Intensive speech and language therapy in patients with chronic aphasia after stroke: a randomised, open-label, blinded-endpoint, controlled trial in a health-care setting

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Summary

Background Treatment guidelines for aphasia recommend intensive speech and language therapy for chronic (≥6 months) aphasia after stroke, but large-scale, class 1 randomised controlled trials on treatment effectiveness are scarce. We aimed to examine whether 3 weeks of intensive speech and language therapy under routine clinical conditions improved verbal communication in daily-life situations in people with chronic aphasia after stroke.

Methods In this multicentre, parallel group, superiority, open-label, blinded-endpoint, randomised controlled trial, patients aged 70 years or younger with aphasia after stroke lasting for 6 months or more were recruited from 19 inpatient or outpatient rehabilitation centres in Germany. An external biostatistician used a computer-generated permuted block randomisation method, stratified by treatment centre, to randomly assign participants to either 3 weeks or more of intensive speech and language therapy (≥10 h per week) or 3 weeks deferral of intensive speech and language therapy. The primary endpoint was between-group difference in the change in verbal communication effectiveness in everyday life scenarios (Amsterdam–Nijmegen Everyday Language Test A-scale) from baseline to immediately after 3 weeks of treatment or treatment deferral. All analyses were done using the modified intention-to-treat population (those who received 1 day or more of intensive treatment or treatment deferral). This study is registered with ClinicalTrials.gov, number NCT01540383.

Findings We randomly assigned 158 patients between April 1, 2012, and May 31, 2014. The modified intention-to-treat population comprised 156 patients (78 per group). Verbal communication was significantly improved from baseline to after intensive speech and language treatment (mean difference 2·61 points [SD 4·94]; 95% CI 1·49 to 3·72), but not from baseline to after treatment deferral (–0·03 points [4·04]; –0·94 to 0·88; between-group difference Cohen's *d* 0·58; p=0·0004). Eight patients had adverse events during therapy or treatment deferral (one car accident [in the control group], two common cold [one patient per group], three gastrointestinal or cardiac symptoms [all intervention group], two recurrent stroke [one in intervention group before initiation of treatment, and one before group assignment had occurred]); all were unrelated to study participation.

Interpretation 3 weeks of intensive speech and language therapy significantly enhanced verbal communication in people aged 70 years or younger with chronic aphasia after stroke, providing an effective evidence-based treatment approach in this population. Future studies should examine the minimum treatment intensity required for meaningful treatment effects, and determine whether treatment effects cumulate over repeated intervention periods.

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Introduction

Chronic aphasia (ie, persisting for ≥6 months after stroke) affects about 20% of all patients who have had a stroke.[1] Aphasia is one of the most devastating symptoms in stroke survivors,[2,3] and the presence of aphasia after stroke predicts the extent of rehabilitation services required[4] and likelihood of failure to return to work.[5] Survival rates after initial stroke are increasing,[6] contributing additional financial costs to health-care providers. Aphasia is responsible for roughly 8·5% of stroke-related health-care costs during the first year after stroke.[7]

Such dramatic consequences of aphasia after stroke call for evidence-based effective interventions.[8] Results of meta-analyses[9–12] have concluded that speech and language therapy after stroke is effective even in the chronic stage, if administered with sufficient intensity (5–10 h per week). However, most of these studies rank below level 2 according to the classification scheme of the Centre for Evidence-Based Medicine. The few high-quality studies had either small sample sizes, no untreated or low-intensity therapy control group,[13–16] or low treatment intensity (<5 h per week).[17–20] Large, multicentre, randomised controlled clinical trials to

Research in context

Evidence before this study

We searched PubMed and PsychInfo on June 28, 2016, for manuscripts published in English from inception until June 28, 2016, with the term "stroke rehabilitation" in combination with "aphasia", "outcome", "evidence-based practice", or "activities of daily living". We also searched with the term "stroke" in combination with "incidence rates" or "health care costs". We had no additional inclusion or exclusion criteria for the studies searched.

For decades, it had been postulated that improved verbal communication could not be achieved in patients with chronic (≥6 months duration) aphasia after stroke. Several randomised controlled trials have been done to assess the effectiveness of speech and language therapy in this population, but the reported results were inconclusive because of the low methodological quality of the studies. Previously published randomised controlled trials on treatment effectiveness in chronic post-stroke aphasia had small sample sizes (fewer than 20 patients per group), non-intensive administration of therapy (ie, <5 h per week), and often failed to report long-term outcomes of therapy. Meta-analyses and systematic reviews published in the past 15 years have provided strong evidence that speech and language therapy, if administered with sufficient intensity (≥5 h per week), is effective even in patients with chronic aphasia after stroke. Despite this evidence derived from systematic reviews, patients with chronic aphasia after stroke are frequently denied access to speech and language therapy. The main reason for this failure is the lack of any large-scale multicentre randomised controlled trial with sound statistics that demonstrates lasting improvement in everyday language function after intensive speech and language therapy.

Added value of this study

Our multicentre FCET2EC (From Controlled Experimental Trial 2 Everyday Communication) trial is the largest appropriately controlled randomised trial to date in patients with chronic aphasia after stroke to evaluate the effectiveness of intensive speech and language therapy compared with a control group who received no or only low-intensity treatment during treatment deferral. The findings provide robust evidence for the superiority of 3 weeks of intensive (≥10 h per week) individualised speech and language therapy over 3 weeks of treatment deferral in this patient group. Treatment effects remained stable after the follow-up period of 6 months. The study confirms the results of previous underpowered studies that also suggested a positive and lasting effect of intensive speech and language therapy in patients with chronic aphasia after stroke. By contrast with previous studies, in which performance was usually assessed for isolated linguistic functions with low ecological validity (ie, low relevance for patients' communicative participation in daily life), the primary outcome of the FCET2EC trial was verbal communication in everyday life scenarios.

Implications of all the available evidence

In combination with the evidence derived from systematic reviews, results of the FCET2EC trial show that intensive speech and language therapy is an evidence-based intervention for patients with chronic aphasia after stroke. In comparison with previous studies, inclusion criteria were liberal with respect to stroke cause (ischaemic, haemorrhagic, and subarachnoid haemorrhage), aphasia type, and aphasia severity, allowing generalisation of the trial results to the population of patients aged 70 years or younger with chronic aphasia after stroke. Furthermore, as no participant dropped out during the 3 weeks of intensive speech and language therapy, which was provided under routine clinical conditions, demonstration of the intervention's feasibility for routine health-care settings is not necessary. Results of the FCET2EC trial could fundamentally change the allocation of rehabilitation resources for patients with chronic aphasia after stroke.

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assess the effectiveness of intensive therapy for aphasia with reliable and valid outcomes are urgently required.

The aims of our multicentre randomised controlled trial, From Controlled Experimental Trial 2 Everyday Communication (FCET2EC), were to assess the effectiveness of 3 weeks or more of intensive (≥10 h per week) speech and language therapy in chronic aphasia after stroke compared with 3 weeks of treatment deferral in terms of improved everyday verbal communication.

Methods

Study design

We did a randomised, open-label, blinded-endpoint, multicentre, stratified-by-centre, waiting-list-controlled, parallel-group, superiority trial to evaluate the effectiveness of 3 weeks of intensive speech and language therapy versus 3 weeks of treatment deferral (figure 1). The trial protocol was published previously.[21] Speech and language therapy was given in 19 German inpatient or outpatient rehabilitation centres that specialised in stroke rehabilitation; each centre treated a median of 688 patients (IQR 97–1040) who had a stroke per year (reference year, 2013). We used deferral of intensive speech and language therapy as a control because any active control condition has the risk of providing language stimulation.[17] No major changes in methodology were required after the trial had started.

The study coordination centre was based at the General Neurology Department at the University Hospital Münster, Germany. The trial steering committee—comprising two neurologists, one neurolinguist, one neuropsychologist, one biostatistician, and one patient delegate (appendix p 4)—monitored study progress during patient recruitment. Except for the patient delegate, the committee

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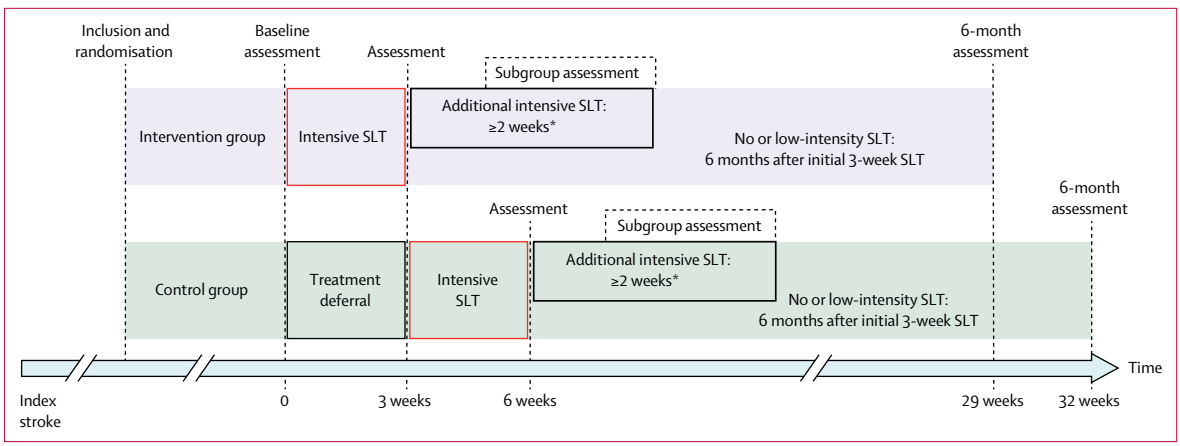

Figure 1: **Study design**
SLT=speech and language therapy. *Actual length of additional intensive SLT was not pre-planned; individual decisions to extend treatment were made by the respective health-care provider.

members were experts on stroke and aphasia treatment. All members of the committee were independent of the principal investigators, their employing organisations, funders, and sponsors. No interim analyses were planned and the steering committee had no access to the data before final analyses were completed. The study was approved by the institutional review board of the lead trial physician (AF) at the Charité-Universitätsmedizin Berlin, Berlin, Germany, as well as by the ten review boards of the participating centres.

Participants

Inclusion criteria, which aimed to replicate realistic routine health-care conditions, were chronic aphasia (confirmed using the Aachen Aphasia Test [AAT])[22] lasting 6 months or more after an ischaemic or haemorrhagic stroke, age 18–70 years, German as first language, basic comprehension abilities and at least rudimentary attempts to verbally communicate (communication score >0 on the AAT spontaneous speech scale), and the ability to follow simple instructions (at least one correct response on the first ten items of the AAT Token Test). Exclusion criteria were severe untreated medical conditions, severe uncorrected vision or hearing impairments, aphasia owing to traumatic brain injury or neurodegenerative disease, or participation in an alternative intensive intervention to relieve stroke symptoms during the 4 weeks before enrolment in this trial.

Speech and language therapy was provided as part of routine clinical care, funded by the patients' health-care provider or retirement fund. All sites applied a uniform recruitment strategy. After routine referral to a given centre, potential study participants were contacted by phone by a centre representative. Sites carried log files documenting each eligible patient referred to the centre and, if applicable, reasons for not including the patient. After study completion, all log files were made available to the study coordination centre. Every patient, and his or her legal representative if required, gave written informed consent before trial participation.

Randomisation and masking

Participants were randomly assigned, by computer-generated, blockwise random sequence, to either the intervention group (immediate speech and language therapy) or the control group (deferred speech and language therapy), in a 1:1 ratio. Randomisation was stratified by centre, and consecutive inclusion codes for each centre were kept in sealed opaque envelopes. The biometrician allocated participants to groups. Group allocation was faxed to the study coordination centre for implementation. The personnel in the study coordination centre were aware of group allocations to schedule assessments, but were not involved in the assessments or the intervention.

Assessments at baseline and follow-up were done by 40 study assessors (all professional speech and language therapists) who were not otherwise involved in the study. All assessors were trained in administration and scoring of the outcome measures and closely supervised by the trial coordinator and the personnel of the study coordination centre during data acquisition. Patients and study assessors were not masked with respect to group allocation because patients in the treatment deferral group had two baseline assessments (ie, before and after their 3-week waiting period) compared with only one in the intervention group. However, offline assessment of the primary outcome was done by an independent endpoint committee of eight raters, trained for this purpose, who were masked to group assignment and assessment by random labelling of the respective audio files using the names of the planets in our galaxy. Masking of data was done in the study coordination centre by a study assistant who was not involved in patient assessment or treatment. For quality assurance, each dataset was independently monitored in the study coordination centre by two research assistants

who were not otherwise involved in the trial and were masked to group allocation. All data for the primary outcome and 30% of secondary outcome data were checked by an external monitor; the value of 30% was decided by the monitor and the trial steering committee given the very low error rates in the databank.

Procedures

Participating therapists were trained to use the study speech and language therapy manual (appendix pp 3–4) and the monitoring and documentation forms before participants were enrolled. Therapists were closely supervised by the authors of the manual (a subgroup of the study authors [TG, AB, SA, RG, FD, FR, K-JS, and MT]). The intervention was based on best-practice guidelines (appendix p 3), combining linguistic and communicative-pragmatic approaches individualised to the baseline profile of each patient. Speech and language therapy was provided for 3 weeks or more, with 10 h or more per week offered by professional therapists in one-to-one and group therapy sessions and 5 h or more per week self-managed (mostly computer-based) training targeting individual linguistic deficits. Initial individual therapy targets were based on the patients' baseline linguistic and communicative-pragmatic performance (appendix p 2). Daily therapy duration and content were recorded by the centres.

The control group received an identical intensive speech and language therapy starting immediately after the 3-week waiting period. Because this trial was done within the health-care system, patients in the control group could continue to receive conventional low-intensity speech and language therapy in private practice during the 3-week waiting period. Total rehabilitation duration depended on a patient's individual health-care plan, but lasted at least 3 weeks for all patients. We chose a treatment period of 3 weeks because, based on our clinical experience, most German health-care insurance companies limit aphasia rehabilitation to a period of 3 weeks. The decision about whether or not to extend the rehabilitation period beyond 3 weeks was made by the health-care funder, not by the therapist. Patients could continue speech and language therapy (of any intensity) during the follow-up period of 6 months.

We collected demographic, cognitive, speech, language, and clinical characteristics at baseline from medical records and in an initial screening session before study inclusion (appendix pp 1–2). Primary and secondary outcome assessments were done within 3 working days before and 3 working days after the 3-week intensive speech and language therapy for the intervention group and within 3 working days of the beginning and end of the 3-week treatment deferral period for the control group. Additionally, the control group was assessed after the 3-week speech and language therapy. Both groups were reassessed within 10 working days of 6 months after completion of the 3-week intensive speech and language therapy (29 weeks from baseline for the intervention group and 32 weeks from the first baseline for the control group).

A subgroup of patients from both groups had 5 weeks or more of intensive speech and language therapy. We also did additional outcome assessments in the subgroup of patients from both groups who had 5 weeks or more of intensive speech and language therapy; assessments were done within 3 working days of completion of the intensive treatment period.

Data were collected at baseline and follow-up at treatment sites or patients' homes, whichever was more convenient for the patient.

Outcomes

The centrally assessed primary outcome measure was effectiveness of verbal communication in ten everyday life situations, assessed using the two parallel versions of the Amsterdam-Nijmegen Everyday Language Test (ANELT) A-scale.[23] We randomly selected which of the two ANELT versions was to be given to a patient at their first assessment; versions were then alternated across subsequent assessments in an individual patient (eg, if a patient had four assessments and started with version I, the sequence would have been: I, II, I, II). Audio recordings of assessments using ANELT were made for masked offline evaluation. All ANELT sessions for an individual patient were rated by two of the eight raters (rater pairs were assigned to individual patients using a computer-generated random algorithm with the constraint that the eight raters evaluated similar numbers of datasets). The ANELT included ten scenarios in each version. Patients received a score for each scenario on the basis of degree of verbal effectiveness (A-scale), ranging from 1 (no relation to communicative scenario at all) to 5 (all information required for successful communication has been provided). For each patient, the mean score of the two raters for each of the ANELT scenarios was calculated, then the overall score was calculated as the sum of the mean individual scores (minimum, 10; maximum, 50). The primary endpoint was change from baseline in ANELT A-scale score immediately after the 3-week intervention in the intervention group or after the 3-week treatment deferral in the control group.

Change in ANELT A-scale score 6 months after the 3-week intervention was a secondary endpoint. As part of the secondary analyses, ANELT A-scale score was also analysed immediately after 3 weeks of speech and language therapy in the control group. The other secondary outcomes were stroke severity (modified Rankin Scale [mRS]);[24] auditory intelligibility in everyday communication (ANELT B-scale);[23] impairment specific language measures (Sprachsystematisches APhasieScreening [SAPS]; assessing comprehension and production abilities in the core language domains of phonology, lexicon, and syntax;

appendix p 2); patient's perceived quality of life (Stroke and Aphasia Quality of Life Scale-39 [SAQOL-39]);[25] communication rated by the patient's partner or (in absence of a partner) a close friend (Communicative Effectiveness Index [CETI];[26] assessed at baseline and at the 6-month follow-up); non-verbal learning (Nonverbal Learning Test [NVLT]);[27] and visual attention and executive functioning (Trail Making Test [TMT], versions A and B).[28] All secondary outcome measures except for CETI were assessed at baseline (two baselines in the control group), after 3 weeks of intensive speech and language therapy, after the extension of therapy to 5 weeks or longer (subgroup only), and at the 6-month follow-up.

The study coordination centre was informed of adverse events by the centres within 24 h of first occurrence. Unexpected or serious adverse events were reported to the trial steering committee, who had the authority to halt recruitment or to stop the trial.

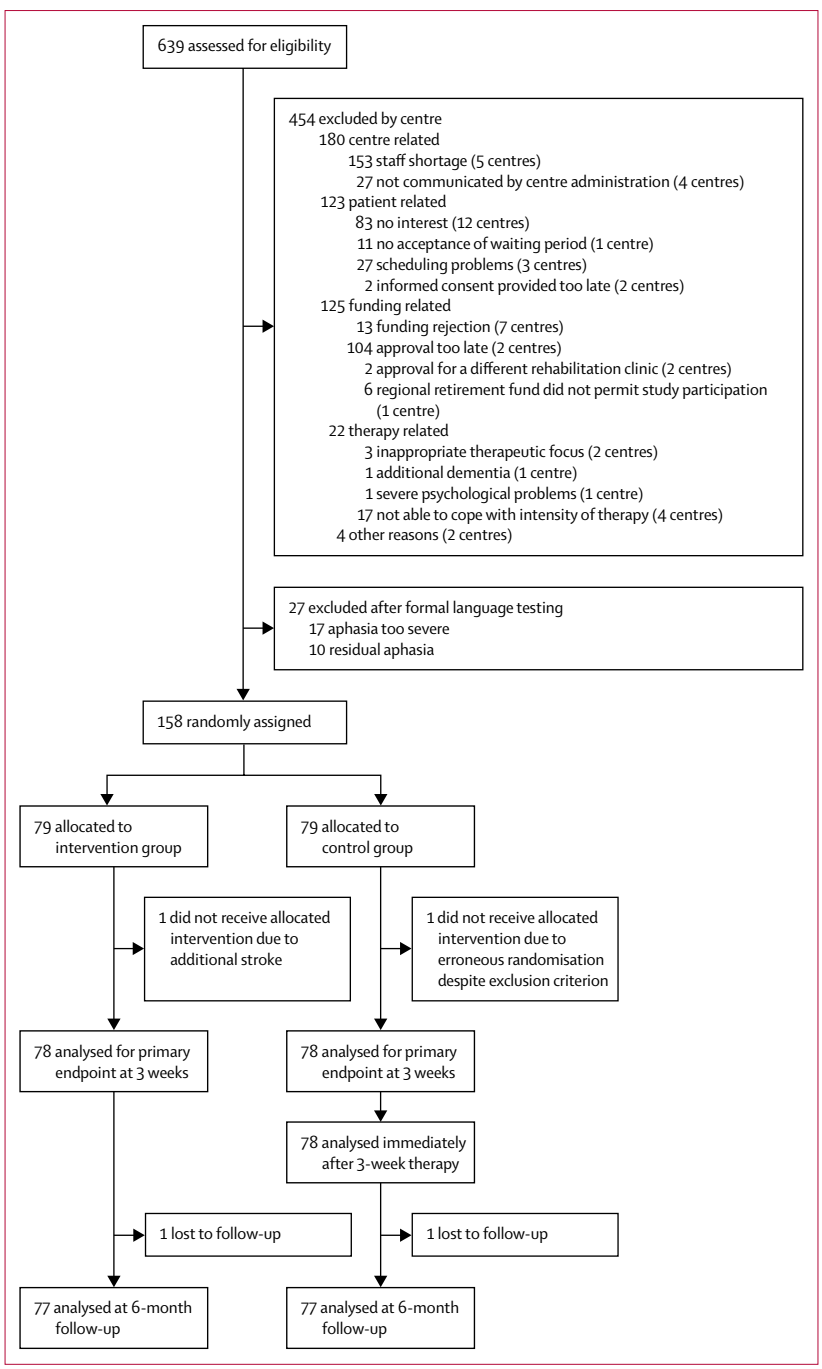

Figure 2: **Trial profile**

Statistical analysis

We did an a-priori sample size calculation to detect a significant increase in the primary outcome measure (based on data from Jong-Hagelstein and colleagues[19]) from baseline to after the 3-week intensive speech and language therapy with a statistical power of 0·90, an estimated effect size of 0·71, and a two-sided α significance level of 0·05, which yielded a required sample size of 63 patients per group. We anticipated a dropout rate of 25%, on the basis of clinical experience of our centre representatives during the study design period, so planned to enrol 84 patients per group during a 26-month recruitment phase.

Statistical analyses were done by a biometrician (PM) who was not employed at the coordination centre. The analyses of primary and secondary endpoints were done in the modified intention-to-treat population, which included all randomised patients who received at least 1 day of therapy or treatment deferral. Additional prespecified analyses were done in the per-protocol population, which excluded patients with minor or major deviations from the treatment protocol. Data were complete for all patients in the primary analysis, so imputation for missing data was not done. For normally distributed data, parametrical methods were used. For non-normally distributed data, the Mann-Whitney *U*-test was used for between-group comparisons and the Wilcoxon signed-rank test was used for pairwise intra-subject comparisons. We used an ANCOVA model to assess the primary outcome with the ANELT A-scale score after 3 weeks of speech and language therapy or treatment deferral as a dependent variable, treatment group as an independent variable, and baseline ANELT A-scale score as a covariate. To assess possible moderator effects on the primary endpoint, interactions of treatment group with demographic, clinical, cognitive, and linguistic variables (appendix pp 1–2) were also analysed within additional ANCOVA model calculations. To assess demographic, cognitive, stroke-related, or aphasia-related predictors of immediate and long-term treatment success with regard to the primary outcome (appendix p 1), the results of therapy in both groups were pooled. The secondary outcomes were also evaluated with both the ANCOVA model (immediate and long-term treatment effects) and the pooling method (long-term treatment effects). No adjustment for multiple testing was applied to secondary analyses.

Thus, analyses were not strictly confirmatory with the exception of the analysis for the primary endpoint. All statistical analyses were done using SPSS (version 22.0).

This study is registered at ClinicalTrials.gov, number NCT01540383.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

158 patients were recruited between April 1, 2012, and May 31, 2014 (figure 2). Patients were randomly assigned to one of two groups (79 per group). One patient in each group dropped out before beginning therapy or treatment deferral, and was excluded from further analyses. All patients were assessed at baseline and after 3 weeks of therapy or treatment deferral, but one patient in each group did not complete the 6-month follow-up assessment. Ten patients in the intervention group and five in the control group presented with minor deviations, and four in the intervention group and one in the control group had major deviations.

Patients received 3–10 weeks of speech and language therapy (median 4·8 weeks [IQR 3·0–5·6] in the intervention group *vs* 4·0 weeks [3·0–5·0] in the control group), including 22·5–49·0 h of intensive therapy within the first 3 weeks of intensive therapy (median 31·0 h [30·0–34·5] *vs* 32·0 h [30·0–34·6]). In the 3-week waiting period in the control group, patients received 0–22·5 h of speech and language therapy (median 4·5 h [IQR 3·0–6·8 h] over 3 weeks, or 1·5 h [1·0–2·3] per week; appendix p 12). 71 (92%) patients in the intervention group and 72 (94%) patients in the control group continued speech and language therapy during the follow-up period of 6 months, at a median intensity of 1·0 h (IQR 0·6–1·7) per week (appendix p 12). Baseline demographic and clinical characteristics are reported in table 1 and the appendix (pp 10–11). No between-group differences were noted in stroke-related or aphasia-related variables (table 1; appendix p 1), except for a higher frequency of initial thrombolysis in the control group (28 [36%] *vs* 15 [19%]). A longer median duration of time from stroke to baseline was noted in the intervention group (43 months [IQR 16–68]) than in the control group (27 months [13–49]).

The interrater agreement between the eight ANELT raters was highly satisfactory (Krippendorff's α=0·81). 42 (54%) of 78 patients in the intervention group were first assessed with version I of ANELT and 36 (46%) were first assessed with version II. In the control group, 41 (53%) of 78 patients started with version I and 37 (47%) with version II.

Mean difference since baseline in ANELT A-scale score (ie, effectiveness of verbal communication) was significantly larger after 3 weeks of intensive therapy (2·61 points [SD 4·94], 95% CI 1·49 to 3·72) than after 3 weeks of treatment deferral (–0·03 points [4·04], –0·94 to 0·88; group difference p=0·0004; Cohen's *d* 0·58; figure 3; table 2). The group difference was independent of potential

	Intervention group (n=78)	Control group (n=78)
Demographic characteristics		
Age (years)	53·5 (9·0)	52·9 (10·2)
Sex		
Men	32 (41%)	24 (31%)
Women	46 (59%)	54 (69%)
Education (years)	10 (10–19)	10 (10–16·5)
Stroke characteristics		
Stroke severity (mRS score)	2 (2–3)	2 (2–3)
Months since stroke	43·0 (16·0–68·3)	27·0 (13·0–48·8)
Stroke subtype		
Ischaemic	45 (58%)	56 (72%)
Ischaemic with haemorrhagic transformation	19 (24%)	11 (14%)
Haemorrhagic	9 (12%)	8 (10%)
Subarachnoid haemorrhage	5 (6%)	3 (4%)
Stroke risk factors		
Previous stroke or transient ischaemic attack		
With aphasia	2 (3%)	7 (9%)
Without aphasia	7 (9%)	3 (4%)
Hypertension	50 (64%)	57 (73%)
Hyperlipidaemia	37 (47%)	25 (32%)
Heart disease		
Atrial fibrillation	8 (10%)	7 (9%)
Congestive heart failure	6 (8%)	4 (5%)
Previous myocardial infarction	11 (14%)	9 (12%)
Coronary heart disease	12 (15%)	9 (12%)
Type 2 diabetes	6 (8%)	7 (9%)
Peripheral artery occlusive disease	3 (4%)	0
No medical risk factors	17 (22%)	15 (19%)
Epilepsy and depression		
Antiepileptic medication	38 (49%)	34 (44%)
Antidepressant medication	24 (31%)	23 (29%)
Depression score (VAMS sadness score)	2·2 (2·8)	2·6 (2·9)
Aphasia characteristics		
Aphasia subtype		
Global	20 (26%)	13 (17%)
Wernicke	11 (14%)	14 (18%)
Broca	22 (28%)	25 (31%)
Anomic	18 (23%)	20 (26%)
Not classifiable	7 (9%)	6 (8%)
Aphasia severity (AAT profile height*; T-score)	50·9 (6·6)	52·3 (5·4)
Aphasia severity classification†		
Minimal	3 (4%)	3 (4%)
Mild	30 (38%)	34 (44%)
Medium severe	38 (49%)	41 (53%)
Severe	7 (9%)	0

(Table 1 continues on next page)

	Intervention group (n=78)	Control group (n=78)
(Continued from previous page)		
Basic therapy data		
Duration of rehabilitation (weeks)	4·8 (3·0–5·6)	4·0 (3·0–5·0)
Intensity of SLT during 3-week intensive treatment (h)		
With speech and language therapist	31·0 (30·0–34·5)	32·0 (30·0–34·6)
One-to-one sessions	22·0 (21·0–24·2)	22·3 (21·0–24·0)
Group sessions	9·0 (8·0–10·5)	9·0 (8·0–10·5)
Intensity of self-managed language exercises during 3-week intensive treatment (h)	15·0 (15·0–15·0)	15·0 (15·0–15·3)
Intensity of non-SLT treatment during 3-week intensive treatment (h)		
Physiotherapy	8·8 (3·0–12·5)	8·5 (3·8–11·6)
Occupational therapy	4·0 (0·0–8·0)	6·0 (2·0–9·8)
Cognitive therapy	0·0 (0·0–0·5)	0·0 (0·0–0·0)

Data are mean (SD), n (%), and median (IQR). mRS=modified Rankin Scale. VAMS=visual analogue mood scales. AAT=Aachen Aphasia Test. SLT=speech and language therapy. *AAT profile height is the average of the weighted T-scores of the AAT subtests. †Patients with global aphasia (and to a lesser degree with Wernicke's aphasia) were not necessarily always categorised as "severe" using the AAT because they were in the chronic stage after stroke and because our inclusion criteria specified basic comprehension abilities, rudimentary attempts to verbally communicate, and the ability to follow simple instructions; therefore, some discrepancies between aphasia syndrome categorisation and aphasia severity categorisation are to be expected.

***Table 1*: Baseline and therapy characteristics**

moderator variables—eg, age or time since latest stroke (appendix pp 1–2). The control group had similar improvements to the intervention group in verbal communication after 3 weeks of intensive speech and language therapy (figure 3; appendix pp 15–16). 69 (44%) of 156 patients had improved verbal communication by at least 3 points on the ANELT A-scale from baseline to 3 weeks after intensive therapy and only 16 (10%) patients had a decline of at least 3 points over the same timeframe. Treatment effects remained stable in both study groups after 6 months (figure 3; table 2).

Subgroup analysis of 34 patients (19 in the intervention group and 15 in the control group) who received 5 weeks or more of intensive speech and language therapy showed that the mean change in ANELT A-scale score from baseline was roughly 1 point larger (4·23 points [SD 4·28], 95% CI 2·74–5·73) after a median of 6 weeks (IQR 5–7) of intensive therapy than after the initial 3 weeks of intensive therapy (3·32 points [5·64], 1·35–5·29; appendix p 12). Patients who had intensive speech and language therapy limited to 3 weeks versus those who had at least 5 weeks of therapy did not differ with respect to age, sex, years of education, initial stroke severity, aphasia severity, or aphasia syndrome distribution (data not shown; all p>0·13).

Scores on the linguistic screening measure (SAPS; total score, and lexicon, syntax, language comprehension, and language production subtotals) and patients' perceived health-related quality-of-life ratings (SAQOL-39; total score) were significantly improved from baseline to after the 3-week intensive therapy compared with from baseline to after the 3-week treatment deferral (all p<0·05; table 2; figure 4). Between-group differences in linguistic gains (SAPS scores) were not correlated with the analysed moderator variables (appendix pp 1–2). No significant between-group differences were noted from baseline to after the 3-week intensive speech and language therapy versus treatment deferral for the ANELT B-scale (acoustic intelligibility), the SAPS phonology score, non-verbal cognitive functions (NVLT, TMTs), or stroke-related physical dependency (mRS). Treatment-related gains in secondary outcomes, including partners' assessment of the patients' communicative effectiveness (CETI), remained stable over the 6-month follow-up period in both groups (appendix pp 13–14).

Of all patient-related, stroke-related, aphasia-related, and therapy-related variables (appendix p 1), only baseline stroke severity was a significant predictor of immediate treatment success in verbal communication (data not shown); patients with less severe stroke at enrolment had greater improvement after treatment than those with more severe stroke (p<0·0001). No significant predictors of long-term treatment stability over 6 months were noted (data not shown).

Additional analyses done in the per-protocol population (n=64 in the intervention group; n=72 in the control group) yielded the same pattern of results and are not reported.

Five (6%) of 78 patients in the intervention group had adverse events during therapy (one common cold, three gastrointestinal or cardiac symptoms, and one recurrent stroke before initiation of therapy) compared with two (3%) of 78 patients in the control group (one car accident and one common cold) during therapy or treatment deferral. A further patient had a recurrent stroke after screening but before randomisation. All adverse events were deemed unrelated to study participation by the local principal investigator in conjunction with the trial steering committee.

Discussion

The results of the randomised, multicentre FCET2EC trial show that 3 weeks of intensive speech and language therapy administered under routine clinical conditions significantly improved verbal communication in patients with chronic aphasia after stroke, compared with 3 weeks deferral of intensive speech and language therapy. Additionally, specific linguistic measures and communication-related quality-of-life item ratings by patients, and patients' communication effectiveness ratings by a partner or friend, increased in response to intensive speech and language therapy. No significant moderators of the treatment effect were noted, indicating that no particular feature of patient subgroups was driving the effect, and that therapy setting (inpatient or outpatient) did not influence the outcome. Cognitive functions that were not predominantly targeted by the therapy—such as non-verbal learning or executive functioning—did not change from baseline to after therapy, confirming the specificity of treatment effects.

	Intervention group					Control group					Between-group difference		
	Baseline		After 3-week SLT		p value	Baseline		After 3-week deferral		p value	ANCOVA *F* (df1, df2)	p value	Effect size (Cohen's *d*)*
	n	Mean (SD)	n	Mean (SD)		n	Mean (SD)	n	Mean (SD)				
Primary outcome													
ANELT A-score	78	28·79 (10·90)	78	31·39 (11·27)	<0·0001	78	29·63 (10·94)	78	29·60 (11·11)	0·95	12·97 (1, 153)	0·0004	0·58
Secondary outcomes													
Acoustic intelligibility (ANELT B-score)	77	37·46 (8·25)	77	38·16 (7·58)	0·13	78	37·61 (6·85)	78	37·67 (7·35)	0·87	1·12 (1, 152)	0·29	0·17
Linguistic performance (SAPS)													
Total	69	456·76 (159·74)	69	523·89 (164·29)	<0·0001	72	469·32 (144·33)	72	494·86 (142·15)	<0·0001	18·73 (1, 138)	<0·0001	0·73
Phonology	75	164·97 (62·13)	75	182·68 (64·22)	<0·0001	76	167·84 (60·97)	76	179·73 (58·87)	<0·0001	1·89 (1, 148)	0·17	0·23
Lexicon	77	186·38 (68·83)	78	202·68 (61·56)	<0·0001	78	193·06 (53·63)	78	199·53 (54·52)	0·0174	5·30 (1, 152)	0·0227	0·38
Syntax	73	104·33 (55·74)	74	133·20 (58·97)	<0·0001	77	106·40 (59·00)	75	112·60 (59·55)	0·22	17·24 (1, 141)	0·0001	0·68
Language comprehension	71	182·04 (61·42)	71	213·66 (53·81)	<0·0001	75	189·61 (53·53)	75	199·47 (51·89)	0·0002	18·67 (1, 143)	<0·0001	0·71
Language production	76	280·33 (130·14)	75	317·71 (143·11)	<0·0001	76	287·76 (117·61)	75	302·91 (117·91)	0·0010	8·49 (1, 148)	0·0041	0·48
QoL (patient's view; SAQOL-39)													
Total	78	3·67 (0·52)	78	3·90 (0·54)	<0·0001	78	3·58 (0·61)	78	3·69 (0·61)	0·0216	4·45 (1, 153)	0·0365	0·27
Physical	78	4·05 (0·65)	78	4·18 (0·64)	0·0120	78	3·88 (0·79)	78	3·97 (0·75)	0·06	1·24 (1, 153)	0·27	0·08
Communication	78	2·78 (0·74)	78	3·15 (0·73)	<0·0001	78	2·66 (0·76)	78	2·90 (0·78)	0·0011	3·41 (1, 153)	0·07	0·21
Psychosocial	78	3·64 (0·79)	78	3·90 (0·78)	0·0003	78	3·63 (0·88)	78	3·71 (0·79)	0·37	3·86 (1, 153)	0·0513	0·27
Energy	78	3·72 (0·83)	78	4·01 (0·85)	0·0012	78	3·77 (0·94)	78	3·87 (0·90)	0·23	2·27 (1, 153)	0·13	0·24
QoL (partner's view; CETI)†	76	83·61 (28·15)	..	..	..	74	83·64 (25·56)	74	83·05 (28·84)	0·76	..		..
Non-verbal cognitive function													
NVLT hits (minus false alarms)	72	17·17 (8·60)	72	19·89 (8·84)	0·0019	76	13·53 (9·26)	76	16·43 (11·29)	0·0002	0·84 (1, 145)	0·77	–0·03
TMT (time to completion [s])													
Version A	65	73·34 (39·53)	65	61·45 (29·61)	0·0001	70	76·54 (35·20)	70	63·77 (25·58)	0·0001	0·03 (1, 132)	0·86	0·04
Version B	34	176·03 (56·63)	34	162·74 (56·33)	0·14	30	175·43 (54·00)	30	153·03 (55·16)	0·0006	0·84 (1, 61)	0·36	0·21
Stroke severity (mRS)	78	2·21 (0·80)	78	2·21 (0·83)	0·99	78	2·41 (0·96)	78	2·33 (0·85)	0·21	0·19 (1, 153)	0·66	0·15

SLT=speech and language therapy. df=degrees of freedom. ANELT=Amsterdam–Nijmegen Everyday Language Test. SAPS=Sprachsystematisches Aphasiescreening (language-systematic aphasia screening). QoL=quality of life. SAQOL-39=Stroke and Aphasia Quality of Life Scale-39. CETI=Communicative Effectiveness Index. NVLT=Nonverbal Learning Test. TMT=Trail Making Test. mRS=modified Rankin Scale. *Cohen's *d* refers to the average group difference (and SD) of the differences from baseline to after assessments. †CETI was not administered at the assessment after 3-week SLT.

***Table 2*: Treatment effects from baseline to after 3 weeks of speech and language therapy or treatment deferral**

Once the control group had received intensive speech and language therapy, these patients showed similar improvements in primary and secondary language outcomes to the intervention group, thus replicating the primary treatment effect. That 44% of patients had improved verbal communication by at least 3 points on the ANELT A-scale from baseline to 3 weeks after intensive therapy and only 10% patients had a decline of at least 3 points over the same timeframe indicates that the observed treatment effect is not based on a small group of outliers. Of note, although the control group received a median of 1·5 h of outpatient speech and language therapy per week during the treatment deferral period, verbal communication did not improve during this time. Additionally, the whole study group also received a median of 1·0 h of outpatient speech and language therapy per week during the 6-month follow-up period (figure 3; appendix p 12), but even this extended period of low-intensity therapy did not result in a significant treatment effect.

No study participants dropped out of the study during intensive speech and language therapy. Clearly, this mitigates the concern expressed in the most recent Cochrane review[9] on rehabilitation for aphasia, that superior outcomes of studies with intensive versus non-intensive speech and language therapy could be biased by a higher dropout rate in studies of intensive therapy, resulting in selection of particularly motivated patients. The absence of patient dropouts during the intervention period also demonstrates the general feasibility of intensive speech and language therapy for routine clinical care. However, health-care cost seems to be a barrier to implementing intensive speech and language therapy in routine clinical practice; during our study, 153 screened patients could not participate in the intensive

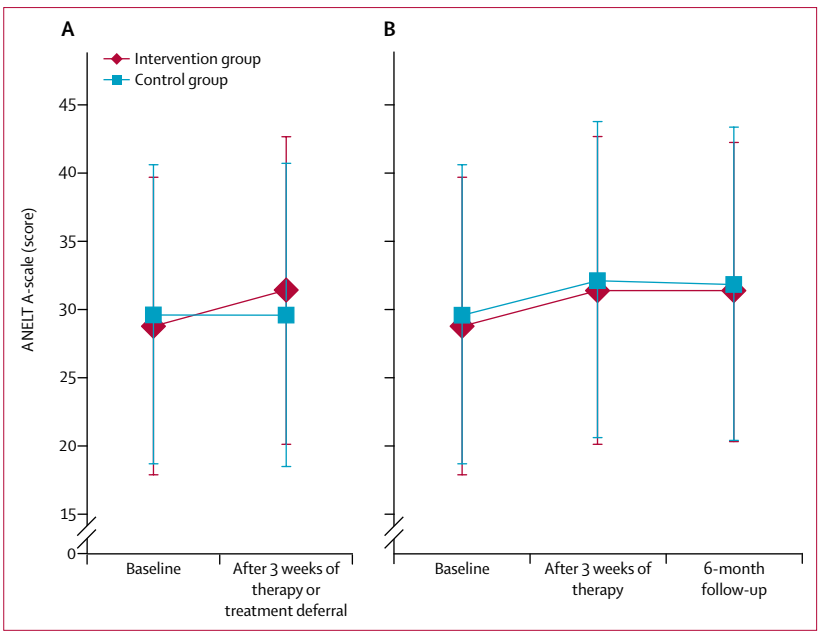

Figure 3: **ANELT A-scale score**
(A) Mean ANELT A-scale score from baseline to after 3 weeks of intensive speech and language treatment in the intervention group and from baseline to after 3 weeks of treatment deferral in the control group. (B) Mean ANELT A-scale score from baseline to after 3 weeks of treatment and 6 months after end of treatment in both the intervention and control groups. Minimum ANELT A-scale score is 10 points, maximum is 50 points. Error bars represent SD. ANELT=Amsterdam-Nijmegen Everyday Language Test.

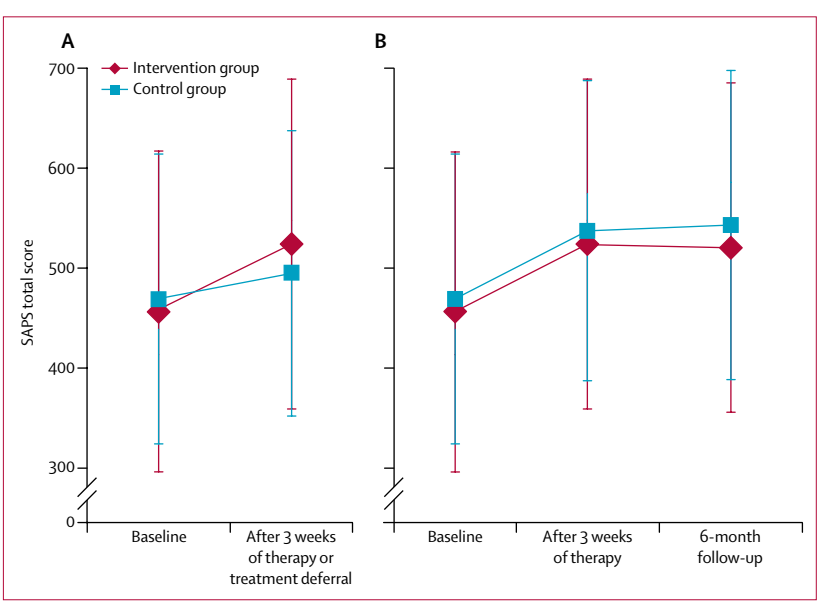

Figure 4: **SAPS total score**
(A) Mean score for the linguistic measure (SAPS total score) from baseline to after 3 weeks of intensive speech and language therapy in the intervention group and from baseline to after 3 weeks of treatment deferral in the control group. (B) Mean SAPS total score from baseline to after 3 weeks of treatment and 6 months after end of treatment in both the intervention and control groups. Minimum SAPS total score is 0 points, maximum is 900 points. Error bars represent SD. SAPS=Sprachsystematisches Aphasiescreening (language-systematic aphasia screening).

speech and language therapy intervention due to staff shortages in their rehabilitation centre at the time of referral.

The only significant predictor of primary treatment success was stroke severity. Patients with milder stroke severity (according to the mRS) at inclusion showed larger increases in verbal communication effectiveness from baseline to after speech and language therapy. Furthermore, both study groups retained speech and language treatment gains over at least 6 months, demonstrating the persistence of the effect.

To our knowledge, no previously published studies exist on the association of change in ANELT scores with clinical effect. The mean increase of roughly 3 points on the primary outcome ANELT A-scale from baseline to after intensive speech and language therapy might seem moderate with respect to the clinical effect but, from a clinical perspective, even a 1-point increase in verbal effectiveness in daily-life situations is important because it could represent a change from having no relation to a communicative scenario at all (score 1) to the minimum requirements of a communicative scenario being fulfilled (score 2). A numerically small change could thus reflect a categorical shift from no social participation at all to at least a low level of social participation, and could be clinically meaningful in that it could allow a patient to, for example, change a doctor's appointment by phone.

A few trials using the ANELT A-scale as a therapy outcome measure reported average gains of at least 5 points from baseline to after the intervention period. However, these studies included patients in the acute and postacute (roughly 3 months after stroke) phases after stroke. This magnitude of change is not directly comparable with our study of patients with chronic stroke symptoms, because spontaneous language recovery is common during the first 6 months after stroke. For example, the RATS-1 study[15] found an average gain of about 5 points on the ANELT A-scale when comparing verbal communication at the postacute phase with a second assessment roughly 7 months later. The RATS-2 study[19] reported therapy-induced changes in ANELT A-scale scores of 10 points from the acute phase (3 weeks after stroke) to the postacute phase; and from the postacute to the chronic (6 months after stroke) phase, the incremental improvement was a mean of 2 points. Patients in the present study had a median of 31·0 months (IQR 14·3–62·0) from their most recent stroke, had received only 3 weeks of intensive speech and language therapy before the outcome assessment after treatment, and still gained a mean of 3 points, more than 50% of the intraindividual SD. Therapy duration might also be an important determinant of treatment effects: the subsample of 34 patients in our study who had 5 weeks or more of intensive speech and language therapy had mean increases of more than 4 points from baseline to after therapy. This result shows that prolonged intensive treatment or repeated periods of intensive speech and language therapy in the chronic stage after stroke might yield stronger treatment effects than those observed in the spontaneous recovery

phase early after stroke. Thus, our findings undermine the dogma that functional improvements cannot be achieved in the chronic stage after stroke. The magnitude of the observed therapy effect is similar to the typical improvement observed after physiotherapy programmes that last several weeks in patients with chronic motor problems after stroke,[29] and might represent a physiological limit of training-induced functional recovery after a single training episode to treat chronic problems after stroke.

The independent committee who did offline scoring of the primary outcome measure was masked to treatment assignment; however, we concede that the staff who did the assessments for the primary outcome measure were not masked because the study was being done in a health-care setting. Assessors were comprehensively trained in ANELT assessment; however, they did not assign scores for ANELT. The scenario instructions had to be read word-for-word to the patient, no other verbal or non-verbal interactions with the patient were allowed during assessment. During the scoring process, the independent committee verified that assessors had complied with this protocol.

Major strengths of our trial are the statistically significant improvement, with medium to large effect sizes, in verbal communication and linguistic abilities; the parallel increases in communication-related quality-of-life item ratings by patients and ratings of patients' verbal effectiveness as viewed by a partner or friend; the provision of therapy under routine clinical conditions; and the large sample of patients with chronic aphasia after stroke.

Our study also has several limitations. First, low intensity speech and language therapy was provided to the control group during the treatment deferral period and to both groups during the 6-month follow-up. Although this therapy seemed to be ineffective, we cannot rule out that low-intensity therapy after the intensive study intervention could have supported the maintenance of the treatment effect. Regardless, intensive speech and language therapy still seems to be key to successful treatment of chronic aphasia after stroke, and low-intensity treatment might merely support the maintenance of intensive therapy effects, suggesting a need for urgent changes to the way rehabilitation resources are currently used. Second, the study design did not address whether a critical time window exists after stroke for maximum treatment effects to be achieved. Patients were enrolled at least 6 months after the initial stroke to control for the effects of spontaneous recovery, and most patients were enrolled several years after their initial stroke. However, a study by Wertz and colleagues[30] provided the first evidence that intensive speech and language therapy (8–10 h per week for 12 weeks) is effective when initiated during the first 6 months after stroke, regardless of whether it is initiated in the acute or postacute stages after stroke. Third, our findings cannot predict whether other approaches might also be effective or whether other patient groups might also benefit. For example, a less intense speech and language therapy (eg, 6 h per week)[13] could be sufficient to achieve similar effects to those seen in our study; the observed treatment effect might not be specific to the agreed best-practice speech and language therapy used; the total number of hours of therapy provided might be as important as treatment intensity;[10] low-intensity speech and language therapy might be required to maintain treatment effects following the intensive intervention; cumulative treatment effects could be achieved with extended treatment periods or repeated intensive speech and language therapy periods; and patients older than 70 years could benefit similarly from intensive speech and language therapy, as suggested by a recent cohort analysis.[31]

In conclusion, FCET2EC is the first multicentre randomised controlled trial in patients with chronic aphasia after stroke to show the superiority of intensive speech and language therapy over treatment deferral (with no or low-intensity treatment). 3 weeks of intensive speech and language therapy of 10 h or more per week in an inpatient or outpatient setting can be considered an evidence-based intervention for patients aged 70 years or younger with chronic aphasia after stroke.

Contributors

AB, CB, AF, WZ, TG, LS, and PM devised the study protocol. PM, WH, KW, EBR, and KGH were members of the FCET2EC Trial Steering Committee; EBR was the chairman. TG, SA, FD, RG, FR, K-JS, MT, LS, and AB developed the intensive speech and language therapy treatment manual. RR, FW, IH, HO, EdL, CR, and JL participated in data collection and processing. PM, CB, AB, KW, WH, EBR, and KGH contributed to data analysis and interpretation. CB wrote the first draft of the report with input from AB and PM. AF, WZ, TG, WH, KW, EBR, KGH, HO, SA, and FD edited the report. All authors were members of the FCET2EC study group and approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

FCET2EC study group

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