitney U p-value	0.2335		
Venting			
Median (IQR)	4 (3 – 5)	3 (3 – 4)	3 (3 – 4)
Min - max	2 - 8	2 - 8	2 - 8
Mann Whitney U p-value	0.3243		
Positive reframing			
Median (IQR)	4 (3 – 5)	4 (3 – 5)	4 (3 – 5)
Min - max	2 - 8	2 - 8	2 - 8
Mann Whitney U p-value	0.3890		
Planning			
Median (IQR)	5 (4 – 7)	5 (4 – 7)	5 (4 – 7)

Min - max	2 - 8	2 - 8	2 - 8
Mann Whitney U p-value	0.9400		
Humour			
Median (IQR)	3 (2 – 4)	2 (2 – 4)	2 (2 – 4)
Min - max	2 - 8	2 - 8	2 - 8
Mann Whitney U p-value	0.9358		
Acceptance			
Median (IQR)	6 (5 – 7)	6 (5 – 7)	6 (5 – 7)
Min - max	2 - 8	2 - 8	2 – 8
Mann Whitney U p-value	0.4331		
Religion			
Median (IQR)	2 (2 – 4)	2 (2 – 4)	2 (2 – 4)
Min - max	2 - 8	2 - 8	2 - 8
Mann Whitney U p-value	0.2450		
Self-blame			
Median (IQR)	4 (3 – 5)	4 (2 – 5)	4 (3 – 5)
Min - max	2 - 8	2 - 8	2 - 8
Mann Whitney U p-value	0.6988		

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\COPING.sas

Table 6-81: MANOVA COPE subscales at 24 Weeks

Source	Statistic	F statistic	p-value
Treatment (REACT versus control)			
Wilks' lambda	1.0	0.5	0.9322
Pillai's trace	0.01	0.5	0.9322
Lawley-Hotelling trace	0.01	0.5	0.9322
Roy's largest root	0.01	0.5	0.9322

Number included in analysis - REACT: N=243; RD: N=265.

Stata file: O:\REACT\Statistical Analysis\Web Analysis\Programs\REACT Final Analysis – MANOVA.do

Table 6-81 shows the results from a multivariate analysis of covariance model where the outcome variables are the subscales for the COPE at 24 weeks: Self-distraction; Active coping; Denial; Substance use; Use of emotional support; Use of instrumental support; Behavioural disengagement; Venting; Positive reframing; Planning; Humour; Acceptance; Religion; Self-blame. The p-values for the tests are non-significant indicating no evidence of a difference between randomised groups for one or more of the outcomes.

Instrumental variable (IV) regression

IV regression, with the interaction between randomised group and baseline score of the mediator as the instrument, was performed in order to assess whether the 24 week mediator score was a predictor of the 24 week GHQ-28 score. Tests of redundancy were used to assess whether the choice of instrument was appropriate. Results from the tests are displayed in Table 6-82 and Table 6-84.

Table 6-82 shows the summary statistics from the first-stage regressions. In each instance the partial R^2 is very low, which suggests the instruments are weak. Further confirmation of weak instruments comes from inspection of the F-statistic which range from 0.1 to 1.6. Finally, in each case, the minimum eigenvalue statistic is lower than all the critical values displayed in Table 6-83 giving further evidence of weak instruments.

Table 6-82: Tests of redundancy – First-stage regression summary statistics - COPE

Item	Partial R^2	F-statistic/ Minimum eigenvalue statistic
COPE		
Self-distraction	0.001	0.3
Active coping	0.001	0.3
Denial	0.001	0.3
Substance use	0.003	1.6
Use of emotional support	0.002	0.9
Use of instrumental support	0.002	0.9
Behavioural disengagement	0.0002	0.1
Venting	0.001	0.4
Positive reframing	0.001	0.4
Planning	0.0004	0.2
Humour	0.003	1.5
Acceptance	0.001	0.3
Religion	0.002	1.0
Self-blame	0.004	2.0

Table 6-83: Critical values for the 2SLS size of a nominal 5% Wald test

Critical Values 2SLS size of nominal 5% Wald test			
10%	**15%**	**20%**	**30%**
16.4	9.0	6.7	5.5

Tests of exogeneity were also performed to assess whether IV regression was appropriate or whether ordinary least squares (OLS) regression would have been more appropriate. Results displayed in Table 6-84 show that in most cases OLS regression would have been appropriate, however, the COPE self-blame score p-values of <0.05 give evidence that this variable should be treated as endogenous.

Table 6-84: Tests of exogeneity - COPE

	Tests of exogeneity *H0: Variables are exogenous*	
	Durbin score p-value	**Wu-Hausman p-value**
COPE		
Self-distraction	0.9565	0.9567
Active coping	0.9565	0.9567
Denial	0.9362	0.9366
Substance use	0.8163	0.8172
Use of emotional support	0.4671	0.4694
Use of instrumental support	0.5910	0.5930
Behavioural disengagement	0.9724	0.9726
Venting	0.7440	0.7453
Positive reframing	0.4998	0.5020
Planning	0.6426	0.6444
Humour	0.7231	0.7245
Acceptance	0.6131	0.6149
Religion	0.5096	0.5118
Self-blame	0.0113	0.0115

Causal mediation methods were used to estimate the average causal mediated effect (ACME) of GHQ-28 score at 24 weeks. These methods rely on the sequential ignorability assumption which stipulates that assignment to each treatment group is random (satisfied by randomisation) and that there are no unmeasured confounders. Sensitivity analyses, to assess the impact of any unmeasured confounders, were conducted.

The results displayed in Table 6-85 indicate that none of the putative mediators have a significant mediation effect on outcome (as the 95% CIs for the ACME include 0 for each mediator). Thus, the sensitivity analyses investigating the potential impact of any unmeasured confounders on the true ACME are less crucial. However, the interpretation of the sensitivity analysis results are as follows:

- “Rho at which ACME = 0” indicates the magnitude of the correlation between the error terms from the model predicting the effect of treatment on mediator and the error terms from the model predicting the effect of treatment on outcome that would be required to reduce the ACME to 0

- “R2_M*R2_Y* at which ACME = 0” indicates the product of the proportion of the remaining variance explained by the unmeasured confounder on mediator by the proportion of the remaining variance explained by the unmeasured confounder on outcome that would be required to reduce the ACME to 0. For example, if there was an unmeasured confounder that explained 2% of the remaining variation in Self-distraction and 10% of the remaining variation in GHQ-28 score (giving a product of 0.02*0.1 = 0.002), this confounder would reduce the ACME of Self-distraction on GHQ-28 to 0.

- “R2_M~R2_Y~ at which ACME = 0” indicates the product of the proportion of the total variance of the mediator explained by the unmeasured confounder by the proportion of the total variance of the outcome explained by the unmeasured confounder that would be required to reduce the ACME to 0. For example, if there was an unmeasured confounder that explained 2% of the total variation in Self-distraction and 5% of the total variation in GHQ-28 score (giving a product of 0.02*0.05 = 0.001), this confounder would reduce the ACME of Self-distraction on GHQ-28 to 0.

Table 6-85: Mediation results - COPE

Mediator at 24 weeks	Mean average direct effect, ADE (95% CI)	Average causal mediated effect, ACME (95% CI)	Total effect (95% CI)	Proportion of effect mediated, % (95% CI)	Rho at which ACME = 0	R^2_M*R^2_Y* at which ACME = 0	R^2_M~R^2_Y~ at which ACME = 0
Self-distraction	-0.9 (-3.4, 1.4)	0.04 (-0.1, 0.2)	-0.9 (-3.4, 1.4)	-0.02 (-0.3, 0.4)	0.04	0.002	0.001
Active coping	-0.9 (-3.4, 1.4)	-0.01 (-0.3, 0.3)	-0.9 (-3.4, 1.4)	0.01 (-0.1, 0.1)	-0.1	0.01	0.01
Denial	-0.8 (-3.2, 1.4)	0.002 (-0.6, 0.6)	-0.8 (-3.3, 1.5)	-0.001 (-0.02, 0.02)	0.3	0.1	0.04
Substance use	-0.8 (-3.3, 1.5)	-0.07 (-0.5, 0.4)	-0.9 (-3.4, 1.5)	0.04 (-0.7, 0.5)	0.2	0.04	0.02
Use of emotional support	-0.7 (-3.2, 1.6)	0.002 (-0.1, 0.1)	-0.7 (-3.2, 1.6)	-0.001 (-0.03, 0.02)	-0.002	0	0
Use of instrumental support	-0.8 (-3.3, 1.5)	0.001 (-0.1, 0.1)	-0.8 (-3.3, 1.5)	-0.01 (-0.1, 0.08)	-0.01	0.0001	0.0001
Behavioural disengagement	-0.7 (-3.1, 1.5)	-0.2 (-0.8, 0.5)	-0.9 (-3.4, 1.5)	0.1 (-1.8, 1.6)	0.3	0.1	0.05
Venting	-1.1 (-3.6, 1.1)	0.2 (-0.2, 0.7)	-0.9 (-3.4, 1.5)	-0.1 (-1.5, 2.3)	0.2	0.04	0.03
Positive reframing	-0.8 (-3.3, 1.5)	-0.03 (-0.3, 0.3)	-0.9 (-3.4, 1.4)	0.02 (-0.3, 0.4)	-0.1	0.02	0.01
Planning	-0.8 (-3.3, 1.5)	-0.1 (-0.5, 0.3)	-0.9 (-3.3, 1.5)	0.05 (-0.7, 0.7)	0.2	0.02	0.01
Humour	-0.9 (-3.4, 1.4)	0.04 (-0.09, 0.2)	-0.9 (-3.4, 1.4)	-0.03 (-0.5, 0.5)	-0.04	0.002	0.001
Acceptance	0.7 (-3.2, 1.6)	-0.09 (-0.5, 0.2)	-0.8 (-3.3, 1.5)	0.06 (-1.0, 1.5)	-0.1	0.02	0.01
Religion	-0.6 (-3.2, 1.7)	-0.3 (-0.7, 0.03)	-0.9 (-3.4, 1.4)	0.2 (-3.8, 4.1)	-0.1	0.01	0.002
Self-blame	-1.0 (-3.3, 1.1)	-0.1 (-0.9, 0.8)	-1.0 (-3.5, 1.3)	0.03 (-0.4, 0.6)	0.4	0.2	0.1

Number included in analysis - REACT: N=243; RD: N=264.

6.6.10 Additional analyses

Bivariate analyses, adjusting for baseline GHQ-28 and each baseline covariate in turn

Table 6-86: Bivariate analysis adjusting for baseline GHQ and age

Covariate	Coefficient (95% CI)	p-value
Treatment	-1.35 (-3.57, 0.87)	0.2328
Baseline GHQ-28	0.52 (0.44, 0.61)	<.0001
Age	-0.03 (-0.12, 0.06)	0.5110

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PO_ADJUSTED.sas
Number included in analysis - REACT: N=292; RD: N=307.

Table 6-87: Bivariate analysis adjusting for baseline GHQ and gender

Covariate	Coefficient (95% CI)	p-value
Treatment	-1.44 (-3.65, 0.77)	0.2024
Baseline GHQ-28	0.53 (0.45, 0.62)	<.0001
Gender (Male vs. reference category: Female)	3.02 (0.09, 5.94)	0.0432

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PO_ADJUSTED.sas
Number included in analysis - REACT: N=292; RD: N=306.

Table 6-88: Bivariate analysis adjusting for baseline GHQ and ethnicity

Covariate	Coefficient (95% CI)	p-value
Treatment	-1.34 (-3.55, 0.87)	0.2342
Baseline GHQ-28	0.53 (0.45, 0.61)	<.0001
Ethnicity (Non-British vs. reference category: British)	2.98 (-0.79, 6.75)	0.1206

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PO_ADJUSTED.sas
Number included in analysis - REACT: N=292; RD: N=307.

Table 6-89: Bivariate analysis adjusting for baseline GHQ and marital status

Covariate	Coefficient (95% CI)	p-value
Treatment	-1.47 (-3.70, 0.76)	0.1970
Baseline GHQ-28	0.50 (0.42, 0.58)	<.0001
Marital status (Married/civil partnership vs. reference category: Single/divorced/separated/widowed)	-3.73 (-6.07, -1.38)	0.0019

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PO_ADJUSTED.sas
Number included in analysis - REACT: N=284; RD: N=299.

Table 6-90: Bivariate analysis adjusting for baseline GHQ and living arrangements

Covariate	Coefficient (95% CI)	p-value
Treatment	-1.46 (-3.66, 0.74)	0.1932
Baseline GHQ-28	0.51 (0.43, 0.59)	<.0001
Living arrangements (reference category: Alone)		0.0804
Partner	-3.23 (-6.07, -0.39)	
Other	-3.13 (-7.94, 1.69)	

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PO_ADJUSTED.sas
Number included in analysis - REACT: N=291; RD: N=306.

Table 6-91: Bivariate analysis adjusting for baseline GHQ and number of dependents

Covariate	Coefficient (95% CI)	p-value
Treatment	-1.40 (-3.61, 0.82)	0.2152
Baseline GHQ-28	0.53 (0.45, 0.61)	<.0001

Number of dependents	0.35 (-0.63, 1.34)	0.4803

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PO_ADJUSTED.sas
Number included in analysis - REACT: N=292; RD: N=307.

Table 6-92: Bivariate analysis adjusting for baseline GHQ and education level

Covariate	Coefficient (95% CI)	p-value
Treatment	-1.27 (-3.47, 0.93)	0.2582
Baseline GHQ-28	0.52 (0.44, 0.60)	<.0001
Highest education (reference category: School)		0.0044
College	3.14 (-0.32, 6.60)	
University	-1.12 (-4.26, 2.02)	

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PO_ADJUSTED.sas
Number included in analysis - REACT: N=292; RD: N=307.

Table 6-93: Bivariate analysis adjusting for baseline GHQ and employment status

Covariate	Coefficient (95% CI)	p-value
Treatment	-1.30 (-3.50, 0.89)	0.2444
Baseline GHQ-28	0.53 (0.45, 0.61)	<.0001
Employment (reference category: None/unpaid)		0.0052
Part-time	-2.65 (-5.46, 0.17)	
Full-time	-4.19 (-6.74, -1.64)	

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PO_ADJUSTED.sas
Number included in analysis - REACT: N=292; RD: N=307.

Table 6-94: Bivariate analysis adjusting for baseline GHQ and internet access

Covariate	Coefficient (95% CI)	p-value
Treatment	-1.46 (-3.68, 0.76)	0.1965
Baseline GHQ-28	0.53 (0.45, 0.61)	<.0001
Home internet access (Yes vs. reference category No/Intermittent or poor quality)	-6.86 (-19.04, 5.32)	0.2692

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PO_ADJUSTED.sas
Number included in analysis - REACT: N=292; RD: N=307.

Table 6-95: Bivariate analysis adjusting for baseline GHQ and caring role

Covariate	Coefficient (95% CI)	p-value
Treatment	-1.34 (-3.68, 1.00)	0.2612
Baseline GHQ-28	0.54 (0.46, 0.63)	<.0001
Caring role (reference category: Friend/other)		0.7860
Parent	-2.78 (-8.82, 3.27)	
Partner	-2.36 (-8.53, 3.82)	
Wider family	-1.70 (-8.27, 4.88)	

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PO_ADJUSTED.sas
Number included in analysis - REACT: N=292; RD: N=307.

Table 6-96: Model adjusting for baseline GHQ and caring role (parents), including an interaction term between parental relationship and intervention

Covariate	Coefficient (95% CI)	p-value
Treatment	-1.17 (-4.45, 2.12)	0.4857
Baseline GHQ-28	0.54 (0.46, 0.63)	<.0001
Caring role: Parent (Yes vs. No)	-0.61 (-3.87, 2.65)	0.4977
Service user parental relationship*intervention	-0.39 (-5.05, 4.28)	0.8703

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PO_ADJUSTED.sas
Number included in analysis - REACT: N=267; RD: N=280.

Table 6-97: Model adjusting for baseline GHQ and caring role (mother), including an interaction term between mother and intervention

Covariate	Coefficient (95% CI)	p-value
Treatment	-1.63 (-4.55, 1.28)	0.2719
Baseline GHQ-28	0.53 (0.45, 0.61)	<.0001
Caring role: Mother (Yes vs. No)	-0.78 (-3.90, 2.33)	0.6480
Service user maternal relationship*intervention	0.52 (-3.97, 5.02)	0.8193

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PO_ADJUSTED.sas
Number included in analysis - REACT: N=292; RD: N=307.

Table 6-98: Multivariable analyses, adjusting for baseline GHQ-28 and significant baseline covariates (stepwise selection)

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

Number included in analysis - REACT: N=292; RD: N=307.

When each of the baseline variables are added to the model separately (Table 6-86 to Table 6-97), the variables of gender, marital status, education level, and employment status appear to have a statistically significant effect on the 24 week GHQ-28 score when adjusting for baseline GHQ-28 and treatment. For the multivariable analysis, a stepwise selection process is performed to determine the significant predictors of outcome which should be included in the final model (using p-value criteria of 0.05 for entry and 0.1 for removal) along with baseline GHQ-28 and treatment (the latter which is forced into the model), and the variables of gender, marital status, and employment status are chosen (Table 6-98).

6.6.11 Retention strategies

Table 6-99: Retention rates at 24 weeks according to randomised value/nature of reward

	Completed GHQ		Did not complete GHQ	
	REACT	RD	REACT	RD
Overall	292	307	96	83
Value of the reward				
£10	148	146	51	44
£20	144	161	45	39
Nature of the reward				
Unconditional	145	158	41	45
Conditional	147	149	55	38

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\RETENTION_STRATEGY.sas

Table 6-100: Chi-Squared results for retention rates at 24 weeks

	Relative risk (95% CI)	p-value
Value of the reward £20 (versus £10)	1.0374 (0.9606, 1.1203)	0.3488
Nature of the reward Conditional (versus unconditional)	0.9769 (0.9046, 1.0549)	0.5510

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\RETENTION_STRATEGY.sas

Table 6-101: Logistic regression assessing value of the reward, adjusting for randomised intervention group

Covariate	β (SE)	e^{β} (95% CI)	p-value
Randomised intervention group			
REACT (versus RD)	-0.192 (0.171)	0.825 (0.590, 1.154)	0.2619
Value of the reward			
£20 (versus £10)	0.155 (0.171)	1.168 (0.835, 1.633)	0.3641

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\RETENTION_STRATEGY.sas

Table 6-102: Logistic regression assessing nature of the reward, adjusting for randomised intervention group

Covariate	β (SE)	e^{β} (95% CI)	p-value
Randomised intervention group			
REACT (versus RD)	-0.192 (0.171)	0.825 (0.590, 1.154)	0.2620
Nature of the reward			
Conditional (versus unconditional)	-0.094 (0.171)	0.910 (0.651, 1.273)	0.5825

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\RETENTION_STRATEGY.sas

6.6.12 Recruitment strategies

Table 6-103: Recruitment strategies for randomised participants

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

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\REASONS.sas

Table 6-104: Recruitment strategies for randomised participants by baseline demographics

	Recruitment strategy														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Age															
<30	27	8	11	3	9	5	3	1	2	3	0	0	1	0	0
30 – 39	29	22	22	11	14	9	6	5	2	1	0	2	0	0	0
40 – 49	62	34	22	19	18	17	7	5	6	1	3	2	0	2	1
50 – 59	58	48	33	21	17	15	14	6	5	2	2	1	0	0	1
60 – 69	27	28	28	20	12	9	12	7	0	1	3	1	1	0	0
≥70	3	11	5	3	2	4	0	1	0	0	0	0	2	0	0
Gender															
Male	19	33	23	12	22	12	11	11	3	1	1	2	1	0	0
Female	187	117	98	65	52	47	31	14	12	7	7	4	3	2	2
Missing	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Ethnicity															
White															
British	190	138	112	64	66	56	37	23	13	6	8	6	4	2	2
Irish	2	2	2	3	0	0	0	0	1	1	0	0	0	0	0
Any other White background	6	4	3	6	6	1	1	1	0	0	0	0	0	0	0
Mixed	1	3	2	1	0	1	2	1	0	1	0	0	0	0	0
Asian or Asian British	4	2	2	3	1	1	0	0	1	0	0	0	0	0	0
Other Ethnic group	3	2	0	0	0	0	1	0	0	0	0	0	0	0	0
Rather not say	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0
Highest education level															
School level	39	28	21	10	13	13	2	8	2	0	0	0	1	1	0
Further (College level)	54	49	37	17	24	17	14	5	2	3	0	2	1	0	0
Higher (University level)	113	74	63	50	37	29	26	12	11	5	8	4	2	1	2
Income decile															
1	22	11	6	6	6	8	2	0	0	1	0	0	0	0	0
2	18	10	10	9	6	2	4	4	3	3	2	0	0	0	0
3	22	16	10	7	5	4	6	4	1	0	1	0	0	0	1
4	21	12	14	5	6	10	5	2	1	1	1	0	0	1	0
5	22	14	7	5	6	1	1	1	1	1	2	1	0	0	0
6	21	16	12	9	8	9	3	1	1	1	1	1	1	0	0
7	20	14	17	4	12	5	6	2	2	0	0	1	1	0	0
8	15	23	15	3	6	8	2	2	1	0	0	2	1	1	1
9	24	23	17	10	11	8	4	1	3	0	0	0	1	0	0

10	16	11	9	19	6	3	7	7	2	0	0	1	0	0	0
Missing	5	1	4	0	2	1	2	1	0	1	1	0	0	0	0

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\REASONS.sas

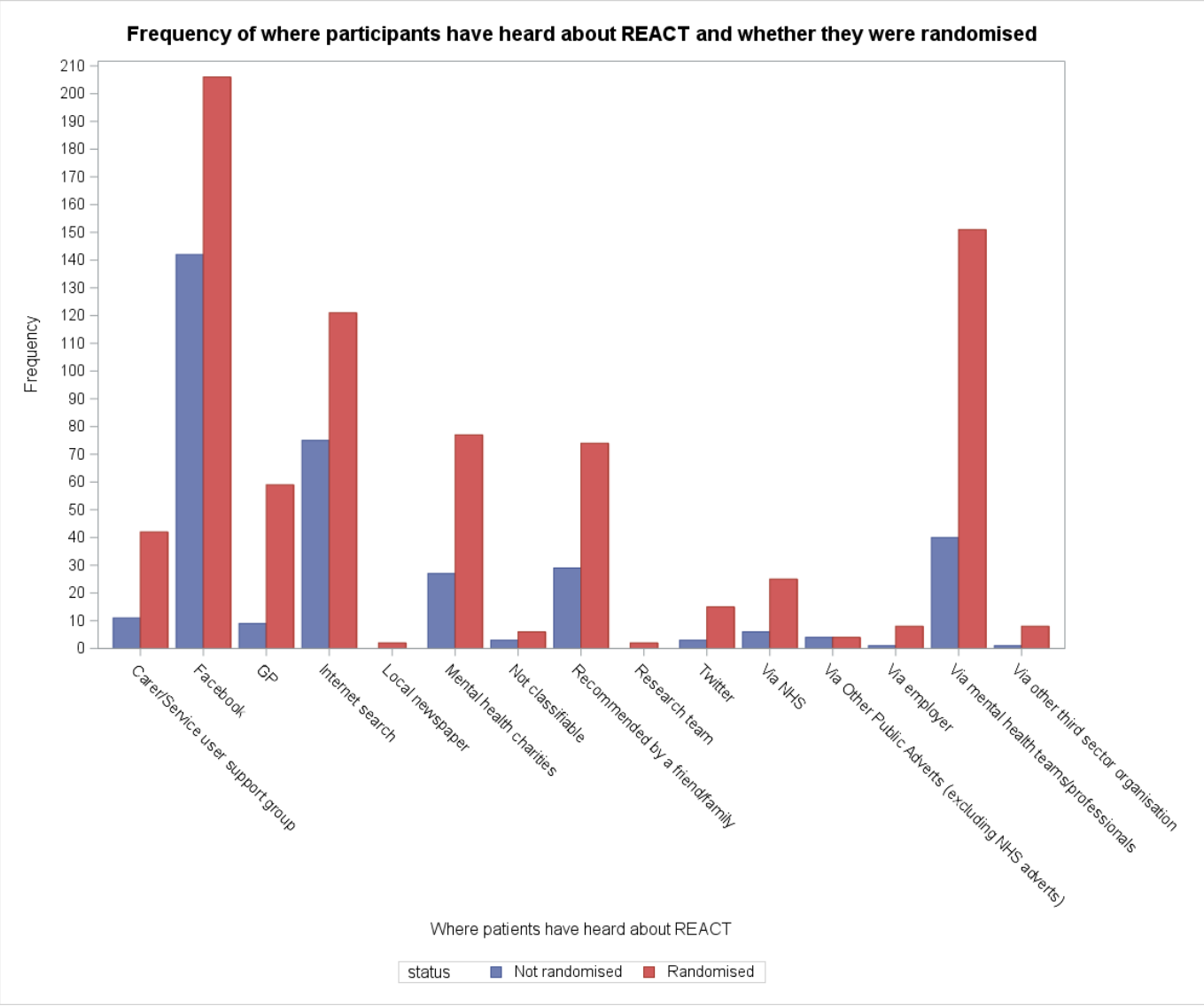
Table 6-105: Online/offline recruitment strategies for randomised participants by baseline demographics

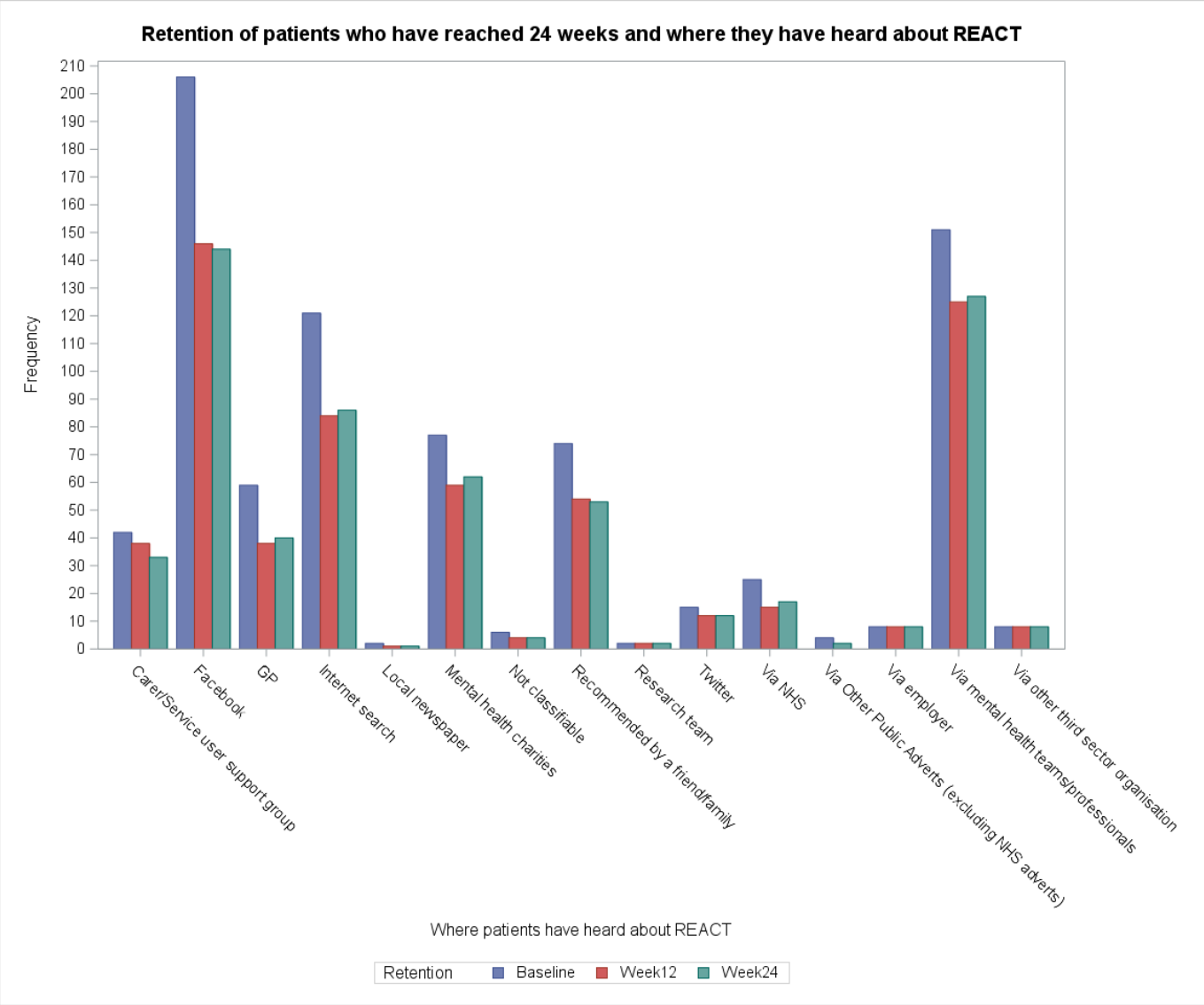
Frequency Column percentage Row percentage	Recruitment strategy	
	Online N = 421	Offline N = 379
Age		
<30	43 10.21% 57.33%	32 8.44% 42.67%
30 – 39	64 15.20% 52.03%	59 15.57% 47.97%
40 – 49	111 26.37% 55.78%	88 23.22% 44.22%
50 – 59	117 27.79% 52.47%	106 27.97% 47.53%
60 – 69	75 17.81% 50.34%	74 19.53% 49.66%
≥70	11 2.61% 35.48%	20 5.28% 64.52%
Gender		
Male	57 13.54% 37.75%	94 24.80% 62.25%
Female	364 86.46% 56.17%	284 74.93% 43.83%
Missing	0 0.00% 0.00%	1 0.26% 100.00%
Ethnicity White		
British	381 90.50% 52.41%	346 91.29% 47.59%

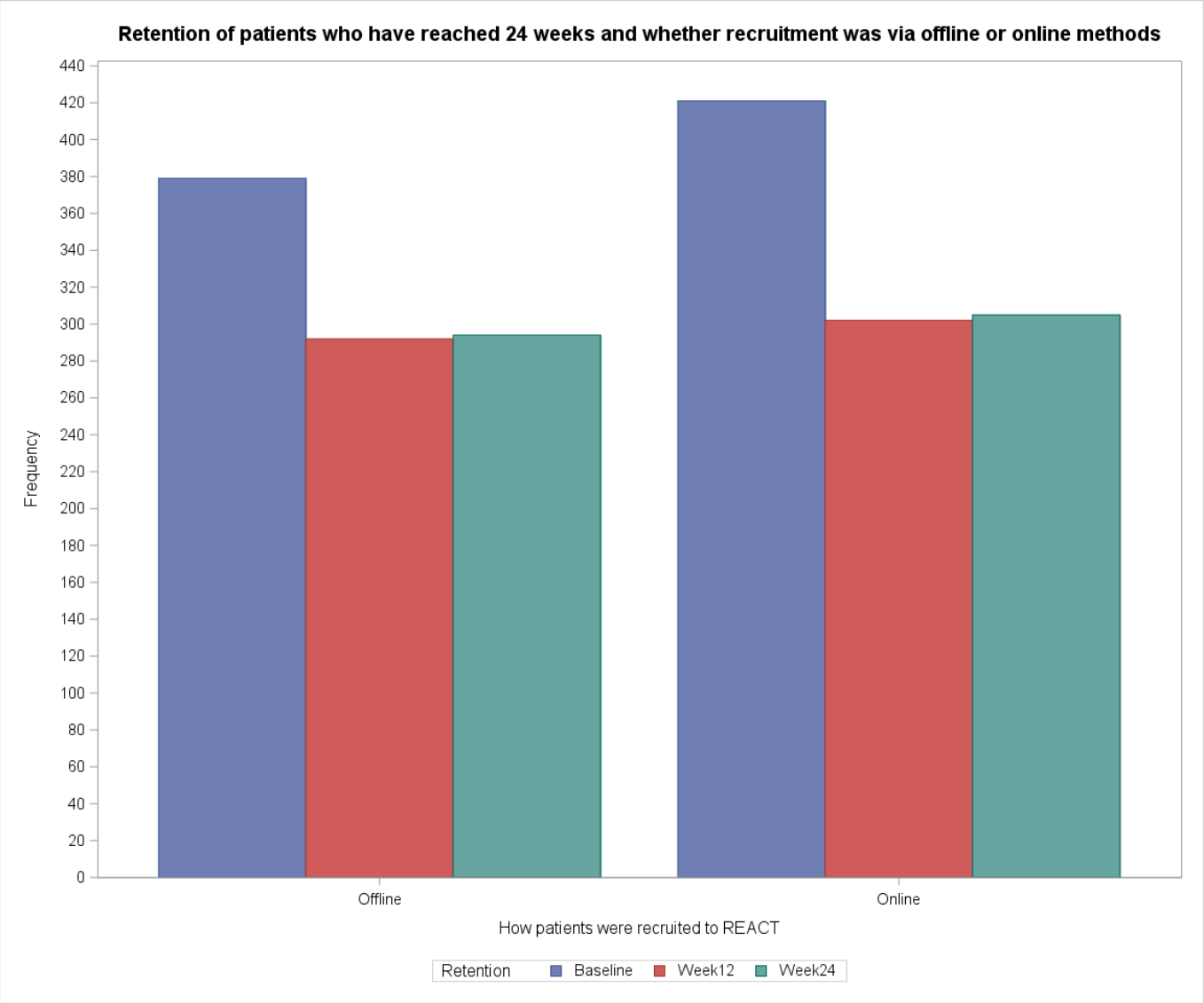
Frequency Column percentage Row percentage	Recruitment strategy	
	Online N = 421	Offline N = 379
Irish	8 1.90% 72.73%	3 0.79% 27.27%
Any other White background	23 5.46% 58.97%	16 4.22% 41.03%
Mixed	4 0.95% 33.33%	8 2.11% 66.67%
Asian or Asian British	10 2.38% 71.43%	4 1.06% 28.57%
Other Ethnic group	3 0.71% 50.00%	3 0.79% 50.00%
Rather not say	0 0.00% 0.00%	2 0.53% 100.00%
Highest education level		
School level	73 17.34% 52.90%	65 17.15% 47.10%
Further (College level)	110 26.13% 48.89%	115 30.34% 51.11%
Higher (University level)	238 56.53% 54.46%	199 52.51% 45.54%
Income decile		
1	34 8.08% 54.84%	28 7.39% 45.16%
2	40 9.50% 56.34%	31 8.18% 43.66%
3	40	37

Frequency Column percentage Row percentage	Recruitment strategy	
	Online N = 421	Offline N = 379
	9.50% 51.95%	9.76% 48.05%
4	42 9.98% 53.16%	37 9.76% 46.84%
5	35 8.31% 56.45%	27 7.12% 43.55%
6	43 10.21% 51.19%	41 10.82% 48.81%
7	43 10.21% 51.19%	41 10.82% 48.81%
8	35 8.31% 43.75%	45 11.87% 56.25%
9	54 12.83% 52.94%	48 12.66% 47.06%
10	46 10.93% 56.79%	35 9.23% 43.21%
Missing	9 2.14% 50.00%	9 2.37% 50.00%

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\REASONS.sas


Frequency of where participants have heard about REACT and whether they were randomised
Frequency
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Carer/Service user support group
Facebook
GP
Internet search
Local newspaper
Mental health charities
Not classifiable
Recommended by a friend/family
Research team
Twitter
Via NHS
Via Other Public Adverts (excluding NHS adverts)
Via employer
Via mental health teams/professionals
Via other third sector organisation
Where patients have heard about REACT
status
Not randomised
Randomised


Retention of patients who have reached 24 weeks and where they have heard about REACT
Frequency
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Carer/Service user support group
Facebook
GP
Internet search
Local newspaper
Mental health charities
Not classifiable
Recommended by a friend/family
Research team
Twitter
Via NHS
Via Other Public Adverts (excluding NHS adverts)
Via employer
Via mental health teams/professionals
Via other third sector organisation
Where patients have heard about REACT
Retention
Baseline
Week12
Week24


Retention of patients who have reached 24 weeks and whether recruitment was via offline or online methods
Frequency
440
420
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
Offline
Online
How patients were recruited to REACT
Retention
Baseline
Week12
Week24

6.6.13 Participants' experience of the REACT intervention

Table 6-106: Participants' experience of the REACT intervention

	REACT: n (%)			
	Strongly agree	Agree	Disagree	Strongly disagree
Always feel supported by REACT supporters				
12 weeks (N = 226)	65 (28.76%)	132 (58.41%)	24 (10.62%)	5 (2.21%)
24 weeks (N = 239)	69 (28.87%)	141 (59.00%)	24 (10.04%)	5 (2.09%)
Always feel supported by REACT group				
12 weeks (N = 226)	58 (25.66%)	138 (61.06%)	27 (11.95%)	3 (1.33%)
24 weeks (N = 239)	67 (28.03%)	145 (60.67%)	24 (10.04%)	3 (1.26%)
Always feel the REACT site was a safe and confidential environment				
12 weeks (N = 226)	118 (52.21%)	95 (42.04%)	10 (4.42%)	3 (1.33%)
24 weeks (N = 239)	125 (52.30%)	105 (43.93%)	6 (2.51%)	3 (1.26%)

6.6.14 Appropriate use of the site

Table 6-107: Appropriate use of the site

	REACT		Overall	
	Events: n	Participants: n(%)	Events: n	Participants: n(%)
Participant flagged content as requiring attention	0	0 (0.0%)	0	0 (0.0%)
REACT supporter hid comment from the site	2	2 (0.5%)	2	2 (0.5%)
Participants' account suspended	0	0 (0.0%)	0	0 (0.0%)

6.6.15 Clustering

Evidence of clustering if participants are attending the same support groups (as assessed using CSRI): Sensitivity analysis to assess the impact of clustering, if the exact ICC cannot be estimated: multiply standard error by sqrt(1.05) or use significance level of 4.5% rather than 5%.

Table 6-108: Analysis of covariance, adjusting for baseline GHQ-28 (significance level 0.045)

Covariate	Coefficient (95% CI)	F statistic	p-value
Baseline GHQ-28	0.53 (0.45, 0.61)	165.27	<0.0001
Treatment (REACT versus control)	-1.39 (-3.65, 0.88)	1.51	0.2189

SAS file: O:\REACT\Statistical Analysis\Final analysis\Analysis\SAS code\PRIMARY_OUTCOME.sas
Number included in analysis - REACT: N=292; RD: N=307.

7. Listings shells

N/A

8. Plots and graphs

8.1 Longitudinal trajectory plots

Longitudinal trajectory plots will be produced for each of the joint models.

Appendix 1: Mapping report contents to SAP

This report has been created following the REACT Statistical Analysis Plan V3.0 (dated 26/07/2018).

The following table lists each item (tables, figures and section when applicable) in this report and maps each to the relevant SAP section that describes the methods used to compute it.

Section/subsection of SAP	Item within report	Additional details (if required)
Section 14.1	Section 3 CONSORT diagram shell	
Section 14.1	Table 3-1: Eligibility details	
Section 14.1	Section 5 Recruitment	
Section 17.2	Table 6-1 Demographic details	
Section 17.2	Table 6-2 Baseline assessments	
Section 17.1	Table 6-3 Data sets analysed	
Section 15	Table 6-4 Protocol deviations	
Section 15	Table 6-5 Protocol deviations	
Section 17.3	Table 6-7 Compliance with treatment	
Section 17.3	Table 6-8 Resource directory usage	
Section 17.3	Table 6-9 REACT module usage	
Section 17.3	Section 6.3.2 Reminders	
Section 16	Table 6-12: Unblinding reasons	
Section 22.2	Table 6-14 Risk protocol triggers	
Section 22.2	Table 6-15 Red flag items	
Section 17.7	Table 6-16: Primary efficacy results	
Section 17.7	Table 6-17: Analysis of covariance, adjusting for baseline GHQ-28	
Section 17.7	Table 6-18 GHQ-28 subscales	
Section 17.7	Table 6-19: Analysis of covariance for Somatic symptoms, adjusting for baseline Somatic symptoms	
Section 17.7	Table 6-20: Analysis of covariance for Anxiety/insomnia, adjusting for baseline Anxiety/insomnia	
Section 17.7	Table 6-21: Mann Whitney U test for Social dysfunction	
Section 17.7	Table 6-22: Mann Whitney U test for Severe depression	
Section 17.7	Table 6-23: MANOVA GHQ-28 subscales - 24 Weeks	
Section 17.10	Table 6-32: GHQ at 12 weeks	
Section 17.10	Table 6-33: Analysis of covariance, adjusting for baseline GHQ-28 (12 weeks)	

Section 17.10	Table 6-34: Analysis of covariance for Somatic symptoms, adjusting for baseline Somatic symptoms (12 weeks)	
Section 17.10	Table 6-35: Analysis of covariance for Anxiety/insomnia, adjusting for baseline Anxiety/insomnia (12 weeks)	
Section 17.10	Table 6-36: Mann Whitney U test for Social dysfunction (12 weeks)	
Section 17.10	Table 6-37: Mann Whitney U test for Severe depression (12 weeks)	
Section 17.10	Table 6-38: MANOVA GHQ-28 subscales - 12 Weeks	
Section 17.10	Table 6-39: Joint model results – GHQ-28	
Section 17.13	Table 6-41: CWS at 12 weeks	
Section 17.13	Table 6-42: Analysis of covariance, adjusting for baseline Well-being (12 weeks)	
Section 17.13	Table 6-43: Analysis of covariance, adjusting for baseline Support (12 weeks)	
Section 17.13	Table 6-44: CWS at 24 weeks	
Section 17.13	Table 6-45: Analysis of covariance, adjusting for baseline Well-being (24 weeks)	
Section 17.13	Table 6-46: Analysis of covariance, adjusting for baseline Support (24 weeks)	
Section 17.13	Table 6-47: Joint model results – CWS well-being	
Section 17.13	Table 6-48: Joint model results	
Section 19.1	Table 6-49 IV regression of GHQ-28 at 24 weeks on web-page downloads in 24 weeks of follow-up, adjusted for baseline GHQ-28 score	
Section 19.1	Table 6-50 Tests of exogeneity – web-page downloads	
Section 19.1	Table 6-51: Tests for redundancy – web-page downloads	
Section 19.1	Table 6-52: IV regression of GHQ-28 at 24 weeks on total number of logins in 24 weeks of follow-up, adjusted for baseline GHQ-28 score.	
Section 19.1	Table 6-53: Tests of exogeneity – total number of logins	
Section 19.1	Table 6-54: Tests for redundancy – total number of logins	
Section 19.1	Table 6-55: IV regression of GHQ-28 at 24 weeks on total time spent on intervention site in 24 weeks of follow-up, adjusted for baseline GHQ-28 score	
Section 19.1	Table 6-56 Tests of the exogeneity – total time spent	
Section 19.1	Table 6-57 Tests for redundancy – total time spent	
Section 20.1	Table 6-64: BIPQ at 12 weeks	
Section 20.1	Table 6-65: Analysis of covariance, adjusting for baseline Carer (12 weeks)	
Section 20.1	Table 6-66: Analysis of covariance, adjusting for baseline Service user (12 weeks)	
Section 20.1	Table 6-67: Analysis of covariance, adjusting for baseline Additional (12 weeks)	
Section 20.1	Table 6-68: MANOVA BIPQ subscales - 12 **Weeks**	
Section 20.1	Table 6-69: BIPQ at 24 weeks	
Section 20.1	Table 6-70: Analysis of covariance, adjusting for baseline Carer (24 weeks)	

Section 20.1	Table 6-71: Analysis of covariance, adjusting for baseline Service user (24 weeks)	
Section 20.1	Table 6-72: Analysis of covariance, adjusting for baseline Additional (24 weeks)	
Section 20.1	Table 6-73: MANOVA BIPQ subscales at 24 Weeks	
Section 19.1	Table 6-74: Tests of redundancy – First-stage regression summary statistics - BIPQ	
Section 19.1	Table 6-75: Critical values for the 2SLS size of a nominal 5% Wald test	
Section 19.1	Table 6-76: Tests of exogeneity - BIPQ	
Section 20.2.3	Table 6-77: Mediation results - BIPQ	
Section 20.2.2	Table 6-78: Brief COPE at 12 weeks	
Section 20.2.2	Table 6-79: MANOVA COPE subscales - 12 Weeks	
Section 20.2.2	Table 6-80: Brief COPE at 24 weeks	
Section 20.2.2	Table 6-81: MANOVA COPE subscales at 24 Weeks	
Section 19.1	Table 6-82: Tests of redundancy – First-stage regression summary statistics - COPE	
Section 19.1	Table 6-83: Critical values for the 2SLS size of a nominal 5% Wald test	
Section 19.1	Table 6-84: Tests of exogeneity - COPE	
Section 20.2.3	Table 6-85: Mediation results - COPE	
Section 21.1	Table 6-86: Bivariate analysis adjusting for baseline GHQ and age	
Section 21.1	Table 6-87: Bivariate analysis adjusting for baseline GHQ and gender	
Section 21.1	Table 6-88: Bivariate analysis adjusting for baseline GHQ and ethnicity	
Section 21.1	Table 6-89: Bivariate analysis adjusting for baseline GHQ and marital status	
Section 21.1	Table 6-90: Bivariate analysis adjusting for baseline GHQ and living arrangements	
Section 21.1	Table 6-91: Bivariate analysis adjusting for baseline GHQ and number of dependents	
Section 21.1	Table 6-92: Bivariate analysis adjusting for baseline GHQ and education level	
Section 21.1	Table 6-93: Bivariate analysis adjusting for baseline GHQ and employment status	
Section 21.1	Table 6-94: Bivariate analysis adjusting for baseline GHQ and internet access	
Section 21.1	Table 6-95: Bivariate analysis adjusting for baseline GHQ and caring role	
Section 21.1	Table 6-96: Model adjusting for baseline GHQ and caring role (parents), including an interaction term between parental relationship and intervention	
Section 21.1	Table 6-97: Model adjusting for baseline GHQ and caring role (mother), including an interaction term between mother and intervention	
Section 21.2	Table 6-99: Retention rates at 24 weeks according to randomised value/nature of reward	
Section 21.2	Table 6-100: Chi-Squared results for retention rates at 24 weeks	
Section 21.2	Table 6-101: Logistic regression assessing value of the reward, adjusting for randomised intervention group	

Section 21.2	Table 6-102: Logistic regression assessing nature of the reward, adjusting for randomised intervention group	
Section 21.3	Table 6-103: Recruitment strategies for randomised participants	
Section 21.3	Table 6-104: Recruitment strategies for randomised participants by baseline demographics	
Section 21.4	Table 6-106: Participants' experience of the REACT intervention	
Section 21.5	Table 6-107: Appropriate use of the site	
Section 21.6	Table 6-108: Analysis of covariance, adjusting for baseline GHQ-28 (significance level 0.045)	