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Patient-reported outcomes following accelerated vs. standard TMS with the H1 coil for major depression: A multisite randomized trial

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ABSTRACT

Objective: Clinician-rated measures remain the gold standard in depression trials, but patient-reported outcomes (PROs) provide essential insights into real-world experiences. This study compared PROs in patients with Major Depressive Disorder (MDD) receiving either accelerated H1-coil Transcranial Magnetic Stimulation (ACC-iTBS) or standard once-daily high-frequency H1-coil TMS (SOC-HF).

Methods: In this randomized, multisite trial, 104 adults with moderate-to-severe MDD were assigned to ACC-iTBS (five sessions/day for six days, 50min intersession-interval, 50 Hz triplets, 5 Hz bursts frequency, 2s on, 8s off, 1800 pulses/session) or SOC-HF (daily sessions for four weeks, 18 Hz, 2s on 20s off, 1980 pulses/session), each followed by continuation treatment through week 6. PROs included the daily Clinically Useful Depression Outcome Scale (CUDOS-D), Clinically Useful Anxiety Outcome Scale (CUXOS-D), and the Quality-of-Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Outcomes assessed were response/remission rates, time to perceived improvement, and quality-of-life changes.

Results: Both protocols produced significant and comparable improvements in depressive symptoms, anxiety, and quality-of-life. Week 6 CUDOS response/remission rates were 70.0%/57.5% (ACC-iTBS) and 75.6%/58.5% (SOC-HF); CUXOS rates were 70.0%/67.5% (ACC-iTBS) and 75.6%/69.0% (SOC-HF). Patients in the ACC-iTBS arm reported a shorter median time to CUDOS response (11 vs. 16 days, $p = 0.0377$). Anxiety improvements emerged early and were sustained across both groups. By week 6, severe quality-of-life impairment declined to 15–17%, compared with 85–100% at baseline. No significant between-group differences were observed.

Conclusions: Accelerated TMS with the H1 coil provides patient-perceived benefits comparable to standard treatment while delivering faster relief of depressive symptoms. ACC-iTBS may represent a time-efficient, patient-centered alternative that improves accessibility and satisfaction for individuals with MDD.

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1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive, effective, well-tolerated, and FDA-cleared treatment for major depressive disorder (MDD), supported by broad insurance coverage in the United States and increasing adoption within national health systems globally. Emerging evidence suggests that incorporating TMS into the treatment continuum for MDD may yield superior outcomes compared to pharmacological strategies such as medication switching or augmentation [1]. Despite the strong safety and efficacy profiles established in pivotal trials [2–5], real-world utilization remains limited. A major contributing factor is the logistical burden of the standard TMS protocol, which includes one in-clinic session of TMS per day, each weekday over 4 to 6 weeks. This is not logistically feasible for many patients with demanding work schedules, caregiving responsibilities, or transportation barriers.

In response to the need for more patient-centered-care decisions, the field has increasingly focused on innovative dosing schedules, which involve administering multiple treatment sessions per day over a shorter overall treatment period [6,7]. Several open-label and randomized controlled trials demonstrated that high-density, accelerated stimulation protocols can produce antidepressant effects that are comparable to and/or faster than standard once-daily regimens [8–11]. In some designs, treatments may also be spaced flexibly over non-sequential days, offering additional convenience and alignment with real-world patient needs. These innovations reflect a broader shift toward patient-centered models of neuromodulation care, where reducing logistical barriers is viewed as critical for improving access, adherence, and long-term engagement.

The effect of an accelerated versus standard TMS dosing schedule was evaluated through a **multicenter, randomized, controlled FDA-regulated trial** comparing an accelerated intermittent theta burst protocol (ACC-iTBS; five sessions per day over six treatment days) to a standard of care high-frequency H1-coil Deep TMS protocol (SOC-HF; one session per day over four weeks). The primary outcome of this trial—change in clinician-rated depressive symptoms on the Hamilton Depression Rating Scale (HDRS)—demonstrated that the accelerated protocol was non-inferior to standard treatment and achieved a shorter median time to remission [12]. While these findings support the antidepressant efficacy of this accelerated schedule, they do not fully capture the **patient experience** of treatment burden, perceived benefit, quality of life or functional recovery. Additionally, clinician-rating scales are typically carried out weekly, and may miss the day-to-day changes that can occur during high-dose accelerated protocols.

The goal of the current study was to evaluate the effect of an accelerated versus standard H-coil TMS dosing schedule on patient-rated outcomes (PRO) of depression, anxiety, and quality of life. To achieve this goal, we acquired patient rated outcome scales for depression and anxiety daily during the trial using the **Clinically Useful Depression Outcome Scale-Daily Version (CUDOS-D)** and the **Clinically Useful Anxiety Outcome Scale-Daily Version (CUXOS-D)** [13,14]. Changes in patient rated quality of life were also assessed at the 6-week endpoint via the **Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)** [15]. These measures provide high-resolution insights into how patients perceive symptom changes, functional improvements, and treatment-related burden following the treatment, across accelerated versus standard H-coil TMS dosing schedules. These metrics were secondary outcomes of the parent trial (NCT06357832), which achieved its primary noninferiority outcome (non-inferiority margin of 3 points on the HDRS-21 ($\delta = 3$) between standard of care and accelerated treatment; [12]).

2. Materials and methods

2.1. Study design

This investigation was part of a prospective, randomized, controlled, single-blinded, parallel-group, multisite FDA-regulated trial evaluating two dosing schedules of H1-coil Deep TMS for individuals with major depressive disorder (MDD). The study compared an **accelerated intermittent theta burst stimulation protocol (ACC-iTBS)** with a **standard of care once-daily high-frequency (SOC-HF)** H-coil TMS regimen. The trial was conducted across eight sites—seven in the United States and one in India—between May 2024 and February 2025. Oversight was provided by a central Institutional Review Board (Sterling IRB), and the study was registered on ClinicalTrials.gov (NCT06357832). BrainsWay Ltd. served as the study sponsor, and an external clinical research organization (A. Stein Regulatory Affairs Ltd, Inc.) managed study operations. The Sponsor was responsible for all aspects of the final protocol design. The CRO was then responsible for site initiation, certification of the raters, ongoing day-to-day monitoring and handling operational questions from the sites, all data management, and all statistical analyses.

2.2. Participants

A total of 104 adults aged 22 to 86 years were enrolled following screening and informed consent procedures. All participants met DSM-5-TR criteria for a primary diagnosis of MDD (single or recurrent episode). Inclusion required a history of 1 to 4 failed antidepressant trials during the current episode, and pharmacotherapy had to remain stable for at least two months prior to randomization. Eligibility criteria also included a minimum Hamilton Depression of 20 at screening and baseline 7 days apart, with less than a 30% fluctuation between assessments. Exclusion criteria included significant neurological or psychiatric comorbidities, including psychosis, primary anxiety disorders, active substance use disorders within the past three months, high-risk suicidality, and seizure history. The complete set of inclusion and exclusion criteria is available on ClinicalTrials.gov (NCT06357832) and in the initial publication [12]. A detailed description of the demographics, a CONSORT diagram, and study flow chart are in the Supplementary Material.

2.3. Power analysis and sample size calculation

An apriori power calculation was used to determine the required sample size for this non-inferiority study based on the primary outcome of the trial (see [12] for more details). Briefly, a non-inferiority margin of 3 points on the HDRS-21 ($\delta = 3$), as was used as a minimally important difference assuming a standard deviation of 6.6 in both groups, and an actual difference between the mean changes from baseline of the groups of −1 (treatment – control). This led to a sample size of 44 subjects per group (total 88) which would be required to provide 80% power to detect non-inferiority at significance level of 2.5%. Assuming a drop-out rate of 15%, 104 individuals were enrolled in the ITT set for this study.

2.4. Randomization and masking

Patients were randomized into the study with stratification by clinical center and disease severity, as determined by ATHF level. Once a subject met eligibility criteria, they were randomized in a 1:1 ratio to either the iTBS stimulation protocol or the HF stimulation protocol. Allocation was stratified by ATHF group (Group 1: $\geq$2 medications at an inadequate level or 1 medication at an adequate level; Group 2: 2–4 medications at an adequate level) and by clinical center. Randomization followed a stratified, permuted block design using the SAS (version 9.4) random number generator.

2.5. The randomization plan was prepared by an independent statistician

While treatment operators and participants were aware of their group assignment following randomization, the evaluators (certified

raters) were blinded throughout the study (as were the site principal investigators and the sponsor). The integrity of the blind for the certified raters was assessed using a five-choice forced question at the final post-randomization assessment. A logistic model was used to assess if the response to the treatment question is predictive to the treatment received, which was nonsignificant ($p = 0.8215$).

2.6. Intervention protocols

Both treatment arms utilized the H1 TMS Coil (BrainsWay Ltd., Israel), which stimulates the left and right dorsolateral prefrontal cortex bilaterally with a stronger field on the left (Supplementary Fig. S1). The treatment administrator (operator) determined the subjects' motor threshold (MT) and administered the treatments. Before each treatment, subjects were instructed to insert earplugs to minimize any potential adverse effects on hearing. At the start of the trial, individual MTs were determined by positioning the coil over the hand area of the motor cortex per the official FDA instructions for use (IFU) document. At specified time points - prior to the first treatment, once weekly, or as otherwise deemed necessary - the MT was reassessed by delivering single pulses to the motor cortex (one pulse administered every 5 s (0.2 Hz)), until the threshold was identified via visual observation. The initial MT determination and coil positioning prior to the first treatment session required approximately 5-10 min.

For treatment, the coil was positioned 6 cm anterior to the identified "hot spot" per the official FDA IFU. A TMS session was then conducted according to the subject's assigned randomization group. For the first session, TMS operators were encouraged to titrate the intensity of stimulation in alignment with participant feedback regarding tolerability– starting the first train at approximately 80% motor threshold, and increasing in increments of 5-10% with each subsequent train. A summary of the dosing protocols for both arms can be seen in Fig. 1.

ACC-iTBS Protocol: Administered at 110% of the resting motor threshold (rMT), the protocol consisted of triplet bursts at 50 Hz, delivered at a burst frequency of 5 Hz, using a 2-s stimulation/8-s rest cycle (1800 pulses per session; 9 min, 42 s total). Participants received five sessions per day across six treatment days (within a two-week window), with a minimum intersession interval of 50 min. A four-week continuation phase followed, consisting of twice-daily sessions administered one day per week. Overall, patients received 38 sessions and 68,400 pulses across 10 visit days. For patients that were unable to tolerate 110%, a minimum dosing of 90% MT was required in order to remain in the study.

SOC-HF Protocol: Delivered at 120% rMT using 18 Hz stimulation, with 2-s trains and 20-s inter-train intervals. Each session included 55 trains (1980 pulses total) over approximately 20 min. Treatment was delivered once daily, five days per week for four weeks, followed by a two-week continuation phase (two sessions per week). Overall, patients received 24 sessions and 47,520 pulses across 24 visit days.

2.7. Outcome measures

In the parent trial, the primary outcomes were physician- or provider-rated assessments (HDRS, MADRS) [12]. The primary efficacy timepoint was the change from baseline to the week 6 visit. The efficacy was compared between the treatment groups using a repeated measures analysis of covariance (ANCOVA, SAS® Proc MIXED procedure). Baseline HDRS-21, center and visit were used as covariates. The analysis of non-inferiority was assessed by comparison of the one-sided 97.5% upper confidence limit of the adjusted mean to the pre-selected non--inferiority margin (inferiority margin delta = 3.0). Covariates in the model included sex (M,F), age (<55 years, >55 years), ethnicity (Hispanic-Latino/not Hispanic-Latino) and the number of AD medications at baseline (1-2 medications, >3 medications) together with treatment group, baseline and available weekly HDRS-21 data.

The present manuscript focuses on the secondary outcomes of the FDA-pivotal trial - patient-reported outcomes (PRO) - offering an important perspective on treatment effects that complements clinician ratings and captures the patient's direct experience. Depression severity was assessed using the Clinically Useful Depression Outcome Scale-Daily Version (CUDOS-D) [13], anxiety symptoms via the Clinically Useful Anxiety Outcome Scale-Daily Version (CUXOS-D) [14], and quality of life through the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) [15]. The CUDOS-D and CUXOS-D were administered daily in the clinic. The Q-LES-Q was administered at baseline and at the 6-week endpoint. A detailed description of the assessments is in the Supplementary Material.

Raters. To be eligible to be a rater for the trial, all clinicians had to undergo a three phase Rater Certification Process which was executed by the CRO. This certification process is described in detail elsewhere (Supplementary Material [12]). Briefly, this involved three phases - didactic training between the certified trainer and the clinician, standardized patient video interactions (Phase 1), and a self-recorded demonstration of delivery and scoring for the primary outcome

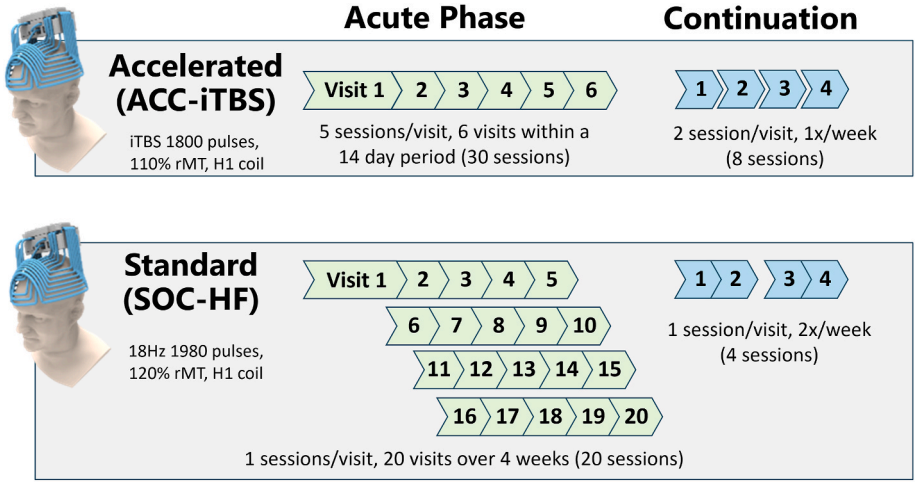


Fig. 1. Study treatment protocol and visit schedule. Participants are assigned to either an accelerated intermittent theta burst stimulation (ACC-iTBS) protocol or a standard high-frequency stimulation (SOC-HF) protocol using the H1 coil. In the ACC-iTBS arm, patients receive 1800 pulses per session at 110% resting motor threshold (rMT), delivered as 5 sessions per visit across 6 visits within a 14-day acute phase (30 total sessions), followed by a continuation phase of 2 sessions per weekly visit over 4 weeks (8 sessions). In the SOC-HF arm, patients receive 18-Hz stimulation totaling 1980 pulses per session at 120% rMT, administered as 1 session per visit across 20 visits over 4 weeks (20 total sessions), followed by continuation treatment consisting of 1 session per visit twice weekly for 4 visits (4 sessions).

measures between the clinician and a mock patient. There was one primary rater associated with each site. This individual was not engaged in psychiatric care for the patient during the trial. Site-specific procedures were put in place at each site to ensure that the rater was not exposed to the patient nay more than necessary during the trial (e.g. entering the clinic through a door not used by patients, avoiding the patient waiting room).

Covariates in the MI model included sex (M,F), age (<50 years, >50 years), race (white, black, other), ethnicity (Hispanic-Latino/not Hispanic-Latino) and the number of AD medications at baseline (1-2 medications, >3 medications) together with treatment group, baseline and available weekly HDRS-21 data.

Analyses for the CUDOS-D and CUXOS-D included remission and response rates, continuous change, and the median and interquartile intervals of number of days required to reach response/remission following ACC-iTBS or SOC-HF (Table 1). Patients who were at remission at baseline by any of the scales were excluded from the analyses of time to response/remission by this scale.

Analyses of Q-LES-Q included rates of patients with severe impairment, defined as two standard deviations below 83% of the maximal score [16], and rates of patients in the normal range of 70-100% of the maximal score [15,17,18]. Q-LES-Q data is typically reported as "percentage maximum possible" score. For the Q-LES-Q-SF the total of the first 14 questions is used. % Max possible = ((sum of questions 1-14)-minimum score (14))/(maximum score (70)-minimum score (14)). % Max possible = (Sum-14)/56). Rapaport et al. [16] describe the community norm of Q-LES-Q-SF as 83% of the max possible score. They define the normal range as 10% of that mean, and severe impairment as 2 standard deviations (2SD: 22.8%), wherein 60.2% is the cutoff for severe.

For comparison of means (continuous variables), the two-sample *t*-test or the Wilcoxon rank sum test or the Mann Whitney test were used, as appropriate. For comparison of proportions (categorical variables) such as response, the Chi-square test or Fisher's exact test were used, as appropriate.

3. Results

3.1. Participant flow and baseline characteristics

Of the 150 individuals screened, 104 met eligibility criteria and were randomized to either the accelerated H1-coil TMS protocol (ACC-iTBS; $n = 51$) or the standard high-frequency protocol (SOC-HF; $n = 53$). The **intent-to-treat (ITT)** population included all 104 randomized participants. See Supplementary Material for CONSORT diagram. The **per-protocol (PP)** population, used for efficacy analyses, included 89 participants who received at least one treatment and had no major protocol deviations (ACC-iTBS: $n = 41$; SOC-HF: $n = 48$). Secondary analysis of the efficacy outcomes in the ITT group is in the Supplementary material.

Demographic and baseline clinical characteristics for the ITT cohort are presented in Table 2. Enrollment was distributed across eight study sites (seven in the U.S. and one in India), with site-level enrollment ranging from 1 to 20 participants. Outcomes from the India site were comparable to those observed across U.S. centers. Demographic and baseline characteristics, CONSORT diagram, and reasons for dropout, are provided in the Supplementary Materials, along with site level enrollment. Fifteen participants did not complete the full six-week protocol (ACC-iTBS: $n = 10$; SOC-HF: $n = 5$).

Antidepressant treatment exposure was well balanced between groups. The majority in both groups had failed one prior medication (ACC-iTBS: 29/51, 56.9%; SOC-HF: 31/53, 58.5%). Failure of two medications was observed in 13 ACC-iTBS participants (25.5%) and 12 SOC-HF participants (22.6%), while three prior failures were reported in 8 (15.7%) and 6 (11.3%) participants, respectively. Only two participants overall (1.9%) had failed four adequate antidepressant trials, both in the SOC-HF group. Sensitivity analysis revealed no significant effect of number of failed medications on the primary efficacy measure ($F = 1.14$, $p = 0.288$).

Efficacy at 6 weeks: Depression symptoms (CUDOS). A significant continuous improvement in symptoms over time was seen on the CUDOS in both groups (Fig. 2, top left). The mean percentage improvement from baseline to 6 weeks was 64% (ACC-iTBS: Mixed-effects Model: $F = 56.57$, $df = 147.9$, $p < 0.0001$) and 66% (SOC-HF: $F = 54.85$, $df = 207.2$, $p < 0.0001$). High remission and response rates were found in both groups after 6 weeks (Fig. 2, top right), with no significant differences between the groups.

For the ACC-iTBS group the median onset of patient-reported response was 11 days [6,18] and patient-reported remission was 23 days (median, [interquartile interval]. For the SOC-HF group the median onset of patient-reported response was 16 days [12,19] and patient-reported remission at 28 days [16,32]. Comparison between the groups demonstrated a significantly shorter time to response in the ACC-iTBS group compared to the SOC-HF group ($p = 0.0377$; Mann Whitney test), with no significant difference in time to remission ($p = 0.99$).

Efficacy at 6 weeks: Anxiety symptoms (CUXOS). A significant continuous improvement in symptoms over time was seen on the CUXOS on both groups (Fig. 2, bottom left). The mean percentage improvement from baseline to 6 weeks was 62% (ACC-iTBS: $F = 33.15$, $df = 134.4$, $p < 0.0001$) and 66% (SOC-HF: $F = 38.92$, $df = 179.3$, $p < 0.0001$). High remission and response rates were found in both groups after 6 weeks (Fig. 2, bottom right), with no significant differences between the groups.

For the ACC-ITBS group the median onset of patient-reported response of their anxiety symptoms 12.5 days [6,18] and patient-reported remission of those symptoms at 23 days [9,29] (median, [interquartile interval]. For the SOC-HF group the median onset of patient-reported response of their anxiety symptoms was 10.5 days [6, 20] and patient-reported remission of those symptoms at 15.5 days [8, 28]. Comparison between the groups demonstrated no difference in the time to response ($p = 0.9975$) or remission ($p = 0.8676$) of anxiety symptoms between the groups.

Relative Onset of Change – CUDOS/CUXOS. The changes in anxiety preceded changes in depression. To evaluate this further we performed a post-hoc analysis. When pooling together the whole sample, CUXOS significantly preceded CUDOS on both time to response ($p = 0.0061$; Wilcoxon test) and to remission ($p < 0.0001$). The difference

Table 1
Criteria for response and remission.

Scale	Definition of Response	Definition of Remission
CUDOS (Patient-rated depression symptoms)	≥50% improvement	CUDOS Total Score <11
CUXOS (patient -rated anxiety symptoms)	≥50% improvement	CUXOS Total Score <11

Table 2
Demographics and baseline characteristics of Intent To Treat analysis set.

Characteristic	ACC-iTBS	SOC-HF
Age [years], Mean (SD)	48.9 (14.2)	48.3 (15.0)
Women, No. (%)	29 (56.9%)	30 (56.6%)
Caucasian, No. (%)	37 (68.5%)	39 (73.6%)
Baseline HDRS, Mean (SD)	25.1 (4.2)	25.3 (4.8)
Baseline MADRS, Mean (SD)	32.7 (4.2)	33.3 (4.7)
Baseline CGI-S, Mean (SD)	5.0 (0.9)	4.9 (0.9)
Baseline CGI-I, Mean (SD)	5.2 (0.6)	5.1 (0.5)
Baseline HARS, Mean (SD)	19.5 (6.8)	19.7 (6.8)
Baseline CUDOS, Mean (SD)	34.6 (11.0)	37.4 (11.2)
Baseline CUXOS, Mean (SD)	28.1 (15.0)	29.2 (14.6)
Baseline Q-LES-Q, Mean (SD)	37.8% (13.7%)	38.7% (9.6%)

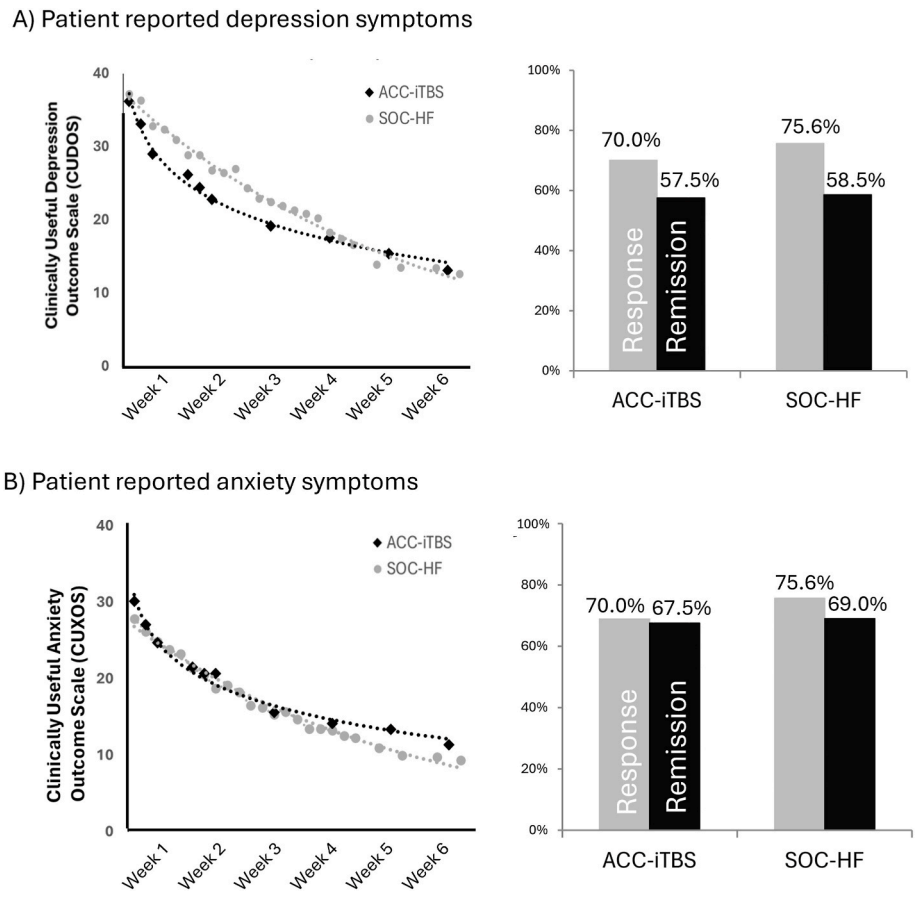
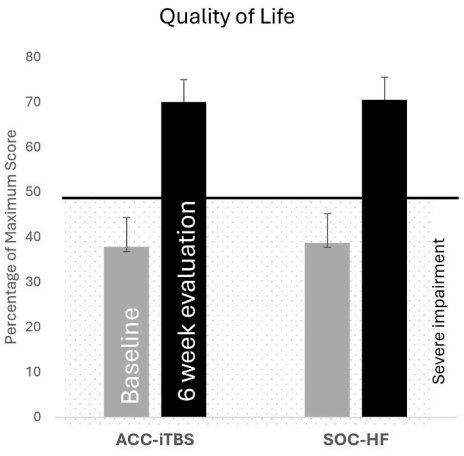


Fig. 2. Patient-reported change in depression and anxiety symptoms. The continuous change in depression (CUDOS, A) and anxiety (CUXOS, B) symptom severity as well as the response/remission rates for both assessments (CUDOS, C; CUXOS D). Continuous change is displayed as a function of days enrolled in the study (Monday-Friday; 6 weeks) for the ACC-iTBS group (blue) and the SOC-HF group (orange). CUDOS & CUXOS measurements were taken at each in-person TMS visit. The line of best fit was approximated for each group wherein the ACC-iTBS group had an exponential decay for both assessments (CUDOS: $y = -6.90\ \ln(x) + 37.30$, $R^2 = 0.99$; CUXOS: $y = -5.66\ \ln(x) + 31.03$) and the SOC-HF group has a logarithmic decay for both assessments (CUDOS: $y = 38.10e^{-0.04x}$, $R^2 = 0.99$; CUXOS: $y = 28e^{-0.042x}$, $R^2 = 0.99$). Remission and response rates are shown for the 6 week endpoint in both groups in the per protocol analysis set.



Percent increase Q-LES-Q scores from baseline to 6 weeks

	ACC-iTBS	SOC-HF
Physical (Health)	44%	41%
Mood (Emotions)	99%	97%
Work (Employment)	65%	66%
Household (Chores)	65%	75%
School (Education)	68%	68%
Leisure (Activities)	55%	47%
Social (Relationships)	54%	75%
Family (Connections)	69%	62%
Romance (Intimacy)	78%	75%
Sexual (Functioning)	19%	19%
Economic (Finances)	15%	20%
Living (Housing)	22%	20%
Neighborhood (Safety)	39%	31%
Overall (Satisfaction)	78%	65%
TOTAL	51%	50%

Fig. 3. Patient reported change in quality of life. Quality of Life ratings at baseline relative to 6 weeks after the ACC-iTBS protocol and the SOC-HF protocol. A graph of the percentage of maximum score (left) demonstrates that the majority of patients had severe quality of life impairment (dotted line) at baseline and that this improved substantially at the 6 week timepoint for both groups. The percentage change in each of the 14 questions on the Q-LES-Q score are shown on the right, demonstrating that the quality of life improvement was consistent across all domains. The data here are from the per protocol analysis set such that every individual has a baseline and a 6 week score.

was most prominent in the SOC-HF group wherein response and remission on the CUXOS were significantly shorter than response and remission on the CUDOS (response: $p = 0.003$, remission: $p = 0.0001$)).

Quality of life. The quality of life as reflected in the Q-LES-Q questionnaire significantly improved after 6 weeks of treatment on both groups from 37.8% ± 13.7% (mean ± SD) at baseline to 70.0% ± 11.7% after 6 weeks in the ACC-iTBS group, and from 38.7% ± 9.6% at baseline to 70.5% ± 12.4% after 6 weeks in the SOC-HF group (Fig. 3). At baseline 85.3% of the patients in the ACC-iTBS group and 100% of the patients in the SOC-HF group had severe impairment. After 6 weeks only 15.0% (ACC-iTBS group) and 16.7% (SOC-HF group) were classified as having severe impairment. Moreover, at baseline none of the patients were in the normal range of quality of life, while after 6 weeks 60.0% of the patients in the ACC-iTBS group and 60.4% of the patients in the SOC-HF group attained the normal range (Table 3).

A significant improvement was seen on all Q-LES-Q domains in both groups (Fig. 3), where in all items the final scores are around 4 (indicating "Good").

Dosing variables: Scheduling treatment. In the ACC-iTBS group the majority of patients chose to have 3 visit days per week on both weeks (83% (34/41)). Six patients had 2 visits on week 1 and 4 visits on week 2 (14.6%, 6/41), and only 1 patient had 5 visit days on week 1 and one on week 2 (2.4%, 1/41)). Regarding the "pacing" of the treatment days, approximately half of the patients (48.8%, 20/41) had a mixture of consecutive days and non-consecutive days (e.g. "Monday, Tuesday, Thursday") rather than 3 consecutive days or "Monday, Wednesday, Friday" each week, while quarter of the patients (24.4%, 10/41) had treatments on consecutive days on both weeks. In the SOC-HF the treatment scheduling was, as expected, highly uniform, with 5 daily sessions/week for 4 weeks and 2 sessions/week on weeks 5 and 6.

Titrating treatment intensity. As described above, per common practice in clinical care, TMS operators were encouraged to slowly ramp the intensity of stimulation for the first few trains – starting the first train at approximately 80% motor threshold and increasing in increments of 5-10% with each subsequent train. Using this method, all participants in the SOC group reached full intensity. Five participants in the ACC-iTBS group (10%) did not reach the full intensity of 110% MT by the end of the first treatment day. Four of these ultimately reached the full intensity, and all four achieved response and remission. The individual that did not ever reach 110% MT, remained at 90% MT by the final visit. This individual did not have a response or remission.

3.2. Adverse events

As described previously [12], there were no serious adverse events reported. A headache was the most common adverse event reported in both groups. A headache occurred at some point during the 6 week study in 21 (41.18%) subjects in the Acc-iTBS group and 8 (15.09%) subjects in the SOC-HF group. There was no relationship between the length of time it took for a patient to reach the full treatment dose and the rate of headaches. There was only one participant in this study that did not reach 110% RMT. Application site discomfort occurred in 1 (1.96%) subject in the Acc-iTBS group and in 1 (1.89%) subject in the SOC-HF group. Application site pain occurred in 4 (7.84%) subjects in the ACC-iTBS group and in no subjects in the SOC-HF group. Anxiety was reported in 3 (5.88%) subjects in the ACC-iTBS and insomnia was reported in 2 (3.92%) of the subjects in the ACC-iTBS group. None of the adverse events were classified as severe. Hypomania was reported in 1 subject in the ACC-iTBS group, who was subsequently withdrawn from the study based on physician judgment. There was no change in the pulse rate, systolic or diastolic blood pressure in either group at the three time-points measures (screening, baseline, 6 weeks).

While the majority of patients reached the full 110%There were 5 patients in the ACC-iTBS group that did not reach the full dose by the end of the first treatment visit. Four of these patients reached the full dose of 110% at sessions 10, 12, 15, & 25. They all achieved remission. The remaining patient had reached 90% by session 38. This individual reported headaches and did not reach response or remission criteria.

Table 3
Percentage of patients with severe quality of life impairment before versus 6 weeks after initiating dTMS. *Defined as ≥60.2% Max (2 st.dev of community mean (Rapaport et al., 2005)).

Patients with Severe Impairment in QOL*	Acc-iTBS	SOC-HF
Baseline	85.3%	100%
6 weeks after dTMS	15.0%	16.7%

4. Discussion

Transcranial magnetic stimulation (TMS) is an established, effective, and well-tolerated treatment for major depressive disorder. However, the conventional treatment schedule - one session per day, five days per week, over 30–36 sessions - can be burdensome for many patients, often requiring six to nine weeks of frequent in-clinic visits. This practical barrier limits access, adherence, and real-world utilization, despite strong evidence for efficacy. The purpose of this multisite, randomized, single-blind controlled clinical trial was to evaluate an alternative accelerated protocol in which patients receive five sessions per day across six treatment days, substantially reducing the total number of in-person visits required. This manuscript evaluates the patient-reported outcomes (PROs) from this trial. These results demonstrate that accelerated TMS (5x/day) with the H1 coil yields patient-reported improvements in depression, anxiety, and quality of life that are comparable to the standard once-daily high-frequency protocol, with the advantage of a shorter time to perceived antidepressant response.

The primary novelty of this analysis lies in its exclusive focus on patient-reported outcomes (PROs) collected in real time - a perspective that complements and extends the clinician-rated results from the parent trial [12]. While clinician-rated scales such as the HDRS and MADRS remain the regulatory gold standard for MDD trials, they are typically administered weekly, may not capture day-to-day changes, and can overestimate improvement compared to self-reports [21,22]. Daily CUDOS-D and CUXOS-D assessments allowed a high-resolution view of symptom dynamics that is rarely reported in TMS studies [20], allowing us to quantify not just the magnitude and the timing, of patient-perceived improvement.

Our results demonstrate that accelerated Deep TMS (ACC-iTBS) with the H1 coil produces comparable patient-reported benefits in depression, anxiety, and quality of life to the standard of care once-daily high-frequency protocol (SOC-HF), with median five days earlier depressive symptom response on the CUDOS. This earlier onset may be clinically meaningful for patients seeking rapid relief, and aligns with emerging evidence that high-density neuromodulation protocols can accelerate therapeutic effects [6–10].

An additional insight from this dataset is the differential temporal trajectory of anxiety and depression symptoms. Across both protocols, patient-reported anxiety (CUXOS) improved earlier than depression, particularly in the SOC-HF group—a pattern consistent with prior findings in comorbid MDD [19]. This reinforces the value of assessing anxiety independently in TMS trials, as its improvement may follow a distinct neural and temporal course from depressive symptom change.

Quality of life, as measured by the Q-LES-Q- SF, improved significantly in both groups, with 60% of patients attaining normal range, while 0% were in the normal range at baseline. In this context, "normal range" reflects a return to normative community functioning - commonly defined as achieving ≥70% of the maximum possible score [15,17,18] - and represents a broader, patient-centered treatment goal beyond symptom reduction. Moreover, while 85-100% of patients were classified with severe impairment at baseline, only 15-17% were classified as severe after 6 weeks. The consistent gains across all Q-LES-Q domains suggest that both protocols not only alleviate core symptoms

but also restore social, occupational, and functional well-being.

From an implementation standpoint, accelerated protocols address one of the most cited barriers to TMS uptake: treatment burden. The accelerated protocol was designed to incorporate flexibility in scheduling. Specifically, the six treatment days comprising the Acute Phase (five sessions per day) could be administered within a 14-day window, allowing sites and patients to tailor the schedule as needed. Standard protocols require 30–40 clinic visits over six to nine weeks, which can be prohibitive for patients with work, caregiving, or transportation constraints. The ACC-iTBS schedule in this study condensed the acute phase into six treatment days - flexibly delivered over two weeks - followed by weekly maintenance, reducing total travel time while preserving efficacy and patient satisfaction. Such logistical advantages may expand access to TMS, particularly for underserved or geographically distant populations.

Regarding adverse event reports, there were more reported headaches in the group that received ACC-iTBS. This could be due to either the cumulative number of pulses given per day (which was much higher in the accelerated group) or it could be due to the iTBS pulse protocol itself. Given that the intensity of TMS delivered in the ACC-iTBS group was lower than the SOC-HF group (90-110% MT versus 120%MT) it is unlikely that it is the iTBS protocol inherently. Instead, it seems more likely that the rate of headaches or other adverse events is related to the cumulative number of pulses (or perhaps the cumulative amount of time) that the participants are receiving TMS each day. Although there were more headaches in the accelerated group than the standard of care group, the completion rate was similar between the groups – suggesting this is not a noteworthy barrier to treatment. However, it is worth keeping in mind that a propensity for headaches may warrant recommending less sessions per day for vulnerable patients. Additionally, it is certainly possible that lower intensity doses of iTBS may be sufficient given prior studies that have observed positive outcomes of accelerated TMS at 80% MT for 1800 pulses per session [8,9].

Several limitations warrant consideration. Although clinician raters were blinded, the patients were not blinded due to the nature of treatment scheduling and acoustic artefact differences between the ACC-iTBS and the SOC-HF arms. Consequently, patient-reported outcomes may therefore be susceptible to expectancy effects. Treatment credibility or expectancy was not formally measured, and differences in treatment schedule intensity (accelerated versus once-daily sessions) could have differentially influenced patients' expectations and self-reported outcomes, including time to perceived improvement. However, the consistency of PRO improvements across depressive, anxiety, and quality-of-life measures, along with comparable response and remission rates between groups, suggests that expectancy alone is unlikely to fully account for the observed effects. PROs were collected more frequently than clinician ratings, precluding direct timepoint-by-timepoint comparison. Our sample size, while adequate for primary endpoints, was not powered for subgroup analyses that could explore moderators such as anxious depression, chronicity, or baseline functional impairment. Future work evaluating the durability of patient-perceived improvements, especially in the context of maintenance TMS, would be a valuable further direction. There were also differences in the number of in-person visits, which may carry some inherent therapeutic value independent of the direct device-specific effects of TMS. The ACC-iTBS group achieved non-inferiority despite the handicap of a shorter period of non-specific therapeutic contact (e.g. less in-person visits overall). Finally, as mentioned above, it is certainly possible that intensities lower than 110% MT for iTBS (1800 pulses) may be sufficient for clinical use. The target dose in this study was 110% MT for the ACC-iTBS group with a minimum of 90% MT (if the patient could not tolerate the full dose). This notion also applies for parameters such as the optimal number of pulses per session given that there are compelling results with 600 and 800 pulses per session, as well as the minimum time between sessions. Further work is needed in order to determine optimal dosing from the perspective of intensity, number of pulses per session, and minimum intersession interval.

In summary, this analysis demonstrates that accelerated TMS with the H1 coil offers equivalent - and in some cases faster - patient-perceived benefits compared to standard treatment, with substantial improvements in both symptom burden and quality of life. By integrating high-frequency daily PROs and focusing on functional recovery, this study provides a uniquely patient-centered perspective on TMS dosing strategies. Given its potential to improve access, reduce treatment burden, and deliver rapid relief, ACC-iTBS represents a compelling option for modern, patient-focused depression care.

CRediT authorship contribution statement

Aron Tendler: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Yiftach Roth:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Mallory Bates:** Writing – review & editing, Project administration, Data curation. **Eliza Brink:** Writing – review & editing, Investigation, Data curation. **Molly Davis:** Writing – review & editing, Investigation, Data curation. **Dawn DeBrocco:** Writing – review & editing, Investigation, Data curation. **Shelli Ellis:** Writing – review & editing, Investigation, Data curation. **Lindsey Jones:** Writing – review & editing, Project administration, Methodology. **Aftab Khan:** Writing – review & editing, Investigation, Data curation. **Spencer Luce:** Writing – review & editing, Investigation, Data curation. **Carlene McMillan:** Writing – review & editing, Investigation, Data curation. **Aswin Kumar Mudunuru:** Writing – review & editing, Investigation, Data curation. **Owen Muir:** Writing – review & editing, Investigation, Data curation. **Gabriel S. Pell:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Conceptualization. **Timothy Prestley:** Writing – review & editing, Investigation, Data curation. **M.S. Reddy:** Writing – review & editing, Investigation, Data curation. **Noelia Rodriguez:** Writing – review & editing, Investigation, Data curation. **Samson Seplow:** Writing – review & editing, Investigation, Data curation. **Natanya Slomowitz:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Ahava Stein:** Writing – review & editing, Project administration, Methodology, Formal analysis, Conceptualization. **Daniel M. Thistlethwaite:** Writing – review & editing, Investigation, Data curation. **Russ Voltin:** Writing – review & editing, Investigation, Data curation. **Nancy Williams:** Writing – review & editing, Investigation, Data curation. **Colleen A. Hanlon:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that they have no competing financial interests or personal relationships that could be perceived to have influenced the work reported in this paper.

Appendix A. Supplementary data

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