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Research paper

Specialist treatment for persistent depression in secondary care: Sustained effects from a multicentre UK study at 24 and 36 months

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ABSTRACT

Background: Despite the known health costs of persistent depression, there is no established service framework for the treatment of this disorder and a lack of long-term outcome data to inform commissioning. To address this gap, we report the long-term clinical effectiveness of a randomised controlled trial (RCT) testing a specialist, collaborative model of care for people with persistent moderate to severe unipolar depression.

Methods: A multicentre, pragmatic, single-blind, parallel-group randomised controlled trial comparing outcomes from a Specialist Depression Service (SDS) offering collaborative treatment with cognitive behavioural therapy (CBT) and pharmacotherapy for 12 months with treatment as usual (TAU) for persistent, moderate-severe depression in UK secondary care. Participants were initially assessed at baseline, 3, 6, 9, 12, and 18 months, with primary endpoints (17-item Hamilton Depression Rating Scale [HDRS17], and a Global Assessment of Functioning [GAF]) reported elsewhere (Morriss et al., 2016). Additional long-term, post-treatment, follow-up was made at 24 and 36 months with outcomes presented here. ClinicalTrials.gov (NCT01047124) and ISRCTN registration (ISRCTN 10963342).

Results: At 24 months there remained a statistically significant between-group difference in $HDRS_{17}$–2.69 (−5.14, −0.23) and a non-significant improvement in GAF 2.85 (−1.23, 6.94), both favouring the SDS. Simple statistics are presented at 36 months, due to attrition, showing higher continued response and remission vs TAU across all measures.

Limitations: Potential bias through loss to follow-up, particularly beyond 24 months.

Conclusions: Compared with standard secondary care, SDS management of persistent moderate-severe depression, produced long-term clinical benefits, sustained following treatment completion, suggesting a model for future specialist care.

1. Introduction

Persistent depression remains a prevalent condition, with around one third of patients remaining unwell even after a year of intensive treatment (Rush et al., 2006b). Although guidelines continue to state that more specialist care should then be considered, including combination cognitive behavioural therapy (CBT) and pharmacotherapy (NICE, 2022), there is no recommended service structure for delivering these treatments in secondary (specialist) care and little evidence to guide decision making in this area. A systematic review conducted for this paper identified only two clinical trials assessing specialist service interventions for persistent depression (search strategy updated on 05 December 2022 documented in S1). This evidence amounts to a 4-month outcome study in Vancouver, finding a significantly higher rate of remission immediately following treatment with collaborative interpersonal therapy (IPT) and medication (Murray et al., 2010); and our

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own previously published RCT of collaborative CBT-pharmacotherapy in 3 UK centres over a median of a 13-month period (IQR 13–15 months) (Morriss et al., 2016). The latter trial showed a significant effect for the collaborative specialist care intervention on depression symptom change and a non-significant trend towards improved function, again immediately following treatment completion. Although this research may be encouraging for the possibility of change, even after many years of persistent depression, it provides a time horizon of interventional evidence that is starkly at odds with decades of observational evidence showing persistence, recurrence, debility and suicide over at least 15 years following standard secondary care treatment for depression, with fewer than one in five people remaining well over the longer-term (Kiloh et al., 1988) (Lee and Murray, 1988). The corollary is that for most patients coming through secondary care, depression runs a chronic, debilitating course, poorly matched by our short-term interventional evidence.

The paucity of longer-term outcome data for depression has received considerable recent attention, as 'a major gap in evidence for the clinical practice of psychiatry' (Uher and Pavlova, 2016); an unmet research priority (James Lind Alliance, 2016); and an important limitation in national guideline development (NICE, 2018a). Here we address this gap, through a report on the longer-term outcomes of Morriss et al., 2016; including a planned 24-month assessment of stability of effect (Morriss et al., 2010) and an additional 36-month assessment conducted as an extension to the original protocol. In doing so, we aim to inform the question of whether there are longer-term clinical effects following completion of an intensive, specialist baseline intervention for persistent depression.

2. Methods

2.1. Study design and participants

The study methodology has been previously described in detail (Morriss et al., 2016). In brief, this was a multicentre, pragmatic, single-blind, parallel-group RCT comparing outcomes from a Specialist Depression Service (SDS) offering CBT and pharmacology, with treatment as usual (TAU) for persistent depression in three UK secondary care sites (Nottingham, Derby and Cambridge). Eligible patients had at least moderate-severe depression (17-item Hamilton Depression Rating Scale (Hamilton, 1960); $HDRS_{17} \geq 16$), with moderately severe functional impairment (Global Assessment of Functioning (American Psychiatric Association, 1994); GAF ≤ 60) and at least 6 months of active treatment within UK secondary care.

2.2. Randomisation and masking

Randomisation was stratified by NHS Trust site and participant arm allocation determined by a computer generated pseudo-random code using random permuted blocks of varying size, through a registered UKCRC clinical trials unit based at the Queens Medical Centre, Nottingham, UK, with equal probability (1:1) allocation to SDS or TAU. The trial administrator had password-controlled access to the randomisation data but research associates who completed outcome assessments did not have access to this or to health service records and were based at a site away from clinical care. Although patients and treating clinicians were aware of treatment allocation, outcome assessors and data managers were masked to study allocation at all timepoints throughout the 36-month follow-up.

2.3. Procedures

The SDS intervention comprised specialist pharmacotherapy and specialist CBT for depression (Moore and Garland, 2003), delivered within a collaborative care model over a period of 13 months (IQR 12–15 months; the original protocol specification of 12 months was extended to allow a graduated transfer of care). TAU was delivered under the care of a Consultant Psychiatrist within a non-specialised community mental health team setting. Further detail on these interventions is available in the initial outcome publication (Morriss et al., 2016).

2.4. Outcomes

At 24 months, per protocol (Morriss et al., 2010), the primary outcome measures assessing stability of treatment effect were mean change in the $HDRS_{17}$ (Hamilton, 1960) and GAF (American Psychiatric Association, 1994). Secondary depression outcomes at 24 months comprised 3 self-rated measures of depression — the Beck Depression Inventory version I (BDI-I) (Beck et al., 1961), the 9-item Personal Health Questionnaire (PHQ-9) (Kroenke et al., n.d.), and the 16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) (Rush et al., 2003). Additionally, self-report measures of function and quality of life were collected, as the modified Social Adjustment Scale (SAS-M) (Cooper et al., 1982) and the Euroqol 5D questionnaire 3 level (EQ-5D-3L) (Euroqol Group, 1990).

Given the importance of longer-term outcome data and the low level of attrition from 18 to 24 months (<2 %), all patients remaining at 24 months were invited by letter to an additional 36-month follow-up session (approved by Trent NHS Research Ethics Committee as an amendment to the original published protocol (Morriss et al., 2010)). All outcome measures were repeated at 36 months.

2.5. Choice of primary depression measure

The $HDRS_{17}$ is regarded as the gold standard outcome measure for depression by authorities including NICE, with established severity thresholds and a minimal clinically important difference of 3 points (Zimmerman et al., 2013a). The $HDRS_{17}$ is a widely used severity and outcome measure, which has been translated into many different languages. Since protocol publication for the current study, we have published a psychometric assessment of the $HDRS_{17}$ in patients with moderate-severe persistent depression, indicating that it does not have a unidimensional structure (Nixon et al., 2020). In the same publication we showed that the 6-item subscale of the Hamilton Depression Rating Scale ($HDRS_6$; assessing depressed mood, pleasure, tiredness, psychic anxiety, guilt feelings and psychomotor retardation) (Bech et al., 1981) does have a unidimensional structure in persistent moderate-severe depression and may therefore be a preferred outcome measure to the traditionally accepted $HDRS_{17}$. We have therefore included $HDRS_6$ data in the current manuscript and encourage consideration of this in future protocol development.

2.6. Statistical analysis

All data was analysed on an intention-to-treat basis, reporting means and standard deviations of the mean. Primary outcome data were analysed to the pre-specified 24-month endpoint through multilevel modelling with time as a discrete variable, treatment group as a binary variable, interaction between time and treatment group as fixed effects. Separate models were used for $HDRS_{17}$ and GAF, with baseline score entered as a covariate, and patient as a level two unit. The treatment differences and 95 % CIs at each follow-up timepoint (6, 12, 18, 24 months), were derived from the multilevel modelling (MLM). Markov chain Monte Carlo multiple imputation was used to impute missing data with REALCOM software under a missing- at-random assumption. To assess the robustness of our results and their sensitivity to missing values, we repeated the MLM using only observed data. Finally, we performed covariate adjustment analysis by including site as a covariate in the MLM. A similar approach, using MLM with the same sensitivity and adjustment analyses, was used to analyse all secondary outcome variables to 24-months.

A significant effect at the primary 24-month endpoint was regarded as justifying further assessment of patient-level effects through rates of individual response (reduction of at least 50 % in symptom level) and remission (defined by specified cut-off points on each of the validated scales). Given the prognostic significance of residual symptoms for relapse-reduction (Rush et al., 2006a), remission provides a particularly important service metric over longer-term follow-up and was also the main outcome in the only other comparable study (Murray et al., 2010). Given the secondary nature of the response and remission analysis (and the inherent multiplicity issues), we have presented all data transparently as raw numbers and percentages, without further statistical testing, both at the 24-month and 36-month time points, in keeping with recommendations (EMA, 2017).

2.7. Trial registration

ClinicalTrials.gov (NCT01047124) and ISRCTN registration (ISRCTN 10963342).

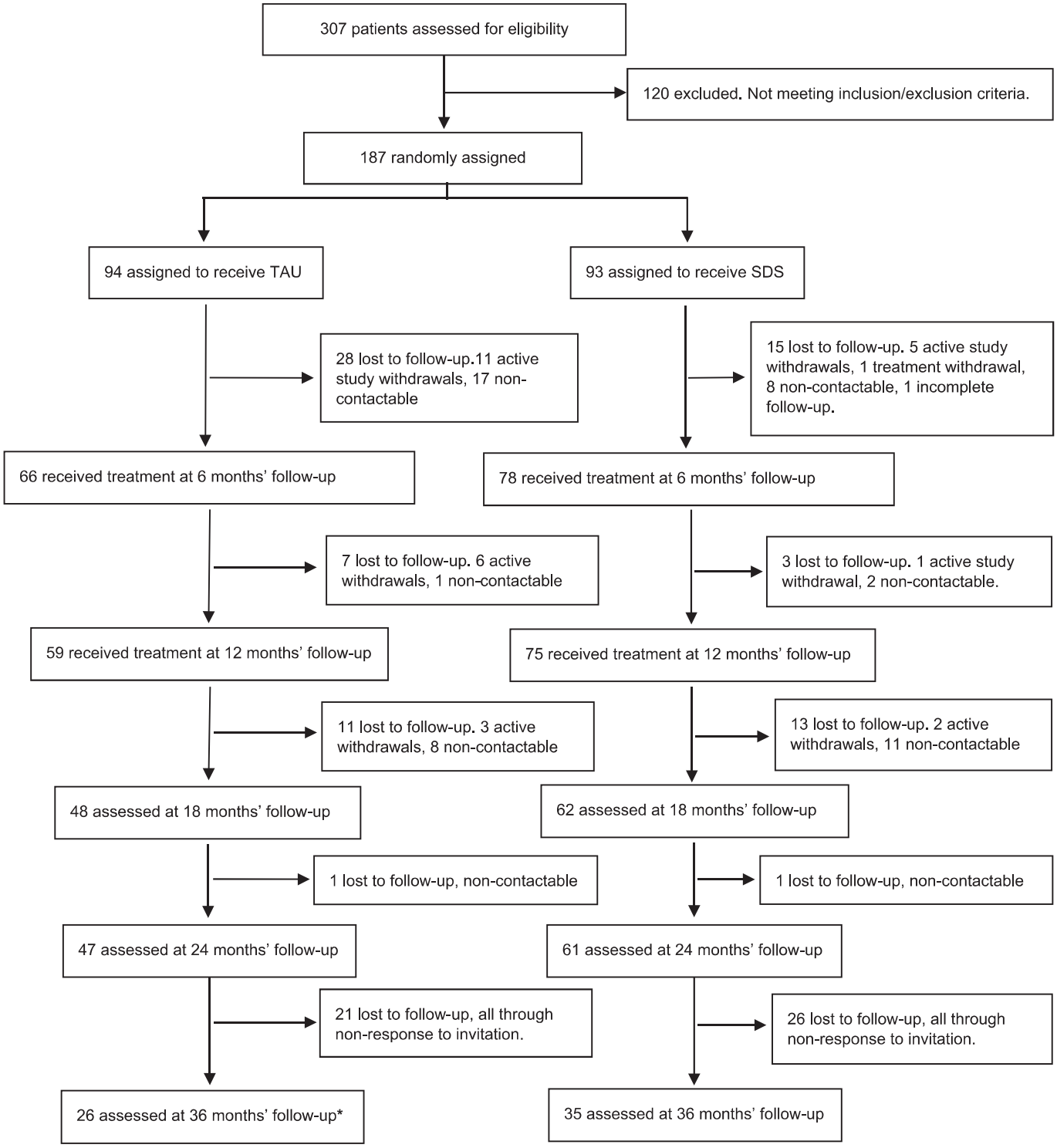

Fig. 1. CONSORT flow through the study to 36 months. All patients were assessed per randomised group, as TAU or SDS.

3. Results

A total of 307 patients were referred to the study between December 2009 and September 2012, as part of the Collaboration for Leadership in Applied Health Research and Care (CLAHRC) persistent depression study that terminated as planned at the end of a five-year funding period. Flow through the study is illustrated in Fig. 1, to the final 36-month follow-up.

Baseline data are given in Morriss et al., 2016, showing no important clinical or demographic differences between randomised groups (Morriss et al., 2016).

As previously reported, at 18 months post-baseline 31 (33 %) of those randomised to the SDS group were lost to follow-up and 46 (49 %) from the TAU group. From new data reported here, at 24-months post-baseline, 32 (36 %) of those randomised to the SDS group were lost to follow-up and 47 (50 %) from the TAU group. Of the participants remaining in follow up at 24 months, only 55 % of the TAU and 57 % of the SDS opted in to the additional 36-month outcome assessment, contributing to a final loss to follow-up at 36 months of 58 (62 %) in the SDS and 68 (72 %) in the TAU group. Additionally, 3 of the TAU patients had been given at least 1 month of SDS treatment between 24 and 36 months, which reflected the ethical commitment to provide this where requested and deemed appropriate at the end of the planned 24-month period. These 3 patients were analysed per randomisation in the TAU group.

Table 1 shows change in depression symptom and function measures from baseline to 24 months. Since the median duration of SDS treatment was 13 months (IQR 12–15), the 18- and 24-month figures indicate post-treatment effects for the majority of patients. At 24 months, the primary endpoint $HDRS_{17}$ showed significant change favouring the SDS −2.69 (−5.14, −0.23), as did the core 6-item subscale $HDRS_6$ −1.67 (−3.11, −0.22). For secondary depression outcomes, there was significant change favouring SDS in both PHQ-9 −3.88 (−6.20, −1.55) and BDI-I −5.20 (−8.93, −1.47); and non-significant change favouring SDS in QIDS-SR −3.26 (−6.53, 0.02). The primary measure of function, GAF, showed non-significant change favouring SDS at 24 months, 2.85 (−1.23, 6.94); with similar SAS-M outcome, showing non-significant change favouring SDS at 24 months, 6.60 (−2.63, 15.82).

Change in the primary outcome measure, $HDRS_{17}$, is shown graphically to the 24-month, primary endpoint in Fig. 2.

Given the statistical significance of the primary depression endpoint for stability of effect ($HDRS_{17}$), we also assessed the proportion of response and remission in each group, to establish the clinical relevance of the observed differences, in keeping with recommended practice (EMA, 2017). Response was defined as 50 % or greater reduction in symptoms, in keeping with all established practice in depression research; and remission was defined as per published cut-off criteria for the outcome scales used ($HDRS_{17} < 8$) (Zimmerman et al., 2013b), (PHQ9 < 10) (Gilbody et al., 2007), (BDI-I < 10) (Beck et al., 1988), ($QIDS\text{-}SR_{16} < 6$) (Rush et al., 2003). In keeping with guidance on multiple comparison (EMA, 2017), we have not used significance testing on these data either at the 24-month or 36-month points.

Since median duration of SDS treatment was 13 months (IQR 12–15), 18-, 24- and 36-month figures should be regarded as post-treatment effects for the majority of patients. Table 2 shows that across all measures within this post-treatment period the relative response rate remained higher in the SDS group (vs. TAU) and that by the final 36-month point the SDS group response rate (vs. TAU) was 2.4 times higher on the $HDRS_{17}$; 3.3 times higher on the PHQ-9; 3.4 times higher on the BDI-I; and 2.2 times higher on the $QIDS\text{-}SR_{16}$.

Remission rates, given in Table 3, show a relative rate of remission remained higher for the SDS group (vs. TAU) across all measures in the post-treatment period to 36 months. At this final 36-month point, SDS group remission rate (vs. TAU) was 2.7 times higher on the $HDRS_{17}$; 1.7 times higher on the PHQ-9; and 3.0 times higher on the BDI-I (the relative rate on the $QIDS\text{-}SR_{16}$ was not calculable since TAU showed a zero rate of remission for on this measure, compared to 15 % for the SDS group).

Table 1
MLM modelled mean change from baseline to 24 months for SDS vs TAU.

	Mean change from baseline (95 % CI)		Change difference (95 % CI)	*p* value
	TAU (n = 94)	SDS (n = 93)		
$HDRS_{17}$				
6 months	−3.75 (−5.49, −2.02)	−4.65 (−6.27, −3.03)	−0.90 (−3.19, 1.39)	0.440
12 months	−4.81 (−6.57, −3.05)	−7.23 (−8.89, −5.56)	**−2.42 (−4.77, −0.07)**	**0.043**
18 months	−5.98 (−8.14, −3.82)	−8.76 (−10.50, −7.03)	**−2.79 (−5.33, −0.25)**	**0.032**
24 months	−6.17 (−8.05, −4.30)	−8.86 (−10.63, −7.09)	**−2.69 (−5.14, −0.23)**	**0.032**
$HDRS_6$				
6 months	−2.52 (−3.55, −1.50)	−2.89 (−3.85, −1.94)	−0.37 (−1.72, 0.98)	0.589
12 months	−2.99 (−4.04, −1.95)	−4.45 (−5.43, −3.48)	**−1.46 (−2.85, −0.08)**	**0.039**
18 months	−3.64 (−4.94, −2.35)	−5.60 (−6.63, −4.57)	**−1.95 (−3.47, −0.44)**	**0.012**
24 months	−4.22 (−5.33, −3.10)	−5.88 (−6.92, −4.84)	**−1.67 (−3.11, −0.22)**	**0.024**
GAF				
6 months	6.68 (3.21, 10.14)	6.32 (3.71, 8.92)	−0.36 (−4.58, 3.87)	0.868
12 months	7.60 (4.41, 10.79)	11.40 (8.58, 14.22)	3.80 (−0.52, 8.12)	0.085
18 months	8.95 (5.42, 12.49)	12.64 (9.57, 15.71)	3.69 (−1.25, 8.63)	0.141
24 months	12.05 (8.76, 15.33)	14.90 (11.97, 17.83)	2.85 (−1.23, 6.94)	0.171
PHQ-9				
6 months	−3.58 (−5.13, −2.04)	−4.75 (−6.28, −3.23)	−1.17 (−3.28, 0.94)	0.277
12 months	−4.22 (−6.28, −2.15)	−6.70 (−8.27, −5.12)	**−2.48 (−4.95, −0.01)**	**0.049**
18 months	−3.55 (−5.05, −2.04)	−7.83 (−9.45, −6.22)	**−4.28 (−6.44, −2.13)**	**0.000**
24 months	−3.78 (−5.56, −2.01)	−7.66 (−9.22, −6.10)	**−3.88 (−6.20, −1.55)**	**0.001**
BDI-1				
6 months	−4.29 (−7.38, −1.19)	−6.84 (−9.28, −4.40)	−2.55 (−6.50, 1.39)	0.203
12 months	−6.17 (−9.33, −3.01)	−11.27 (−13.66, −8.88)	**−5.10 (−9.09, −1.12)**	**0.012**
18 months	−7.39 (−10.51, −4.27)	−12.86 (−15.73, −9.99)	**−5.47 (−9.97, −0.97)**	**0.018**
24 months	−7.79 (−10.62, −4.97)	−12.99 (−15.69, −10.29)	**−5.20 (−8.93, −1.47)**	**0.006**
QIDS-SR				
6 months	−3.54 (−5.53, −1.54)	−5.93 (−7.89, −3.98)	−2.39 (−5.26, 0.48)	0.102
12 months	−4.91 (−6.99, −2.84)	−7.38 (−9.23, −5.53)	−2.47 (−5.22, 0.29)	0.079
18 months	−4.97 (−7.13, −2.81)	−9.25 (−11.34, −7.16)	**−4.28 (−7.34, −1.23)**	**0.006**
24 months	−5.50 (−7.92, −3.08)	−8.75 (−10.75, −6.76)	−3.26 (−6.53, 0.02)	0.051

Data in bold are significant at $p < 0.05$.

4. Discussion

These results show a continued stable effect of specialist collaborative care for moderate-severe depression in secondary care, maintained at the protocol defined endpoint of 24 months, roughly one year following treatment completion for most patients (median treatment 13 months; IQR 12–15 months). This effect was significant (vs TAU) for our primary depression outcome, the 24-month $HDRS_{17}$, and was seen robustly across all other clinician and patient outcome measures of depression. Additional analysis of the $HDRS_6$ (a subset of the $HDRS_{17}$ recently shown to have better psychometric properties for change

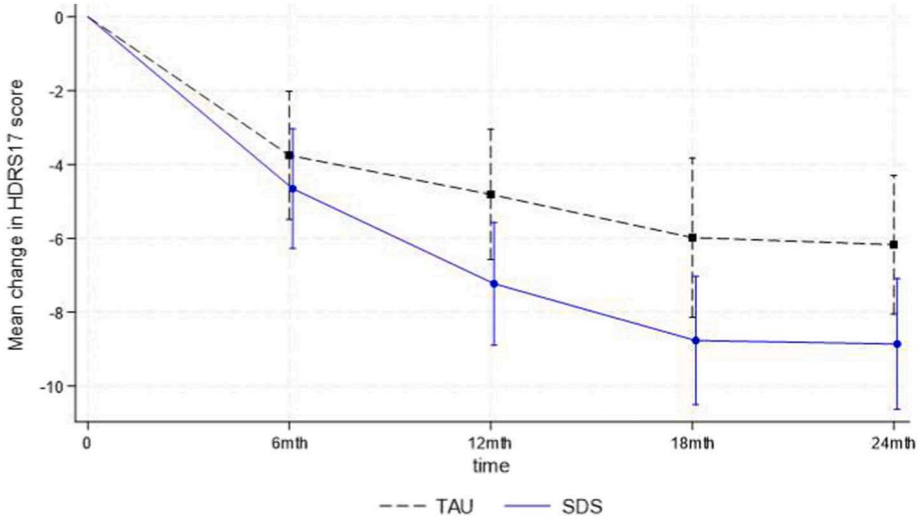

Fig. 2. Mean change in HDRS17 from baseline to 24 months for Specialist Depression Service (SDS) vs treatment as usual (TAU).

Table 2
Observed response rate to 36 months.

	Response rate in observed cases over 36 months as % (n)	
	TAU	SDS
$HDRS_{17}$		
6 months	15.2 (10)	21.8 (17)
12 months	20.3 (12)	29.3 (22)
18 months	25.0 (12)	40.3 (25)
24 months	29.8 (14)	39.3 (24)
36 months	15.4 (4)	37.1 (13)
PHQ-9		
6 months	15.4. (8)	21.0 (13)
12 months	18.2 (8)	43.6 (24)
18 months	18.0 (7)	44.9 (22)
24 months	25.0 (9)	42.3 (22)
36 months	13.6 (3)	45.5 (15)
BDI-1		
6 months	10.5 (6)	13.4 (9)
12 months	18.8 (9)	36.7 (22)
18 months	19.1 (8)	35.9 (19)
24 months	25.6 (10)	31.5 (17)
36 months	13.0 (3)	44.1 (15)
QIDS-SR		
6 months	8.8 (5)	19.4 (13)
12 months	14.6 (7)	27.9 (17)
18 months	23.7 (9)	42.0 (21)
24 months	15.8 (6)	27.8 (15)
36 months	18.2 (4)	39.4 (13)

Table 3
Remission rate to 36 months.

	Remission rate in observed cases over 36 months as % (n)	
	TAU	SDS
$HDRS_{17}$		
6 months	9.1 (6)	12.8 (10)
12 months	11.9 (7)	20.0 (15)
18 months	12.5 (6)	25.8 (16)
24 months	19.2 (9)	27.9 (17)
36 months	11.5 (3)	31.4 (11)
PHQ-9		
6 months	18.5 (10)	23.8 (15)
12 months	28.9 (13)	43.9 (25)
18 months	25.0 (10)	45.1 (23)
24 months	29.7 (11)	36.5 (19)
36 months	22.7 (5)	39.4 (13)
BDI-1		
6 months	5.2 (3)	7.5 (5)
12 months	8.3 (4)	16.4 (10)
18 months	11.9 (5)	24.1 (13)
24 months	15.4 (6)	20.4 (11)
36 months	8.7 (2)	26.5 (9)
QIDS-SR		
6 months	3.5 (2)	1.5 (1)
12 months	8.3 (4)	9.7 (6)
18 months	7.9 (3)	13.7 (7)
24 months	7.9 (3)	9.3 (5)
36 months	0.0 (0)	15.2 (5)

assessment in this population) (Nixon et al., 2020), was also significant at 24-months. The mean effect size (vs. TAU) at 24 months remained similar to the 18-month outcome at just under 3 points on the $HDRS_{17}$, which is regarded as clinically important (Zimmerman et al., 2013a). Given the statistical significance of the a priori depression change measure, we have also presented simple statistics on response and remission, in keeping with recommended practice (EMA, 2017). These show a maintenance of higher response and remission rates in the SDS (vs. TAU) across all measures, throughout the post-treatment period at each time-point from 18 months to final follow-up at 36 months; at which time response rate was between 2.2 and 3.4 times higher for the SDS across all measures and calculated remission rates 1.7–3.0 times higher for the SDS. The absolute response rate at 36 months was between 37 and 46 % for the SDS compared to 13–18 % for TAU; with an absolute remission rate of 15–39 % across all measures for the SDS (vs. 0–23 % for TAU).

As evident from our introduction, there is no other secondary care study with which we can directly compare these longer-term, post-treatment community outcomes for depression. The authors of the only additional study identified in our systematic review, Re-ChORD in Vancouver (Murray et al., 2010), were contacted in the writing of this paper and confirmed there is no further data beyond their published 4-month, end-of-treatment outcomes. Beyond secondary care, a recent review (McPherson and Hengartner, 2019) identified only two primary care studies assessing post-treatment effects of combined CBT to 12-months or more in major depression, one of which is a relapse reduction study (Paykel et al., 1999); though the other, CoBalT, provides 46-month outcome data on remission following depressive episodes treated with CBT as an adjunct to usual care including pharmacotherapy (Wiles et al., 2016). Whilst this may underscore the increasingly recognised paucity of longer-term outcomes data in depression (Uher and Pavlova, 2016) (NICE, 2018a), CoBalT does at least provide some comparison with our findings in a less severe primary care population, with 28 % remission at 46 months from baseline (vs. 18 % TAU, including an initial

4–6 month intervention) (Wiles et al., 2016).

The comparative, longer-term, post-treatment benefit (vs TAU) of both SDS and CoBalT interventions may offer hope; but absolute remission rates in the range of only 15–39 % at 3–4 years should also pose a stark challenge to mental health professionals across primary and secondary care. How can we justify time-intensive baseline interventions for depression that are shown to change the longer-term illness trajectory — but in much more marginal ways than we aspire to? And accepting that major depression is often a lifetime disorder — having median onset by 32 years old (Solmi et al., 2022; Kessler et al., 2005), with high persistence and recurrence through adult life (Eaton et al., 2008; Mueller et al., 1999) how can we work towards improved outcomes across more meaningful time horizons that may be better measured in years or decades (rather than weeks or months)? In considering a justification, we have to acknowledge both the higher costs of a collaborative secondary care model using the same mode of psychotherapy as its primary care comparator over more than twice the duration (a median of 13 months in secondary care (Morriss et al., 2016) vs. 4–6 months in primary care (Wiles et al., 2016)); and evidence that benefit from the SDS (vs. TAU) only begins to emerge beyond 6 months (Morriss et al., 2016), by which time the primary care intervention has been completed. The corollary is that funding a shorter 6-month intervention in secondary care, may provide no additional benefit over standard care and risks wasting resources; indeed, the only other secondary care intervention identified in our systematic review, similarly failed to show statistically significant symptom change over a 4-month period (Murray et al., 2010). And there may be a rationale, through the typically more persistent, severe, complex and higher-risk presentations of depression in secondary care, borne out by comparative baseline data from the SDS and CoBalT, showing: current episode persistence beyond 2 years in >75 % of SDS vs. 59 % in CoBalT (Morriss et al., 2016; Wiles et al., 2013); and symptoms at moderate-severe level in SDS vs. mild-moderate in CoBalT. These, together with high rates of complex psychiatric co-morbidity, interpersonal difficulty and clinical risk (Morriss et al., 2016) will tend to militate against recovery in secondary care populations; driving the observed need for a longer, more resource-intensive baseline intervention, relative to primary care.

This justification is complicated however by functional outcomes from both the GAF (as primary functional outcome) and SAS-M, both showing only non-significant stable improvement favouring the SDS at 24 months (with high attrition rates beyond this point precluding further analysis). The lack of significant evidence on comparative functional improvement (vs TAU) is important not only in its own right but through the closely linked concept of lost productivity, long-known as a key determinant of the economic cost of depression (McCrone et al., 2008); and if short-term interventions appear ineffective, then we may also consider that longer-term interventions need a clearer focus on functional recovery, alongside sustained symptomatic improvement. Indeed, since protocol development for this study, there have been calls for strategies that might improve the efficacy of current treatments on functional outcome (Uher and Pavlova, 2016); and updated guidance specifically recommending consideration of additional social and vocational support, including rehabilitation programmes, for people with persistent depression (NICE, 2022). Additionally, the role of lifestyle interventions has received much greater emphasis, including the importance of adequate nutrition (Mrozek et al., 2023) and recommendations for structured group exercise across the range of depression severity (NICE, 2022). Integration of these vocational and lifestyle interventions, alongside more traditional treatments, might more fully recognise what is often lost through many years of depression: in social networks, occupational function, basic self-care and physical conditioning. Since most people will have experienced their first episode of major depression by age 32, with observational studies through 10- and 15-years showing high persistence (Eaton et al., 2008) and high absolute relapse-rate in secondary-care depression (Solomon et al., 2000; Mueller et al., 1999), these losses will tend to accumulate over a lifetime, deepening complexity and worsening outcome.

Attaining scale-defined anchor points for full remission retains importance through promoting stable recovery and substantially improving this long-term picture (Rush et al., 2006a, 2006b; Rush, 2007); however there has also been recent focus on 'clinically meaningful improvement thresholds' (Rush et al., 2021), as degrees of absolute change that hold relevance for patient's experience of social adjustment and quality of life. In defining these thresholds for depression, Rush et al. (2021) identified an absolute reduction of 7–12 points in the $HDRS_{17}$ as a clinically substantial improvement; a mean change achieved and maintained in the SDS group from 12 months onwards but never attained at any point by TAU. In keeping with this, the minimally clinically important 10-point absolute difference in GAF (Roux et al., 2020) was also reached by 12 months in the SDS group and maintained with an upward trajectory at 24 months (with TAU only attaining this threshold at 24 months).

For people suffering depression and their clinicians, evidence on how to sustain meaningful change through recovery has been identified as a top unmet research priority (James Lind Alliance, 2016). Yet in the years following that report on 'asking the right questions', the call has remained substantially unmet and in the more specific area of persistent secondary care depression there remains an almost total lack of longer-term, outcomes-based evidence to guide specialist service provision. Results presented here may at least begin to address this gap, showing clinically meaningful change maintained across multiple longer-term outcomes through a relatively simple, collaborative baseline intervention, when compared to treatment as usual. These clinically meaningful improved outcomes were maintained long after completion of the active treatment and notably include remission, a well-established prognostic indicator of future stability. The quality of evidence is limited, largely through the inherent problems of longer-term follow up, but shows what can be achieved even after many years of complex illness, evidencing a central model for specialist services that might be adapted further to improve lifespan outcomes in major depression.

4.1. Limitations

The extent of loss to follow up introduces the possibility of bias, particularly beyond 24 months, although the attrition between 24 and 36 months was very similar in both arms (45 % TAU vs 43 % SDS). There is no secondary care study to compare our results with but overall attrition of 67 % to 3 years, compares with 41 % at 4 years in a well-conducted Primary Care study using only patient completed outcome measures (Wiles et al., 2016). Both studies show the real-world difficulties entailed in achieving the longer-term follow-up of depression outcomes that has been called for by guideline bodies charged with making practice recommendations (e.g. NICE, 2018a). The greater attrition in our study compared to Wiles et al., 2016, may relate to the more pronounced challenges faced by a more severely affected and more complex patient group, though in the absence of any truly equivalent study data this is inevitably speculative. Our attrition beyond 24 months also likely relates to the fact that the study was initially only funded for 24 months and we needed to secure additional funding to assess 36-month outcomes. The attendant disruption of study personnel and of contact with patients created additional barriers to effective follow-up and if we are to get longer-term data most effectively in future work, then initial funding arrangements should perhaps reflect this. In light of the attrition, we cannot exclude the possibility that this may bias our results, particularly at 36 months. The depression measures used here were intended to assess symptom change and there is a lack of equivalence between these scales on remission threshold (a problem highlighted in a recent a recent analysis of scale cut-offs published in the 2018 draft NICE update for Depression in Adults (NICE, 2018b)). Perhaps related to this, there are wide ranges for our 24- and 36-month remission rates; and these were particularly low, for both groups, when measured by QIDS.

Additionally, there was some contamination between treatment arms, since 3 patients in the TAU group had SDS treatment between 24 and 36 months due to the unplanned nature of this final follow-up point and the ethical concern to provide SDS care where possible to people from TAU who had requested it. This issue relates both to the general challenge of long-term RCT follow-up and the more specific ethical issues involved in potentially restricting access to treatment (the SDS) over long periods for patients with moderate-severe depression. These patients were analysed per randomisation within their originally assigned group and given the overall results, the effect of this would have likely favoured TAU in treatment comparisons.

5. Conclusions

The treatment model assessed in this paper is in itself uncomplicated, essentially a synthesis of biomedical, psychotherapy and collaborative care approaches recommended by NICE for moderate-severe depression (NICE, 2022). Results from the baseline intervention given over a median 13 months, showed that clinically important improvements in depression were sustained at 24 and 36 months, though there was no significant change in between-group functional outcomes. Whilst interpretation is limited through some of the challenges of longer-term follow up, our findings address a research priority area that is otherwise unmet in current literature, concerning the longer-term effects of a baseline collaborative care intervention for persistent depression in secondary care. The treatment model described here might be developed further, including through assessing the optimal timing, nature and delivery of interventions focused on enhancing functional outcome - ultimately aiming to provide more meaningful, sustained benefit for patients.

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CRediT authorship contribution statement

Neil Nixon: Conceptualisation, Investigation, Writing – original draft preparation. Boliang Guo: Formal analysis, Writing – review & editing. Catherine Kaylor-Hughes: Investigation, Project administration, Data curation, Writing – review & editing. Sandra Simpson: Investigation, Data curation, Writing – review & editing. Anne Garland: Conceptualisation, Investigation, Writing – review & editing. Tim Dalgleish: Conceptualisation, Investigation, Writing – review & editing. Richard Morriss: Conceptualisation, Funding acquisition, Methodology, Investigation, Writing – review & editing.

Declaration of competing interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

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