

RESEARCH ARTICLE

Autopsy of a failed trial part 2: Outcomes, challenges, and lessons learnt from the DAISIES trial

Başak İnce¹  | Matthew D. Phillips¹  | Zohra Zenasni² | James Shearer³ | Bethan Dalton¹  | Madeleine Irish⁴ | Daniela Mercado¹ | Hannah Webb¹ | Catherine McCombie³  | Katie Au⁵ | Nikola Kern⁵ | Sam Clark-Stone⁶ | Frances Connan⁷ | A. Louise Johnston⁸ | Stanimira Lazarova⁹ | Ewa Zadeh⁹ | Ciarán Newell¹⁰ | Tayeem Pathan¹¹ | Jackie Wales¹² | Rebecca Cashmore¹² | Sandra Marshall¹² | Jon Arcelus^{13,14}  | Paul Robinson¹⁵  | Sarah Byford³  | Sabine Landau²  | Vanessa Lawrence³  | Hubertus Himmerich^{1,5}  | Janet Treasure^{1,5}  | Ulrike Schmidt^{1,5} 

Correspondence

Ulrike Schmidt.

Email: ulrike.schmidt@kcl.ac.uk**Handling Editor:** Daniel Le Grange**Funding information**

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Abstract

Objective: The relative merits of inpatient or day-treatment for adults with anorexia nervosa (AN) are unknown. The DAISIES trial aimed to establish the non-inferiority of a stepped-care day patient treatment (DPT) approach versus inpatient treatment as usual (IP-TAU) for improving body mass index (BMI) at 12 months in adults with AN. The trial was terminated due to poor recruitment. This paper presents outcomes and investigates the reasons behind the trial's failure.

Method: Fifteen patients with AN (of 53 approached) participated and were followed-up to 6 or 12 months. Summary statistics were calculated due to low sample size, and qualitative data concerning treatment experiences were analysed using thematic analysis.

Results: At baseline, participants in both trial arms rated stepped-care DPT as more acceptable. At 12 months, participants' BMIs had increased in both trial arms. Qualitative analysis highlighted valued and challenging aspects of care across settings. Only 6/12 sites opened for recruitment. Among patients approached, the most common reason for declining participation was their treatment preference ($n = 12/38$).

Conclusions: No conclusions can be drawn concerning the effectiveness of IP-TAU and stepped-care DPT, but the latter was perceived more positively. Patient-related, service-related and systemic factors (COVID-19) contributed to the trial's failure. Lessons learnt can inform future studies.

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KEYWORDS

anorexia nervosa, day patient treatment, inpatient treatment, RCT, recruitment

Highlights

- Patient-related (e.g., treatment preferences) and service-related (e.g., reduced service capacity) alongside wider systemic (e.g., increased emergency admissions due to COVID-19) factors seem to have contributed to the failure of the DAISIES trial.
- Patients and carers identified valued aspects for both inpatient (e.g., weight gain) and day-patient (e.g., greater link to home environment) treatment settings, but day-patient treatment was perceived as a more holistic and collaborative approach, and thus as more positive.
- Although randomised controlled studies investigating intensive treatments for severe anorexia nervosa are important and necessary, alternative study designs should be explored to overcome implementation challenges.

1 | INTRODUCTION

Anorexia nervosa (AN) is a severe psychiatric disorder associated with significant medical, psychosocial, and economic consequences, and has the highest mortality rate of all psychiatric disorders (Treasure et al., 2020). Around 30% of patients with AN require a course of intensive (inpatient or day patient) treatment (Herpertz-Dahlmann, 2021). Compared to other psychiatric disorders, referral and (re)admission rates for AN display a rising trend (Degli Esposti et al., 2022). Internationally, since the onset of the COVID-19 pandemic, eating disorder (ED) services have experienced further rises in referrals, presentation severity, and emergency admissions (Ayton et al., 2022; Hyam et al., 2023), leading to a bottle neck in the availability of inpatient care, due to longer admissions and temporarily reduced bed-numbers secondary to infection control measures (Schreyer et al., 2023; Webb et al., 2022a). This has placed additional demands on already under-resourced and overburdened ED services, such as those in the UK, and alternatives to inpatient treatment are urgently needed.

The National Institute for Health and Care Excellence (NICE, 2017) guidelines for EDs recommend intensive treatments (i.e., inpatient or day patient/partial hospitalisation) for patients with moderate or severe AN whose health is significantly compromised or for those who do not improve through outpatient treatment. Inpatient treatment as usual (IP-TAU), considered as the gold-standard option, is typically delivered by multidisciplinary ED specialist services, combining medical and nutritional rehabilitation and psychotherapeutic support to achieve weight restoration. IP-TAU should provide a safe and supportive environment aiding recovery. However, research suggests inpatients may feel disempowered,

and disconnected from real-life (Fox et al., 2017; Long et al., 2011). Additionally, IP-TAU is costly to the National Health Service (NHS) and wider society (Byford et al., 2007). Day-patient treatment (DPT) is commonly used as a transition step between IP and outpatient treatment and is considered as a less costly alternative to IP-TAU (Guarda et al., 2017; Serrano-Troncoso et al., 2020). DPT enables patients to return home for weekends and evenings, giving them increased autonomy and greater links to their outside lives, and facilitating the transfer of skills learnt to daily life. However, DPT can lead to difficulty in weight gain for recovery and provides less support and monitoring than IP-TAU. It may also put greater pressure on families (Irish et al., 2022; Serrano-Troncoso et al., 2020; Webb et al., 2022b).

To date, only one randomised controlled trial (RCT) has compared IP-TAU to a stepped-care DPT approach in adolescents with a first episode of AN. This showed that stepping-down to DPT after a 3-week inpatient admission was safe, non-inferior to IP-TAU for weight restoration, and less costly (Herpertz-Dahlmann et al., 2014). No comparable study exists in adults. In response to a commissioned funding call for trials from the National Institute of Health Research (NIHR) under their Health Technology Assessment (HTA) scheme, we designed and subsequently (January 2020) started a two-arm multi-centre open-label parallel-group non-inferiority RCT to investigate the relative merits of a stepped-care DPT approach (with the option of initial inpatient treatment for medical stabilisation) in comparison to IP-TAU in adults with severe AN. This highly pragmatic study opened for recruitment in November 2020 with an internal pilot and an overall recruitment target of 386 participants. However, due to low recruitment, the HTA prematurely terminated the DAISIES trial in March 2022. This paper aims to (a)

provide a brief overview of the trial, (b) present available data collected from randomised participants and their carers (i.e., quantitative clinical outcome data and qualitative process evaluation data), (c) report challenges faced during recruitment and the strategies implemented to overcome them, and (d) try to answer why DAISIES trial failed and what lessons can be learned.

2 | METHOD

Full details of the trial design, methodology, planned baseline and outcome assessments, and study procedure are described in the protocol paper (Irish et al., 2022). Brief descriptions of the study design and methodology are presented in Supporting Information S1: Supplement 1.

2.1 | Study design, setting and participants

The DAISIES trial was a two-arm multi-centre open-label parallel-group non-inferiority RCT with a 4-month internal pilot at the start of the trial. Twelve adult NHS specialist ED services in the UK were involved, 10 with both inpatient and DPT services and two with DPT services only.

Patients from specialist ED inpatient and outpatient services meeting the following inclusion criteria were invited to take part in the study: (1) adults aged 17 years or above; (2) DSM-5 diagnosis of AN or related disorders (e.g., avoidant restrictive food intake disorder; ARFID); (3) BMI of ≤ 16.0 kg/m²; (4) in need of intensive treatment because of either rapid weight loss, and/or evidence of system/organ failure/medical instability and/or unsuccessful outpatient treatment (NHS, 2013); and (5) have the mental capacity to give informed consent to participate in the study.

Exclusion criteria were: (1) insufficient knowledge of English to complete study assessments; (2) severe learning disability; (3) a severe medical or psychiatric (co)morbidity (e.g., psychosis) requiring treatment in its own right; and (4) living too far away from DPT.

2.2 | Assessments

2.2.1 | Participant assessments

Screening

A purposely designed clinician checklist assessing eligibility and recording sociodemographic characteristics of the participants (e.g., age, gender, ethnicity) and clinical

data (e.g., age at ED onset, previous treatments, current treatment status) was administered prior to baseline.

A modified version of the Maudsley Medical Risk Assessment tool (Treasure, 2009), which uses a traffic light system, was completed by the treatment team for assessing physical and psychiatric/psychological risks. This tool facilitated decision making around the most appropriate treatment setting for the patient and was completed for all patients who were assessed for study eligibility prior to baseline. In the stepped care arm, a further weekly decision tool was completed for the duration of intensive treatment (i.e., in inpatient or DPT) providing guidance on patients' suitability for stepping-down into DPT (or stepping-up to IP treatment in the case of deterioration or relapse).

Primary outcome

The primary outcome was BMI (kg/m²) at 12 months post-randomisation.

Secondary outcomes

- Monthly BMI (kg/m²) from baseline to 12 months post-randomisation.
- Monthly ED symptomatology assessment using the Eating Disorder Examination Questionnaire – short form (EDE-QS; Gideon et al., 2016) from baseline to 12 months post-randomisation.
- Clinical outcomes (e.g., anxiety, depression, loneliness) at baseline, 6 and 12 months post-randomisation.
- Motivational rulers assessing the perceived importance of, desire to, and confidence in making personal changes at baseline, 6 and 12 months post-randomisation.

Remission and relapse rates

Remission and relapse rates were constructed based on combined information from secondary outcomes (a) and (b) as defined previously in Schmidt et al. (2015).

Treatment expectations, acceptability, adherence and completion

- Visual analogue scales (VAS, 1–10; Schmidt et al., 2015) to assess (i) expectations of effectiveness for both treatment approaches at baseline only and (ii) perceived treatment acceptability of allocated treatment at 6 and 12 months post-randomisation, adjusted for expected treatment acceptability at baseline.
- The number of IP and DPT days attended per week.

Health economics

- Health-related quality of life assessed using the EQ-5D-5L (Herdman et al., 2011) at baseline, 6 and 12 months post-randomisation.

- b. Use of hospital services, community-based health and social care services, and medications to estimate costs of care using the Adult Service Use Schedule (AD-SUS) adapted for the trial but based on previous versions applied to eating disorder populations (Gowers et al., 2010; Schmidt et al., 2017) completed at baseline, 6 and 12 months post-randomisation.

Carer assessments

- a. A purposely designed record form to assess carers' demographic characteristics (e.g., gender, employment, nature of relationship to study participant) at baseline.
- b. Instruments assessing carers' perceived burden of ED, mood, anxiety and stress symptoms at baseline, 6 and 12 months post-randomisation (for details see protocol paper (Irish et al., 2022))

2.3 | Process evaluation

Semi-structured interviews were conducted at 6 months post-randomisation, focussing on participants' experiences of treatment settings and any changes over time. The topic guides can be found in Supporting Information S2: Supplement 2.

2.4 | Treatment approaches

Treatment programmes in the UK typically follow national guidelines and standards (NICE, 2017; NHS, 2013; National Collaborating Centre for Mental Health, 2019; Royal College of Psychiatrists, 2017). Care plans in IP-TAU and DPT units include multi-disciplinary support (including psychiatrists, psychologists, dieticians, nurses and others), expert refeeding and evidence-based psychological interventions for patients and their carers.

2.4.1 | Inpatient treatment as usual (IP-TAU)

IP-TAU was delivered by multidisciplinary teams, and involved medical care, expert refeeding, supervised meals and snacks, and psychotherapeutic support. Patients stayed in IP-TAU until they completed their course of treatment, where the goal was to normalise eating behaviours and reach a healthy weight or get as close to that as possible, and was either followed by step-down to DPT or discharge to outpatient treatment, based on the treating team's decision.

2.4.2 | Stepped-care day patient treatment (DPT)

This involved intensive DPT with the option of initial hospitalisation for medical stabilisation. If the patient was hospitalised, the aim was to step-down patients to DPT within 1 month of being at an appropriate level of risk. Stepped-care DPT has similar goals as IP-TAU and involves a full-time programme covering 4–5 days a week with two to three meals per day, along with medical and psychological support. Although DPT is usually delivered face-to-face, some sites delivered treatment remotely due to COVID-19. Patients received treatment until their eating was normalised and they reached or got as close to a healthy weight as possible.

2.5 | Procedure

Eligible patients were approached for the study in a two-stage procedure. Initially the study was introduced to the patient by an experienced senior assessing/treating clinician who also facilitated contact with the researchers who then discussed the study further. Written informed consent for participation was obtained from patients and optionally also from their carer. Thereafter, participants received a personal web link to access the baseline self-report questionnaires via Qualtrics, and structured clinical interviews (e.g., AD-SUS) were conducted by researchers via Microsoft Teams.

Upon completion of baseline assessments, randomisation was conducted by the trial coordinator through an online system provided by the King's Clinical Trials Unit and employed minimisation with stratifiers: (i) previous inpatient treatment [yes/no] (ii) illness duration [\leq or $>$ 3 years] and (iii) recruitment centre. Participants were randomly allocated on a 1:1 ratio to either IP-TAU or stepped-care DPT arms.

Optional semi-structured process evaluation interviews were offered to all patients and carers who took part in the study after the 6-month assessment and conducted by a researcher blinded to treatment allocation via Microsoft Teams. Participants were assured of their anonymity and encouraged to express both positive and negative opinions.

Participant recruitment started in November 2020 and ceased in March 2022. The data collection and interviews were completed for all participants until they reached at least the 6-month follow-up at the end of August 2022.

2.6 | Data analysis

2.6.1 | Quantitative analysis

Due to the low sample size, no formal statistical tests were conducted assessing differences between treatment groups on any participant-level baseline or outcome variables. Summary statistics were applied to describe demographic and clinical measures using Stata v17. The mean and standard deviation as well as the median, 25th and 75th quartiles were calculated. Categorical outcomes were described using both numbers and proportions (percentages). Similarly, no statistical analyses of health economic outcomes were performed. Service use by participants is instead reported as the mean (standard deviation) and median by group and as a percentage of the group who had at least one contact (% using).

2.6.2 | Qualitative analysis

Qualitative process evaluation data were analysed in NVivo 12 following a reflexive thematic analysis approach. Coding was inductive and analysis underpinned by an interpretivist framework that recognises the significance of the dual interpretations of experience by participant and researcher (Braun and Clarke, 2006, 2021). After data familiarisation, Authors BĪ and MP independently coded 9 transcripts (6 patients, 3 carers) and met with VL to debate alternative interpretations. The coding framework was then refined, and remaining transcripts were inductively coded. Author MP grouped codes into themes and discussed theme construction at regular intervals with Author BĪ. Both Author BĪ and Author MP kept reflexive diaries throughout to reflect on their professional experiences of ED treatment and potential influences on data interpretation; this process alongside the use of multiple coders and regular analytic discussion enhanced the rigour of analysis.

3 | RESULTS

3.1 | Participant flow and sample characteristics

Fifty three patients were approached over a 16-month recruitment period, and 15 patients from three sites consented to participate, which includes participants from the 4-month internal pilot. The CONSORT diagram is shown in Figure 1. Among those who did not show

interest or declined to take part, the most common reason was a strong treatment preference ($n = 12$). Demographic and clinical characteristics at baseline are summarised in Table 1. The mean BMI of participants was 14.4 ($SD = 1.6$) kg/m^2 , and the majority (80.0%) had a diagnosis of AN restricting type. Most had an illness duration above 3 years (60.0%) and had previous IP admission(s) (60.0%).

A total of 6 carers (IP-TAU, $n = 4$; stepped-care DPT, $n = 2$) consented to participate. They had a mean age of 49.4 years ($SD = 16.0$). The majority were female (83.3%) and all identified as White. The majority were parents (66.7%) and were living with the DAISIES trial participant (83.3%). Quantitative carer data are provided in Supporting Information S3: Supplement 3.

Among those who participated in the study, a total of 6 patients and 3 carers participated in semi-structured qualitative process evaluation interviews.

3.2 | Quantitative results

At baseline, all participants felt that the stepped-care DPT approach would be more effective and acceptable in improving their condition than IP-TAU, with mean effectiveness scores of 8.4 ($SD = 1.6$) versus 5.6 ($SD = 3.5$) out of 10 respectively, and mean acceptability scores of 8.3 ($SD = 1.5$) versus 5.1 ($SD = 3.3$), respectively. Overall, participants felt it important to change their ED behaviours (mean 8.6, $SD = 1.5$) and to increase/adjust their daily food intake, in order to achieve/maintain a healthy weight (mean 7.8, $SD = 2.7$). However, they felt less able to change their ED behaviours (mean 6.9, $SD = 2.6$), and to increase/adjust food intake (mean 6.7, $SD = 2.5$). A similar pattern was observed in both groups. Further information on treatment acceptability and motivation is provided in Supporting Information S4: Supplement 4.

Data on adherence to allocated treatment show that all participants randomised to IP-TAU received their allocated treatment (i.e. IP-TAU) (100.0%). Of those randomised to stepped-care DPT, 6 (75%) received their allocated treatment (i.e. DPT), while one patient (12.5%) self-discharged against medical advice during initial hospitalisation and was not accepted by day-patient services and one (12.5%) disengaged during initial IP treatment and never attended their DPT. For the IP-TAU group, the median number of weeks spent in allocated treatment was 11.6 (IQR = 5.7–15.7), and in DPT after discharge, 9.1 (IQR = 7.1–16.8). For the stepped-care DPT arm, the median number of weeks spent in DPT was 9.0 (IQR = 2.7–17.8), and in IP treatment prior to step-down, 5.2 (IQR = 2.9–10.2).

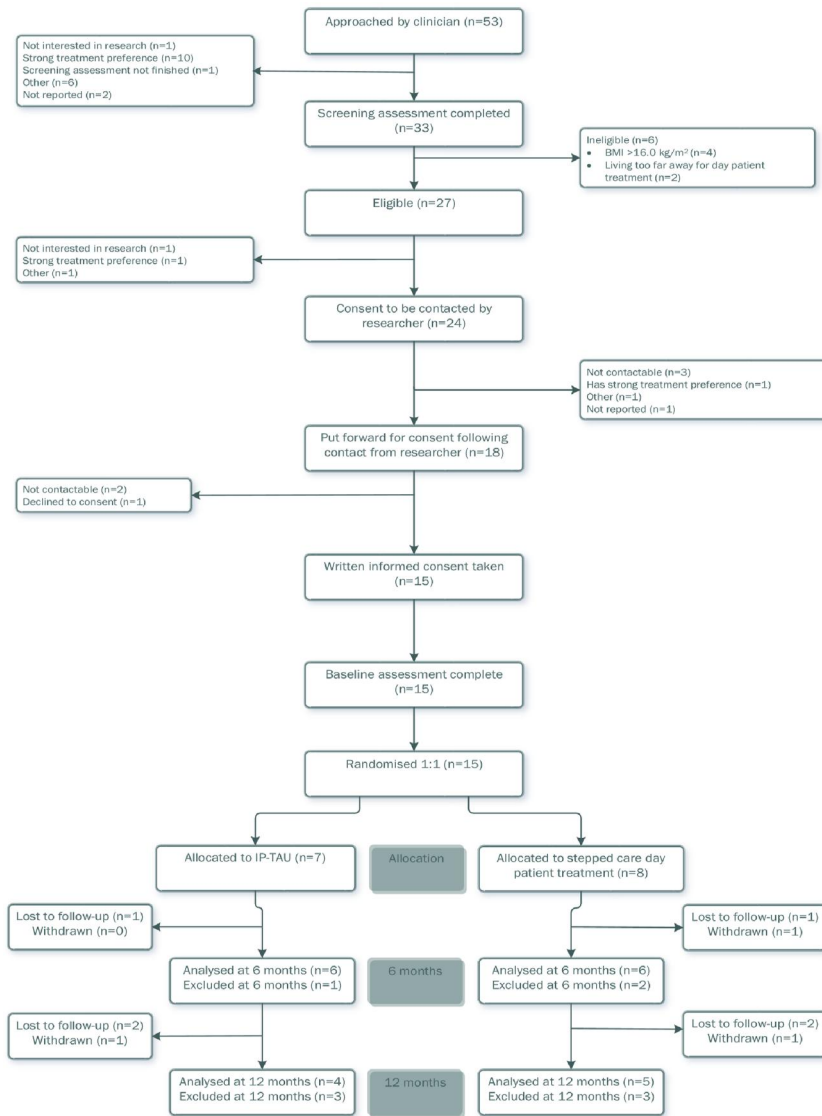


FIGURE 1 Study CONSORT diagram showing participant recruitment, allocation and assessments.

Participants' raw mean monthly BMI scores are presented in Figure 2. Patient clinical outcomes, carer outcomes as well as health economic data (hospital and community-based health and social care service use and medication use data) are presented in Supporting Information S3–S5: Supplements 3–5.

3.3 | Qualitative results

Three overarching themes were generated: Valued aspects of care; challenging experiences across treatment settings; and experiences of transitions. Supporting Information S4: Supplement 4 presents brief information on participants who took part and provides indicative quotes to illustrate identified themes and support the trustworthiness of our interpretations.

3.3.1 | Theme 1: Valued aspects of care

Degrees of collaboration between staff and patient

Across both intensive treatment settings, patients and carers emphasised the importance of collaboration around treatment. Where collaboration was present, it was felt to be *'really beneficial'* (P2), promoting autonomy and keeping treatment *'focused on you'* (P2). However, collaboration was often felt to be absent, particularly within IP settings. Patients reported that their views were not listened to, leading to *'a lack of trust'* (P5) and a feeling that staff made treatment decisions for them, often feeling that their low weights meant that their views were ignored, which they experienced as *'incredibly degrading'* (P6). All carers reported feeling uninvolved in both treatment settings, and desired greater communication.

TABLE 1 Baseline demographic and clinical characteristics of participants.

	IP-TAU (<i>n</i> = 7)	Stepped care DPT (<i>n</i> = 8)	Total (<i>N</i> = 15)
Demographics			
Age			
Mean (SD)	26.7 (9.0)	23.1 (9.4)	24.8 (9.1)
Median (IQR)	22.0 (20.0–32.0)	20.5 (18.0–22.0)	21.0 (18.0–31.0)
Ethnicity, <i>n</i> (%)			
White	6 (85.7)	7 (87.5)	13 (86.7)
Mixed/Multiple ethnic groups	0 (0.0)	1 (12.5)	1 (6.7)
Asian/Asian British	1 (14.3)	0 (0.0)	1 (6.7)
Employment status, <i>n</i> (%)			
Paid full-time employment (35 or more hours per week)	1 (14.3)	0 (0.0)	1 (6.7)
Paid part-time employment (up to 34 h per week)	1 (14.3)	0 (0.0)	1 (6.7)
Unemployed	2 (28.6)	2 (25.0)	4 (26.7)
Unable to work/Sick leave	2 (28.6)	1 (12.5)	3 (20.0)
Student	1 (14.3)	5 (62.5)	6 (40.0)
Marital status, <i>n</i> (%)			
Single	5 (71.4)	6 (75.0)	11 (73.3)
In a relationship	1 (14.3)	1 (12.5)	2 (13.3)
Married or in a civil partnership	1 (14.3)	1 (12.5)	2 (13.3)
Current living situation, <i>n</i> (%)			
Live alone	0 (0.0)	1 (12.5)	1 (6.7)
Live with partner/spouse (with or without children)	1 (14.3)	1 (12.5)	2 (13.3)
Live with parents and/or other family members	4 (57.1)	5 (62.5)	9 (60.0)
Live with housemates/lodgers/tenants (not friends)	2 (28.6)	1 (12.5)	3 (20.0)
Clinical characteristics			
Diagnosis, <i>n</i> (%)			
Anorexia nervosa (restricting type)	6 (85.7)	6 (75.0)	12 (80.0)
Anorexia nervosa (Binge-eating/Purging type)	1 (14.3)	2 (25.0)	3 (20.0)
Illness duration, <i>n</i> (%)			
≤3 years	2 (28.6)	4 (50.0)	6 (40.0)
>3 years	5 (71.4)	4 (50.0)	9 (60.0)
Treatment status prior to randomisation, <i>n</i> (%)			
Inpatient treatment	7 (100.0)	6 (75.0)	13 (86.7)
Outpatient treatment	0 (0.0)	2 (25.0)	2 (13.3)
Previous inpatient treatment, <i>n</i> (%)			
Yes	4 (57.1)	5 (62.5)	9 (60.0)
No	3 (42.9)	3 (37.5)	6 (40.0)

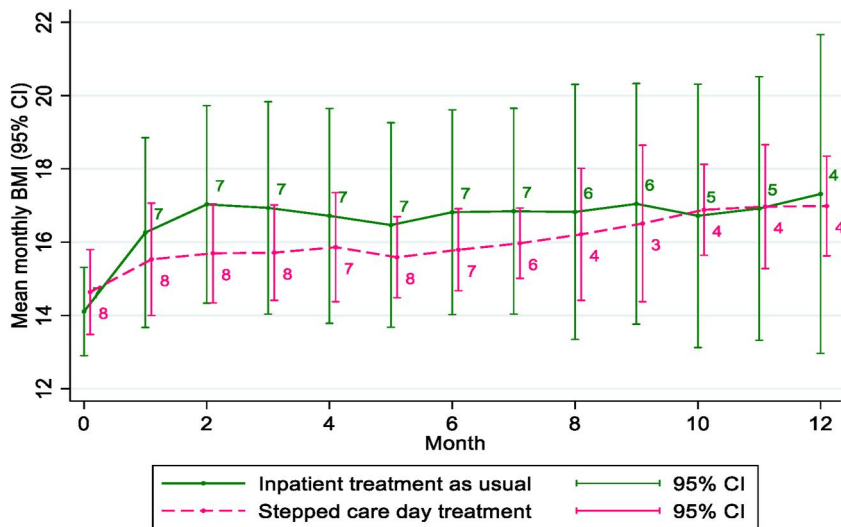


FIGURE 2 Mean monthly BMI and 95% confidence intervals per treatment arm.

The importance of supportive others

The support of staff and patients in both settings was commonly expressed as beneficial for the treatment experience and recovery. The patient peer group was commonly described as *'incredibly supportive and... assets to your stay'* (P5). Generally, the shared experience of treatment was felt to bring closeness, as *'you're all in this together'* (P5), though some expressed that interactions with patients not motivated for recovery *'led to moments that were very difficult'* (P3), such as exposure to triggering behaviours, or a perceived pressure to collude with these patients. Staff support was also highly valued across settings, leading patients to *'feel cared for'* (P2), and certain staff were commonly described as going *'above and beyond their roles'* (P4). However, some staff were described as *'unkind, disrespectful'* (P3) and felt to negatively impact the treatment experience in both settings, with one patient reporting feeling *'patronised and spoken down to'* (P2) and another stating *'they'd ignore people that were clearly in distress'* (P6).

Perceived staff over-focus on eating and weight

Patients and carers commonly mentioned their dislike for a perceived stringent focus on eating and weight gain within intensive treatment settings, feeling that this focus meant that treatment *'didn't take into account... the wider aspects of recovery'* (P2), commonly expressed as the emotional and social aspects where it was felt *'support is most needed'* (P5). IP settings, in particular, were felt to be very *'weight centric'* (P2) and inflexible environments, whereas treatment in DPT settings was generally viewed as more holistic and *'much more flexible'* (P5). Patients also felt that the focus on eating and weight meant they were not being viewed as a complete person, instead through the lens of their AN. Psychotherapy offered within treatment settings was mostly viewed positively,

taking a *'holistic approach'* (P6) to difficulties and helping patients *'cope with emotions and with the eating'* (P1), although some participants were dissatisfied with the level of therapeutic support in both settings, desiring more sessions.

3.3.2 | Theme 2: Challenging experiences across treatment settings

More negative appraisals of the inpatient treatment experience

Many patients and carers expressed an explicit preference for DPT, particularly those who had experienced both settings. The more pronounced presence of the valued aspects of care (as described above) in DPT settings influenced this view. Some still experienced DPT as a *'difficult environment'* (P3) and *'not intensive enough'* (C2), partly due to the increased responsibility over one's own treatment. Carers expressed struggles with the increased *'emphasis on the family unit to support'* (C2) their loved one outside of treatment.

All patients and carers who experienced IP treatment expressed negative views of the environment. Emotive language was typically used, such as *'miserable'* (P5), *'horrific'* (P4), and *'traumatic'* (P6). Reasons for this included the disconnection from the outside world and being in an environment where *'you were constantly surrounded by reminders of the eating disorder'* (C3). Several patients commented on the difficulty of exposure to distressing events such as self-harm and nasogastric feeding under restraint. The benefits of IP treatment were however recognised, including regularising eating and weight gain. Patients commonly commented that their discharge was the *'best bit'* (P4) of their IP experience because they could *'get to go home and be with my family'* (P4).

Negative impact of external factors on treatment

The negative impact of COVID-19 on both treatment settings was commonly mentioned by patients and carers. The impact was felt more acutely for IP treatment, where ward lockdowns and visitation restrictions led to patients feeling 'cut off from everyone' (P5) and carers feeling disconnected from treatment. Staff shortages in both settings were also commonly discussed. Nearly all participants commented on the lack of planning resulting from this, leaving patients with 'a lot of time spent with nothing in particular to do' (P3), both in IP-TAU and DPT, experienced as 'really unhelpful' (P1). Patients also felt that staff shortage led to a decreased standard of care due to a lack of staff time and increased use of bank staff, who were often felt to 'not understand eating disorders' (P5).

3.3.3 | Theme 3: Experiences of transitions between treatment settings

Day patient treatment helping transition after inpatient treatment

Patients and carers commonly expressed that transitioning to DPT after IP assisted in the transition from hospital to home. IP was described as 'cut off from outside life' (P5), which, whilst useful to 'concentrate on me... and recovery' (P4) and to gain weight, contributed to a perceived lack of 'sustained improvement' (P5) if further DPT was not offered post-discharge. DPT was felt to be 'much more transferable and applicable to life outside' (P5), due to the increased 'level of responsibility and ownership' (P6) within treatment, and the ability to go home. One carer described DPT as a 'halfway house' (C1) between intensive treatment and the real world.

Desire for better communication around transition between treatment settings

Several patients and carers commented on the lack of information around transitions, expressing this made them feel 'very scared' (P1), and 'overwhelmed' (P4), especially before admission to IP, as the setting was such a 'drastic change' (C3) from real life. Those who had been admitted to intensive treatment settings several times described the experience as 'demoralising' (C2) and 'demotivating' (P5) due to 'feeling like you're moving backwards' (P5). Where transitions were reported positively, communication was present, with clear goals to denote patient readiness.

3.4 | Implementation challenges

In pre-trial patient and public involvement (PPI) focus groups, patients expressed that they would be open to

both treatment options when they were in their most unwell state. However, in later focus groups conducted towards the end of the study, patients expressed a strong dislike towards the randomisation component and the uncertainty of treatment allocation which then deterred participation. A more detailed narrative summary of PPI focus groups and the key challenges faced in recruiting for the study can be found in Supporting Information S6: Supplement 6.

4 | DISCUSSION

The small sample size in our study made investigating our original research objectives impossible, and interpretation of quantitative data and comparison with previous research became greatly limited. Nevertheless, we have valuable qualitative data and highlight quantitative findings-of-interest here.

Our participants were severely ill (mean BMI at baseline = 14.4 kg/m²) and all of them had had an initial IP stay for medical stabilisation, regardless of their allocated treatment. Furthermore, VAS scores across time-points suggest patients perceived the importance of changing their ED behaviours as higher than their ability to do so. In both groups, patients' BMI increased to a similar level at 12 months, however BMIs in the IP-TAU arm increased at a faster rate than in the stepped-care DPT arm.

IP-TAU and DPT approaches have similar treatment objectives (i.e., normalisation of eating and weight recovery), yet the acceptability of the IP-TAU approach at baseline was considerably lower than it was for the stepped-care DPT approach in our sample. Similar findings were identified in the qualitative analysis. Taken together with the qualitative findings, this may suggest that a strong preference for DPT was present even within the subset of patients who chose to participate, which is also reflected in the views of recruiting clinicians (Phillips et al., 2023).

The themes and subthemes identified in the qualitative analysis convey several perceived beneficial and challenging aspects of intensive ED treatment. Both patients and carers emphasised the importance of intensive treatment incorporating aspects of recovery other than weight and eating, of collaboration around treatment goals and transitions between settings, and of supportive relationships with both staff and patients. The presence of these aspects was perceived to facilitate more positive treatment experiences, more commonly mentioned regarding DPT. Participants commonly reported negative experiences of IP treatment, due to the absence of valued aspects of treatment and the difficult treatment environment. These

findings echo previous qualitative evidence on ED service users' concerns surrounding the perceived over-focus on weight restoration and food intake in intensive treatment, the difficulty of not being seen as a whole person past their ED, the perceived neglect or minimisation of their psychological difficulties by some staff, as well as a desire for enhanced psychotherapeutic and transition/discharge support (Babb et al., 2022; Clark Bryan et al., 2022; Foye et al., 2022; Gustafsson et al., 2021; Ramjan & Gill, 2012; Rance et al., 2017).

Patients' and carers' views mirror findings of our previous qualitative research conducted during the DAISIES trial investigating clinicians' views on intensive treatments before and during the COVID-19 pandemic (Webb et al., 2022a, 2022b) where several advantages (e.g., IP allowing full focus on clinical recovery; DPT allowing greater link to home environment) and challenges (e.g., IP increasing risk of institutionalisation and isolation; DPT placing greater personal responsibility on the recovery) were expressed. Taken together, these qualitative findings suggest that both settings have valued aspects, but both clinicians and patients recognise undesirable aspects which are experienced by patients as particularly difficult (e.g., the stringent focus on eating and weight). Within intensive treatment, patients and carers appear to value a holistic and collaborative approach and transition management, both of which were perceived to be more present within DPT settings. Adapting both IP and DPT settings to better integrate this approach may improve patient experiences and consequently treatment adherence and acceptability.

4.1 | Challenges and lessons learnt

Conducting large RCTs in patients with AN is well-recognised to be challenging due to the nature of the illness (e.g., low motivation to change, high medical risk and low prevalence; Watson & Bulik, 2012; Brockmeyer et al., 2019). Accordingly, the recruitment period may be lengthy or meeting the recruitment target may not be possible even after extending the study period or altering the design (e.g., Lock et al., 2012; Parling et al., 2016). For example, recruiting a target sample ($n = 242$) from 10 sites for the Anorexia Nervosa Treatment of Out-Patients (ANTOP) study took 4 years (Zipfel et al., 2014). Recruitment to studies involving hospital admission might bring additional obstacles, especially in the case of anxious or ambivalent patient attitudes towards recovery (Schreyer et al., 2017). Nonetheless, two previous RCTs targeting in-patients with AN successfully recruited 178 patients and 268 caregivers (Hibbs et al., 2018) and 371 patients plus 371 carers respectively (Cardi, personal communication), albeit prior to the pandemic. Both trials

focused on adjunctive interventions involving families and carers to prevent post-inpatient relapse, and may therefore have been experienced as less demanding by patients.

Although the DAISIES trial is not the first RCT on eating disorders that prematurely terminated due to poor recruitment (e.g., [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02792153) Identifier: NCT02792153; NCT00584688) or due to COVID-19-related reasons (e.g., [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03647943) Identifier: NCT03647943; NCT04028635), the majority of "failed" trials remain unpublished, hindering potential learnings for researchers, clinicians, and funders.

The DAISIES trial was designed by a group of applicants with extensive experience in RCTs. Although effective recruitment strategies were employed (e.g., research champions, PPI involvement; Oduola et al., 2017; Peckham et al., 2018), the DAISIES trial was identified as addressing an important topic by patients and clinicians, and good communication between clinical and research teams was present (Phillips et al., 2023), we failed to recruit adequately.

The challenges that ultimately contributed to the failure of our trial can be grouped into three main categories: patient-related, service-related and wider systemic factors. These seemed to reflect difficulties identified in previous research (King et al., 2005; Phillips et al., 2023; Watson & Bulik, 2012). Patients' dislike of randomisation and treatment preference for DPT were the key challenges for recruitment in our study. COVID-19 caused unprecedented major changes in service provision and structures across the UK. Since the beginning of the pandemic, IP services had dramatically reduced bed capacities. In parallel, increased patient acuity and illness severity required more emergency admissions and longer admissions than pre-pandemic. Furthermore, the imposed strict restrictions on patients leaving wards and accepting visitors may have increased their distress on admission and reduced collaborative after-care planning with informal carers. These curtailments of personal liberties and supports in IP services, together with fears of COVID-19 infection risk in a ward environment, may have increased reservations about taking part in the study. Moreover, many DPT services remained closed, operated online only or at reduced capacity. These factors potentially explain why the number of patients we could approach was limited, recruitment was insufficient and also why participating in the DAISIES trial became less appealing during the pandemic, as indicated by the PPI work. Qualitative research investigating DAISIES trial stakeholders' views and experiences of implementing the trial in intensive services further underlined the pre-existing organisational and systemic barriers to implementation (e.g., low capacity to implement a timely stepped-care pathway in an under-resourced service

structure) and the accentuation of these difficulties during the pandemic (Phillips et al., 2023). These factors jointly hindered patient turnover which in turn dramatically reduced our participant pool and ability to recruit.

Despite the fact that patients and staff thought that a multicentre RCT investigating intensive treatments for severe AN was desirable and important, the numerous challenges encountered during the DAISIES trial, including patient preferences and systemic implementation challenges (Braun & Clarke, 2006), suggest that alternative study designs should be explored (e.g., naturalistic longitudinal studies). Acceptability and feasibility could be improved through offering a partially randomised patient-preference design (Wasmann et al., 2019), allowing patients to participate without randomisation, or through conducting a naturalistic observational study comparing the IP-TAU arm with a broadened stepped-care arm (including DPT or other emerging intensive community treatment approaches) (e.g., Ibrahim et al., 2022; Loeb et al., 2020). We would also recommend that if a future RCT studying intensive treatments were to be undertaken, a feasibility study should be commissioned prior to the full trial.

4.2 | Strengths and limitations

The main strengths of this study are twofold. Firstly, the study provides a comprehensive investigation of factors contributing to the failure of the DAISIES trial and shares recommendations for researchers and funders regarding the design of future studies of intensive services for adults with severe AN. Secondly, our qualitative findings provide valuable insight into treatment acceptability and experiences of patients with severe AN and their carers. However, the sample size was too small to undertake the planned analyses and investigate the original research objectives. Additionally, data could not be collected at 12 months for all participants due to early termination and qualitative data represented only the subgroup of participants who agreed to take part in the interviews, thus the data presented a limited overview of treatment experiences. Finally, the results may be biased towards including people who were more actively involved in the treatment process or those who wanted to share their experiences.

5 | CONCLUSION

Patient- and service-related factors, alongside wider systemic factors, seem to have contributed to the failure of our trial. Although no conclusions can be drawn

concerning the clinical effectiveness and cost-effectiveness of IP-TAU and DPT for adult patients with severe AN, a clear message is that a stepped-care DPT approach is perceived more positively than IP treatment. We believe that the challenges faced in the DAISIES trial provide an opportunity to rethink the treatments we offer to and research we conduct within this population.

AFFILIATIONS

¹Centre for Research in Eating and Weight Disorders (CREW), Department of Psychological Medicine, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK

²Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK

³Department of Health Service & Population Research, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK

⁴The Oxford Institute of Clinical Psychology Training and Research, University of Oxford, Oxford, UK

⁵South London and Maudsley NHS Foundation Trust, London, UK

⁶Gloucestershire Health and Care NHS Foundation Trust, Gloucester, UK

⁷Central and North West London NHS Foundation Trust, London, UK

⁸NHS Grampian, Aberdeen, UK

⁹South West London and St George's Mental Health NHS Trust, London, UK

¹⁰Dorset HealthCare University NHS Foundation Trust, Poole, UK

¹¹Surrey and Borders Partnership NHS Foundation Trust, Leatherhead, UK

¹²Leicestershire Adult Eating Disorders Service, Leicestershire Partnership NHS Trust, Bennion Centre, Glenfield Hospital, Leicester, UK

¹³Institute of Mental Health, University of Nottingham, Nottingham, UK

¹⁴Bellvitge Biomedical Research Institute (IDIBELL), Hospitalet del Llobregat, Barcelona, Spain

¹⁵Division of Medicine, University College London, London, UK

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CLINICAL TRIAL REGISTRATION

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The anonymised data set data can be supplied by the corresponding author upon reasonable request.

ORCID

Başak İnce  <https://orcid.org/0000-0003-1177-3490>

Matthew D. Phillips  <https://orcid.org/0000-0001-8250-5560>

Bethan Dalton  <https://orcid.org/0000-0003-0898-1926>

Catherine McCombie  <https://orcid.org/0000-0002-4456-5121>

Jon Arcelus  <https://orcid.org/0000-0002-3805-0180>

Paul Robinson  <https://orcid.org/0000-0001-8158-4383>

Sarah Byford  <https://orcid.org/0000-0001-7084-1495>

Sabine Landau  <https://orcid.org/0000-0002-3615-8075>

Vanessa Lawrence  <https://orcid.org/0000-0001-7852-2018>

Hubertus Himmerich  <https://orcid.org/0000-0003-1209-6073>

Janet Treasure  <https://orcid.org/0000-0003-0871-4596>

Ulrike Schmidt  <https://orcid.org/0000-0003-1335-1937>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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