Group versus Individual Delivered Cognitive Behavioral Therapy for Complicated Grief Reactions: A Randomized Non-inferiority Trial.

Statistical analysis plan for the non-inferiority study

Version 1.0. July 2024

This statistical analysis plan describes the methods used to analyze the primary and secondary outcomes from the CBTgrief trial pre-registered at www.clinicaltrials.gov (identifier: NCT04694807). This analysis plan was constructed during data collection before data access. Analyses of the hypotheses about moderators and mediators will be registered and reported separately and will not be further mentioned in this registration.

Research objectives and hypotheses for non-inferiority study

Background and rationale: See information at www.clinicaltrials.gov (identifier: NCT04694807).

Aims of the study:

- Evaluate the relative efficacy of an individually delivered versus group-based CBTgrief.

Primary hypothesis:

- Group-based CBTgrief will show non-inferiority in reducing symptoms of PGD (PG-13) compared to individually delivered CBTgrief at six months follow-up.

Secondary hypotheses:

- Group-based CBTgrief will show non-inferiority in reducing symptoms of PGD (PG-13) compared to individually delivered CBTgrief at post-intervention.
- Group-based CBTgrief will show non-inferiority in reducing symptoms of A) posttraumatic stress (PCL-5), B) depression (CESD-10), and C) anxiety (GAD-7) compared to individually delivered CBTgrief at 1) post-intervention and 2) six-month follow-up.
- Group-based CBTgrief will show greater reductions in loneliness (TILS) than individual CBTgrief at 1) post-intervention and 2) six-month follow-up.
- Group-based CBTgrief will show higher levels of received social support (CSS) than individual CBTgrief at 1) post-intervention and 2) six months follow-up.

Moreover, we will examine differences in terms of well-being (WHO-5), quality of life (SF-12), and grief-related functional impairment (SDS) between the two delivery formats.

Study methods

Design

Non-inferiority design of group versus individually delivered CBTgrief. See more information at www.clinicaltrials.gov (identifier: NCT04694807).

Randomization

Block randomization with a 1:1 allocation ratio to individually delivered versus group-based CBTgrief conducted by an independent Danish National Center for Grief employee.

Sample size

See information at www.clinicaltrials.gov (identifier: NCT04694807).

Timing of outcome measures

Baseline characteristics will be assessed at the time of inclusion (T1). Outcome measures will be assessed pre-treatment (T1), post-treatment (T2), 3 months follow-up (T3), and 6 months follow-up (T4).

The study also assessed outcomes at mid-treatment (i.e., after session 6), but this time point was included for investigating therapy processes and will be analyzed and reported separately in another research paper with another research question.

See information about measures at www.clinicaltrials.gov (identifier: NCT04694807).

Statistical principles

Data presentation

The CONSORT reporting guidelines for non-inferiority and equivalence trials will be applied. Results for the non-inferiority hypotheses will be reported accordingly.

Adherence and protocol deviations

Attrition rates will be reported for both groups (received individually delivered vs. group-based CBTgrief). We will make the following categories: 1) Non-starters (participants that were randomized but received no therapy sessions), 2) Completers (participants receiving 8 or more sessions of therapy), and 3) Dropouts (participants dropping out of the treatment will be divided into early dropouts (before session 6) and late dropouts (after session 6)).

Therapist fidelity and adherence to the manual will be assessed for individually delivered CBTgrief and group-based CBTgrief. Thirty percent of all completed individual and group therapies (i.e., completed more than 8 sessions of therapy) will be randomly chosen to be rated for fidelity and adherence to the manual. The presence of the core components of the manual will be assessed as well as the quality of the application of these components session-by-session. Two master psychology students will receive comprehensive training in the manual by KK in doing these. KK will analyze 20% of the selected individual and group therapies for interrater agreement. These will be chosen randomly.

The analysis population

As recommended by the CONSORT guidelines for reporting noninferiority and equivalence randomized trials (Piaggio et al., 2012) we will do Intention-to-treat (ITT), but also per-protocol (PP) analyses as sensitivity analysis.

Trial population

Eligibility

See more information at www.clinicaltrials.gov (identifier: NCT04694807)

Recruitment

See information at www.clinicaltrials.gov (identifier: NCT04694807).

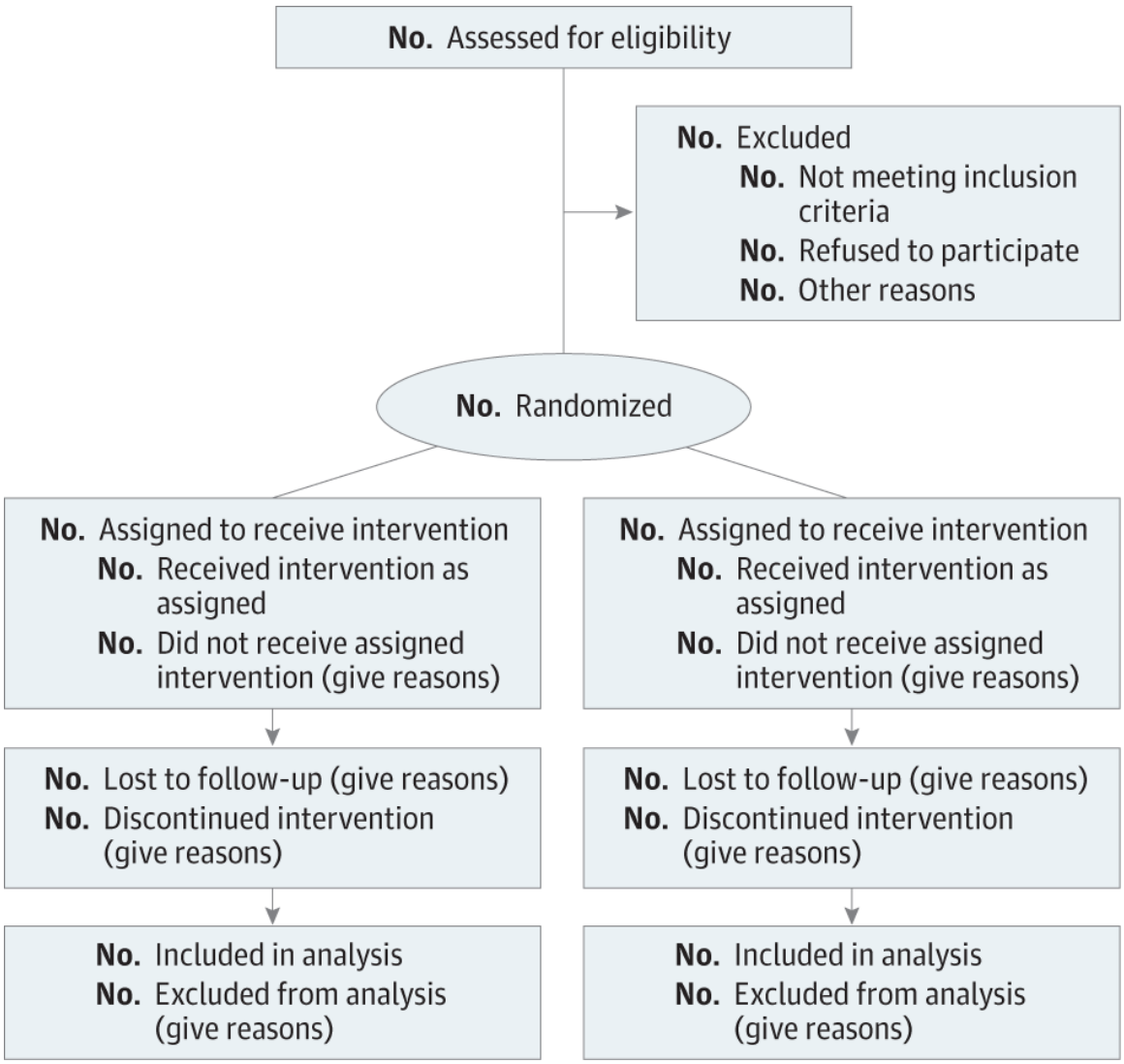
Adjustments: Originally, recruitment was planned at two clinical sites (clinics in Odense and Copenhagen, DK). However, due to difficulties with recruitment at the clinical site in Odense, randomization for group versus individual CBTgrief was not possible at that site. A pilot study has reported data from the clinical site in Odense (https://osf.io/qp67d). In the present non-inferiority trial, we only focus on the data collected at the clinical site in Copenhagen, where randomization of group versus individually delivered CBTgrief was possible.

Participant flow

Example of how the participant flow will be presented for the study according to CONSORT.

Figure 1.

Participant flow in the present study.



Baseline characteristics

See the example below of what baseline characteristics will be reported.

Table 1.

Participant characteristics at baseline.

Characteristic	**Total sample** *(n=)*	**Individual CBT** *(n=)*	**Group CBT** *(n=)*
Age, mean (SD)			
Gender, n (%)			
Female			
Male			
Education[a], n (%)			
Primary education			
Secondary education			
Source of income[b], n (%)			
Salary			
Pension			
Out of employment			
Other			
Relationship to the deceased, n (%)			
Spouse/partner			
Parent			
Other			
Years together, mean (SD)[c]			
Illness prior to death, n (%)			
Yes			
No			
Cause of death, n (%)[d]			
Cancer			
Cardiovascular disease			
Dementia			
Suicide			
Accident			
COVID-19			
Other age-related illness			
Time since loss (months), mean (SD)			
Additional bereavement losses, mean (SD)			
Previous use of psychosocial support prior to intervention, n (%)[e]			
Symptom profiles[f]			
PGD[g] only			
PGD and PTSD[h]			
PGD and depression			
PGD and anxiety			
PGD and ≥ two syndromes			
PGD and ≥ three syndromes			

Notes. a) Education will be categorized as primary education (primary school, high school, vocational training) and secondary education (college, university); b) Source of income will be categorized as 1) salary for those holding a job, 2) pension for those on early voluntary retirement and those receiving self-financed or government-assisted pension, and 3) out of employment (including unemployment benefits, social security payments due to sickness, or government-sponsored support); c) Only relevant for partner

loss; d) cause of death will be reported by the participant; e) Psychosocial support includes contacts with a psychiatrist, psychologist, counseling (e.g., patient organizations), and social support groups; f) Syndromes will be assessed based on self-report measures with cut-off values on clinically relevant symptom levels. Thus, no psychiatric diagnoses will be given; g) Prolonged grief disorder; h) Posttraumatic stress disorder.

Analyses

Primary outcome

Symptoms of PGD. See details at www.clinicaltrials.gov (identifier: NCT04694807).

Secondary outcomes

Symptoms of depression, PTSD, and anxiety, functional impairment, loneliness, social support, quality of life, well-being, treatment satisfaction. See details at www.clinicaltrials.gov (identifier: NCT04694807).

Process variables

Process variables included: Experience of unrealness, negative loss-related cognitions, avoidance behaviors, therapeutic alliance, and therapeutic group processes. See details at www.clinicaltrials.gov (identifier: NCT04694807). These will be reported in a separate paper about therapeutic processes and mechanisms of CBTgrief.

Analysis methods

Descriptive analyses

Baseline group differences will be explored with t-tests and χ^2-tests.

Inferential analyses

The analyses will be based on comparisons of group CBTgrief versus individually delivered CBTgrief.

Primary analysis

The primary analysis will examine whether group CBTgrief is non-inferior to individual CBTgrief.

The analyses for primary and secondary outcomes will consist of multilevel, mixed linear models (MLMs) including time (pre-intervention, post-intervention, 3-month follow-up, and 6-month follow-up), group (Group CBTgrief vs. Individual CBTgrief), and their interaction (Time x Group). Two-level MLMs will be used to test the Time x Group interaction effect taking into account that symptoms are measured at several time points (level 1) that are nested within individuals (level 2).

We will report between and within-group effect sizes (Cohen's *d*) for both group and individual-delivered CBTgrief to assess change in symptoms over time in the respective treatment groups.

The rationale for the non-inferiority limit: The choice of the non-inferiority margin of 0.5 SD was based on a clinical judgment, considering that the minimal important difference has yet not been established on PG-13. 0.5 SD corresponds to the border between a mild and medium effect, which very often corresponds to the border for a clinically meaningful effect (Norman et al., 2003) – also for stressor-related disorders such as PTSD (0.5-0.8 SD; Stefanovics et al., 2018). Moreover, a recent meta-analysis found that grief-focused CBTs delivered individually had a medium pooled effect on PGD symptoms with the lower bound of the 95% confidence interval (CI) of 0.49 (Hedge's g = 0.67, 95% CI: 0.49-0.85; Komischke-Konnerup et al., 2024). Importantly, RCTs investigating individual-delivered grief-focused CBTs that specifically included similar interventions and theoretical backgrounds as CBTgrief have found large effects on PGD symptoms compared to active and passive control groups (Cohen's d= 0.90 – 1.34; Boelen et al., 2007; Reitsma et al.,

2023). Thus, based on previous research, individually delivered CBTgrief was expected to be highly effective in reducing PGD symptoms. Group CBTgrief may have potential advantages over individually delivered CBTgrief for an older bereaved population. In older bereaved individuals, loneliness and less social support are common, and a group format can offer a safe space and community for sharing one's grief experiences with and receiving support from other bereaved individuals. Furthermore, group-based treatment may be associated with more practical and financial advantages such as reduced costs and fewer specialized therapists needed to treat a larger group of individuals. Based on this rationale, a non-inferiority margin of 0.5 was chosen. This means that a mild effect up to the border of medium effect in favor of individual CBTgrief will be acceptable for determining the non-inferiority of group CBTgrief.

The true difference between group and individual delivered CBTgrief is assumed to be 0.0 and the one-sided significance level (alpha) of the test is 0.025 (Flight & Julious, 2016). A one-sided 97.5% CI interval approach will be used to test non-inferiority between group and individual CBTgrief. The 97.5% CI will be calculated for between-group differences at 6-month follow-up and post-intervention (Cohen's *d*). The non-inferiority of group CBTgrief will be accepted if the lower bound of the 97.5% CI lies within the non-inferiority margin (Cohen's $d = -0.5$). If the non-inferiority of group CBTgrief is accepted, we will further assess the potential superiority of group CBTgrief by close testing procedure (i.e., if the lower bound of the 97.5% CI lies above 0) (Flight & Julious, 2016).

Secondary analysis

The secondary analyses will follow the same principle as the primary analysis for PTSD, depression, anxiety, functional impairment, quality of life, treatment satisfaction, and well-being – testing for non-inferiority of group vs. individual CBTgrief.

For loneliness and social support, we will test the superiority of the group-based CBTgrief with MLMs using a two-sided alpha = 0.5 for significant differences, following our hypotheses.

Reliable changes in symptoms of PGD, PTSD, anxiety, and depression were computed by the Reliable Change Index (RCI; Jacobson & Truax, 1991) on the completer sample for both group and individually delivered CBT format and from pre- to post-intervention and 6-month follow-up.
Additionally, we will calculate the percentages of A) recovered participants (scoring above cut-offs before but below after treatment), B) unchanged participants (no change in terms of cut-offs before and after treatment), and C) deteriorated participants (scoring below cut-offs before treatment but above after treatment).
Based on the two-step criterion, individuals will be classified as 1) recovered (met both Cutoff A and RCI), 2) improved (met RCI but not Cutoff A), 3) unchanged (met none of the criteria), or 4) deteriorated (met RCI but symptom scores increased). See the procedure used by e.g., (Papa et al., 2013); Reitsma et al. (2023); (Treml et al., 2021).

Sensitivity analyses

We will analyze both intention-to-treat (ITT) and per-protocol (PP) samples as it has been argued that this provides a more rigorous test of non-inferiority (Brasher & Dobson, 2014; D'Agostino Sr et al., 2003; Groenwold et al., 2022). For the per protocol analysis participants must have completed 8 or more sessions. Additionally, we do a stricter per-protocol analysis as sensitivity analyses (completed all 12 sessions).

Additional analyses

We will analyze the potential influence of treatment preference before randomization to treatment format and analyze potential differences in treatment satisfaction post-intervention.

Statistical software

A range of statistical software will be used (e.g., SPSS and R).

Handling of missing data and blinding

Item level: If less than 50% of items on a scale are missing and Cronbach alpha is above .7, missing items will be handled via multiple imputations. If more than 50% of items on a scale are missing, then it will result in a missing value at the scale level.

Scale level: If the entire scale (e.g., PCL-5 at 3-month follow-up) is not completed then it will be left empty.

Survey-level: We will not impute missing data on the survey level (i.e. if participants have not returned/completed an entire questionnaire).

Analyses level: MLMs handle missing data by using maximum likelihood estimation, assuming that data is missing at random or completely at random.

Treatment conditions (group vs. individual) will randomly be coded “1” or “2” in the data file and concealed until all non-inferiority analyses are done.

Table 2.
Descriptives and main effect results.

Measure	**Group CBT**			**Individual CBT**			**Time x Group Interaction**		
	n	*Mean (SD)*	Within group effect (Cohen's *d*)	*n*	*Mean (SD)*	Within group effect (Cohen's *d*)	*F* value	*p* value	Cohen's *d* (95% CI)
Primary outcome									
Prolonged grief symptoms (PG-13)									
Baseline									
Post-intervention									
3-month follow-up									
6-month follow-up									
Secondary outcomes									
Posttraumatic stress symptoms (PCL-5)									
Baseline									
Post-intervention									
3-month follow-up									
6-month follow-up									
Depressive symptoms (CESD-10)									
Baseline									
Post-intervention									
3-month follow-up									
6-month follow-up									
Anxiety symptoms (GAD-7)									
Baseline									
Post-intervention									
3-month follow-up									
6-month follow-up									
Loneliness (T-ILS)									
Baseline									
Post-intervention									
3-month follow-up									
6-month follow-up									
Social support (CSS)									
Baseline									
Post-intervention									
3-month follow-up									

6-month follow-up	
Well-being (WHO-5)	
Baseline	
Post-intervention	
3-month follow-up	
6-month follow-up	
Grief-related functional impairment (SDS)	
Baseline	
Post-intervention	
3-month follow-up	
6-month follow-up	
Quality of life (SF-12)	
Baseline	
Post-intervention	
3-month follow-up	
6-month follow-up	

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