Internet-based guided self-help for overweight and obese patients with full or subsyndromal binge eating disorder: a multicenter, randomized controlled trial (INTERBED)

Principal investigators (PIs)           Biostatistician
Prof. Dr. med. Martina de Zwaan        Prof. Dr. Olaf Gefeller
University Hospital Erlangen           FAU Erlangen-Nuremberg
FAU Erlangen-Nuremberg                 Department of Medical Informatics, Biometry
Department of Psychosomatic Medicine    and Epidemiology
and Psychotherapy                      Waldstraße 6, 91054 Erlangen
Schwabachanlage 6, 91054 Erlangen      Tel.: 09131/8222750: 09131/85
Tel.: 09131/8535928                    Fax: 09131/8522721
Fax: 09131/8534153                     E-Mail: gefeller@rzmail.uni-erlangen.de
E-Mail: martina.dezwaan@uk-erlangen.de

PD Dr. rer. nat. Anja Hilbert (CoPI)   Data management and randomization
Phillipps-University Marburg           Coordinating Center for Clinical Trials (KKS)
Department of Psychology               Philipps-University Marburg
Gutenbergstrasse 18                    Karl-v.-Frisch-Str. 4
D- 35032 Marburg                       D-35043 Marburg
Tel.: 06421/2823787                    Tel.: 06421-2866456
Fax: 06421/2828904                     Fax: 06421-2866517
E-Mail: hilbert@staff.uni-marburg.de   E-Mail: carmen.brittinger@kks.uni-marburg.de

Study coordination and monitoring
Dipl.-Psych. Frauke Schmidt
University Hospital Erlangen
FAU Erlangen-Nuremberg
Department of Psychosomatic Medicine
and Psychotherapy
Schwabachanlage 6, 91054 Erlangen
Tel.: 09131/8535927
Mobile: 0173/8645092
Fax: 09131/8534153
E-Mail: frauke.schmidt@uk-erlangen.de

Funding
German Federal Ministry of Education and Research (BMBF)
Authors of the study protocol

Prof. Dr. Martina de Zwaan (PI, Erlangen)
PD Dr. Anja Hilbert (PI, Marburg)
Dipl.-Psych. Frauke Schmidt (study coordination and monitoring, Erlangen)
Carmen Schade-Brittinger (KKS, Marburg)
Prof. Dr. Olaf Gefeller (Biometry, Erlangen)

Version 01D01
Date: September 4, 2009
# TABLE OF CONTENT

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. GENERAL INFORMATION</td>
<td>5</td>
</tr>
<tr>
<td>1.1 Investigators</td>
<td>5</td>
</tr>
<tr>
<td>1.2 Project summary</td>
<td>6</td>
</tr>
<tr>
<td>1.3 Study schedule: assessment points and assessment instrument</td>
<td>8</td>
</tr>
<tr>
<td>1.4 Flow chart</td>
<td>9</td>
</tr>
<tr>
<td>2. STUDY GOALS AND OBJECTIVES</td>
<td>10</td>
</tr>
<tr>
<td>2.1 Primary outcome</td>
<td>13</td>
</tr>
<tr>
<td>2.2 Secondary outcomes</td>
<td>13</td>
</tr>
<tr>
<td>3. STUDY DESCRIPTION</td>
<td>14</td>
</tr>
<tr>
<td>3.1 Study design</td>
<td>14</td>
</tr>
<tr>
<td>3.2 Trial sites and number of patients</td>
<td>14</td>
</tr>
<tr>
<td>3.3 Blinding and randomization</td>
<td>14</td>
</tr>
<tr>
<td>3.4 Expected study duration</td>
<td>14</td>
</tr>
<tr>
<td>3.5 Early termination of study</td>
<td>14</td>
</tr>
<tr>
<td>4. STUDY POPULATION</td>
<td>16</td>
</tr>
<tr>
<td>4.1 Inclusion criteria</td>
<td>16</td>
</tr>
<tr>
<td>4.2 Exclusion criteria</td>
<td>16</td>
</tr>
<tr>
<td>5. METHODOLOGY</td>
<td>17</td>
</tr>
<tr>
<td>5.1 Patient information and consent</td>
<td>17</td>
</tr>
<tr>
<td>5.2 Inclusion into the study</td>
<td>17</td>
</tr>
<tr>
<td>5.3 Description of study interventions</td>
<td>17</td>
</tr>
<tr>
<td>5.4 Handling of unexpected physical or mental emergencies</td>
<td>17</td>
</tr>
<tr>
<td>5.5 Assessment instruments and follow-up</td>
<td>17</td>
</tr>
<tr>
<td>5.6 Protocol violations, treatment dropout, study dropout, dropout</td>
<td>17</td>
</tr>
<tr>
<td>6. SAFETY ISSUES</td>
<td>25</td>
</tr>
<tr>
<td>6.1 Benefits, risks, and side effects</td>
<td>25</td>
</tr>
<tr>
<td>6.2 Adverse events (AE)</td>
<td>25</td>
</tr>
<tr>
<td>6.3 Serious adverse events (SAE)</td>
<td>25</td>
</tr>
<tr>
<td>7. BIOMETRICAL/STATISTICAL ASPECTS OF THE STUDY</td>
<td>27</td>
</tr>
<tr>
<td>7.1 Endpoints of the study</td>
<td>27</td>
</tr>
<tr>
<td>7.2 Statistical modelling of the main research question</td>
<td>27</td>
</tr>
<tr>
<td>7.3 Statistical methods</td>
<td>27</td>
</tr>
<tr>
<td>7.4 Interim and final analyses</td>
<td>27</td>
</tr>
<tr>
<td>7.5 Estimation of the effect size of the main endpoint</td>
<td>27</td>
</tr>
<tr>
<td>7.6 Sample size calculation</td>
<td>27</td>
</tr>
<tr>
<td>8. ASSOCIATED RESEARCH PROJECTS</td>
<td>30</td>
</tr>
<tr>
<td>9. ETHICAL ISSUES</td>
<td>31</td>
</tr>
</tbody>
</table>
10 ORGANISATION

10.1 Documentation
Documentation of data in the CRF

10.2 Data management

10.3 Monitoring

11 ADMINISTRATIVE REGULATIONS

11.1 Amendments to the study protocol

11.2 Funding and insurance

11.3 Handling of data and storage of study documents

11.4 Publication agreement

12 APPROVAL AND SIGNATURES

13 REFERENCES

RELEVANT GUIDELINES

AMENDMENTS
## GENERAL INFORMATION

### Investigators

<table>
<thead>
<tr>
<th>Role</th>
<th>Contact Person</th>
<th>Address</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal investigators</td>
<td>Prof. Dr. med. Martina de Zwaan</td>
<td>University Hospital Erlangen, FAU Erlangen-Nuremberg</td>
<td>Tel.: 09131/8535928, Fax: 09131/8534153</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Department of Psychosomatic Medicine and Psychotherapy</td>
<td>E-Mail: <a href="mailto:martina.dezwaan@uk-erlangen.de">martina.dezwaan@uk-erlangen.de</a></td>
</tr>
<tr>
<td></td>
<td>PD Dr. rer. nat. Anja Hilbert</td>
<td>Phillipps-University Marburg, Department of Psychology,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical Psychology and Psychotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gutenbergstraße 18, 35032 Marburg</td>
<td>Tel.: 06421/2823787, Fax: 06421/2828904</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E-Mail: <a href="mailto:hilbert@staff.uni-marburg.de">hilbert@staff.uni-marburg.de</a></td>
<td></td>
</tr>
<tr>
<td>Study coordination</td>
<td>Dipl.-Psych. Frauke Schmidt</td>
<td>University Hospital Erlangen, FAU Erlangen-Nuremberg</td>
<td>Tel.: 09131/8535927, Fax: 09131/8534153</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Department of Psychosomatic Medicine and Psychotherapy</td>
<td>E-Mail: <a href="mailto:frauke.schmidt@uk-erlangen.de">frauke.schmidt@uk-erlangen.de</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Schwabachanlage 6, 91054 Erlangen</td>
<td></td>
</tr>
<tr>
<td>Data management</td>
<td>Coordinating Center for Clinical Trials (KKS)</td>
<td>Philippps-University Marburg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Karl-v.-Frisch-Str. 4</td>
<td>Tel.: 06421-2866541</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D-35043 Marburg</td>
<td>Fax: 06421-2866517</td>
</tr>
<tr>
<td>Biometry</td>
<td>Prof. Dr. Olaf Gefeller</td>
<td>FAU Erlangen-Nuremberg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Department of Medical Informatics, Biometry and Epidemiology</td>
<td>Tel.: 09131/8222750: 09131/85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Waldstraße 6, 91054 Erlangen</td>
<td>Fax: 09131/8522721</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E-Mail: <a href="mailto:gefeller@rzmail.uni-erlangen.de">gefeller@rzmail.uni-erlangen.de</a></td>
<td></td>
</tr>
<tr>
<td>Independent Data Safety and</td>
<td>Prof. Dr. med. Hans-Christian Deter, FU Berlin,</td>
<td>Department of Psychosomatic Medicine and Psychotherapy,</td>
<td></td>
</tr>
<tr>
<td>Monitoring Board (DSMB)</td>
<td></td>
<td>Hindenburgdamm 30, 12200 Berlin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prof. Dr. phil. Silvia Schneider, Department of Psychology,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Missionsstrasse 60/62, CH-4055 Basel</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prof. Dr. med. Ulrike Schmidt, Institute of Psychiatry,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PO59, De Crespigny Park, London, United Kingdom, SE5 8AF</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD Dr. Andreas Faldum: Institute of Medical Biostatistics,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidemiology and Informatics, Johannes-Gutenberg-University Mainz</td>
<td></td>
</tr>
</tbody>
</table>
### Project Summary

<table>
<thead>
<tr>
<th>Study title</th>
<th>Internet-based guided self-help for overweight and obese patients with full or subsyndromal binge eating disorder: a multicenter, randomized controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acronym</td>
<td>INTERBED</td>
</tr>
<tr>
<td>Disease area</td>
<td>Binge-Eating-Disorder (BED)</td>
</tr>
<tr>
<td>Primary objective</td>
<td>To evaluate the efficacy of Internet-based guided self-help (GSH-I) compared to cognitive-behavioral therapy (CBT) in adult patients with BED with regard to the change in the number of binge eating days over the past 28 days (as assessed with the EDE interview).</td>
</tr>
<tr>
<td>Secondary objectives</td>
<td>Exploratory analyses of secondary outcome parameters differential treatment effects and treatment trajectories; moderator and mediator analyses; follow-up assessment to investigate maintenance of change; qualitative analyses of audiotapes that exceed the assessment of treatment adherence with CBT.</td>
</tr>
<tr>
<td>Study design</td>
<td>Multicenter, randomized, controlled non-inferiority trial with two parallel arms and blinded assessment of the main outcome variable.</td>
</tr>
</tbody>
</table>
| Study population | **Inclusion criteria**  
| | • Diagnostic criteria for BED according to DSM-IV or subsyndromal BED (patients can lack one diagnostic criterion, e.g. frequency of less than 2 days with objective binge eating episodes (OBEs), no marked distress, presence of only 2 instead of 3 of the 5 associated criteria, or duration of BED less than 6 months).  
| | • Age ≥ 18 years  
| | • 27 < BMI < 40 kg/m²  
| | • Internet access available (at home, Internet cafe, at the trial site)  
| | **Exclusion criteria**  
| | • Current bulimia nervosa  
| | • Current substance abuse  
| | • Current suicidal ideation  
| | • Psychotic disorder  
| | • Delusional disorder  
| | • Manic episode  
| | • Ongoing psychotherapy  
| | • Serious unstable medical problems or conditions that can influence weight or eating (for example, type 1 diabetes mellitus or thyroid problems)  
| | • Pregnancy or lactation  
| | • Participation in other treatment study  
| | • Insufficient computer skills  
| Number of patients | A sample size of at least 70 participants per treatment group finishing the study is required. Assuming a dropout rate of 20% of study participants, 175 participants need to be included into the study. The study will be conducted at 6 trial sites. |
| Treatments | GSH-I: Internet-based guided self-help (Self-Help Guide, Copyright © NetUnion & HUG). Treatment duration will be 4 months with one weekly e-mail contact and 2 face-to-face contacts between patient and coach before the beginning and |
after the end of treatment.

CBT: individual face-to-face outpatient treatment using an existing manual (Hilbert & Tuschen-Caffier, in press). The treatment will comprise 20 sessions and will last 4 months.

Comprehensive assessments will be conducted at 4 time points: at baseline (T0), midtreatment (T1, after 10 sessions or 2 months, respectively), end of treatment (T2, after 20 sessions and 4 months, respectively), follow-up (T3, 6 months after T2).

<table>
<thead>
<tr>
<th>Primary outcome parameter</th>
<th>Difference in the number of days with OBEs over the past 28 days between baseline (T0) and end of treatment (T2).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary outcome parameters</td>
<td>Changes in eating disorder psychopathology (EDE, DEBQ), depressive symptoms and mental comorbidity (BDI II, SCID-I), quality of life (IWQoL), self-esteem (RSE), physical activity (IPAQ), and weight between T0 and T1 and between T0 and T2. Mediators (e.g., working alliance) und moderators (e.g. personality) of treatment outcome. Follow-up to investigate maintenance of change. Qualitative analyses of audiotapes that exceed the assessment of treatment adherence with CBT.</td>
</tr>
<tr>
<td>Biometry</td>
<td>To test for non-inferiority of the GSH-I intervention toward CBT regarding the number of days with OBE episodes over the past 28 days (primary outcome), we specified a non-inferiority margin of 1 day in favour of CBT. The significance level will be set at .05. Primary and secondary outcomes will also be analyzed using the regression approach of linear hierarchical models (random coefficient model). The choice of sample sizes for analyses will follow the per-protocol (non-inferiority) and the intention-to-treat (exploratory analyses) principles.</td>
</tr>
<tr>
<td>Timeline</td>
<td>Total study duration: 42 months Preparation: 6 months Recruitment: 22 months Treatment duration: 4 months Follow-up: 6 months (after treatment completion) Data analysis: 4 months</td>
</tr>
</tbody>
</table>
### Study schedule: measurement points and assessment instruments

<table>
<thead>
<tr>
<th>Assessment Instrument</th>
<th>Baseline T0 prior to randomization</th>
<th>Midtreatment T1 after 10 sessions or 2 months after randomization</th>
<th>End of treatment T2 after 20 sessions or 4 months after randomization</th>
<th>Follow-up T3 6 months after T2</th>
<th>Weekly until T1, bi-weekly until T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, Body Mass Index (BMI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Eating Disorder Examination - Interview (EDE)*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch Eating Behavior Questionnaire (DEBQ)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structured Clinical Interview for DSM IV (SCID-I)</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beck Depression Inventory II (BDI II)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenberg Self-esteem Scale (RSE)</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impact of Weight on Quality of Life (IWQOL-Lite)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Impairment Assessment Questionnaire (CIA)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Activity (IPAQ)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eating Disorder Examination – questionnaire version (12 items)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working Alliance Inventory - Short Form (WAI-S)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Personality dimensions (ATQ, Barrett Impulsiveness, BIS/BAS)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eating Hedonics Questionnaire (EHQ)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal reasons for participation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment expectations</td>
<td>X**</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The interview version of the Eating Disorder Examination (EDE) will be used for the assessment of the main outcome criterion

** will be filled out after randomization
Flow chart

- Presentation at participating trial site
- Screening for eligibility N=525
  - Exclusion: patient either meets exclusion criteria or does not meet inclusion criteria
- Information about study, written informed consent
- Inclusion
- Comprehensive baseline assessment including interviews and questionnaires, BMI
- Randomization (n=175) KKS Marburg
- Internet-based guided self-help
  - up to 20 e-mail contacts
  - 4 months (+ 6 weeks)
  - completion n=70
- Cognitive-behavioral therapy
  - 20 individual sessions
  - 4 months (+ 6 weeks)
  - completion n=70
- Comprehensive assessment, BMI
  - After 10 sessions or 2 months (+ 2 weeks) after randomization (midtreatment T1)
  - after 20 sessions or 4 months (+ 2 weeks) after randomization (end of treatment T2)
- Comprehensive assessment, BMI
  - 6-month-follow-up, 6 months after T2 (+ 4 weeks)
1 RATIONAL AND BACKGROUND INFORMATION

Binge Eating Disorder (BED) was included into the *Diagnostic and Statistical Manual of Mental Disorders in 1994* as a research diagnosis and as an example for an eating disorder not otherwise specified (EDNOS) (DSM-IV; American Psychiatric Association, 1994). BED is defined by recurrent binge eating episodes (criterion A) that occur, in contrast with those in bulimia nervosa (BN) and anorexia nervosa (AN), in the absence of inappropriate weight control behaviors (for example, purging or fasting) (criterion E). A series of characteristics are associated with binge eating, such as rapid consumption of food, eating until uncomfortably full and marked distress regarding the behavior (criteria B and C). For a BED diagnosis, days with binge eating episodes must have occurred at least twice weekly over a period of 6 months (criterion D).

Since the inclusion of BED into DSM-IV a growing number of studies have shown that BED is significantly associated with substantial psychological and medical comorbidities (Johnson et al., 2001; White & Grilo, 2006). Patients with BED display marked eating disorder psychopathology (e.g. weight and shape concerns), general psychopathology (e.g. depressive symptoms) mental comorbidity (e.g. axis 1 disorders such as affective disorders, anxiety disorders, and substance use disorders), and personality disorders (e.g. axis 2 borderline, obsessive-compulsive, and avoidant personality disorder) (Javaras et al., 2008; Wilfley et al., 2000; Telch & Stice, 1998; de Zwaan et al., 1994). Furthermore, overweight and obesity are common in patients with BED. Comorbid obesity increased the risk for medical complications (e.g. type 2 diabetes mellitus, hypertension, coronary heart disease) (German Obesity Association, 2007). Overall, BED is linked with severe psychosocial problems and reduced quality of life (Rieger et al., 2005; de Zwaan et al., 2002). Increased health care utilization of patients with BED (Striegel-Moore et al., 2004) causes increased costs for the medical system (von Lengerke et al., 2006) which exceed the costs of obesity. This is of utmost importance since BED is the most prevalent eating disorder, affecting 2-5% of the general population (Hudson et al., 2007). In the general population both genders roughly appear to be equally affected, whereas in clinical populations women are overrepresented.

Cognitive-behavioral therapy (CBT) is currently regarded as the first-line specialty treatment for BED (Grilo et al., 2007; Brownley et al., 2007; Wilson et al., 2007; Mitchell et al., 2007; Vocks et al., 2009). Compared to no treatment CBT produces substantial and long-lasting reductions in binge eating and the associated eating disorder and general psychopathology. In addition, remission of binge eating is associated with body weight stabilization (Wilfley et al., 2002); however, does not lead to significant weight reduction. It has to be kept in mind that conservative approaches for weight reduction (diet, exercise, lifestyle interventions) have a short- but not a satisfactory long-term effect on body weight (Jain, 2005; Wilson et al., in press) and are less effective in reducing binge eating (Vocks et al., 2009). A successful and long-lasting reduction of binge eating episodes through psychotherapeutic approaches can be seen as preventive for further weight gain in overweight and obese patients (de Zwaan 2009).

Although CBT is the gold standard treatment for BED patients, this intervention is time-consuming and labor-intensive and is not offered area wide Cognitive-behavioral self-help approaches are considered a cost-effective alternative treatment. First studies have shown that guided cognitive-behavioral self-help interventions can produce similar abstinence rates from binge eating as CBT, at least in the short-term. In a recent meta-analysis the effect size regarding reductions in binge eating episodes of interventions based on self-help manuals was high with $d=.84$. However, the evidence regarding self-help is limited to a small number of studies (Vocks et al., 2009). As recommended by the guidelines of the National Institute for Clinical Excellence (2004), self-help interventions might be useful as initial treatment in a stepped-care approach or while waiting for face-to-face treatment. Stepped care approaches
start with cost-effective and less intensive interventions and proceed to more comprehensive treatments only if the initial treatment is not sufficiently effective. Self-help interventions might be appropriate for patients with less severe conditions, e.g. low levels of eating disorder and general psychopathology.


<table>
<thead>
<tr>
<th>Features of Internet-based treatment</th>
<th>Possible advantages adapted from Berger &amp; Andersson, 2009</th>
</tr>
</thead>
</table>
| Wider reach, easy dissemination over the internet, flexible use; treatment from a distance | • ability to reach people with minimum delay (avoiding long waiting periods)  
• ability to reach people who could not previously be reached by conventional means (rural areas, reduced mobility)  
• ability to reach patients regardless of their time or location  
• programs allow patients to work on their own pace  
• constant quality of materials  
• easy to access and disseminate over the internet  
• can be offered in primary care and delivered by non-specialists |
| Anonymity; absence of personal contact | • respects the patient’s privacy and avoids embarrassment, reduces inhibition threshold to seek help (enables early intervention without long delays). A long illness duration before receiving professional help has been shown to be predictive for a chronic course and less favorable treatment outcome  
• may lead to more openness and honesty (patients “get to the point” more rapidly)  
• reduces social barriers |
| „Written instead of verbal communication“, in asynchronous communication | • no immediate verbal response necessary; patients have the opportunity to reflect on their written text  
• supports active participation of patients in the therapeutic process (e.g. emotions must be put into words)  
• allows patients to renew or update treatment as often as they wish at no extra costs. |

As mentioned above there are only few randomized-controlled treatment studies evaluating the efficacy of self-help interventions in BED (Grilo et al., 2005; Peterson et al., 1998; Carter & Fairburn, 1998; Delinsky et al., 2006; Grilo & Masheb, 2007). Nearly all of them used book-based self-help with manuals („bibliotherapy“) detailing CBT for binge eating, primarily the book “Overcoming Binge Eating” (Fairburn, 1994). One study evaluated a CD-ROM-based self-help intervention (Shapiro et al., 2005). Results of systematic reviews and meta-analyses have shown that guided self-help is superior to waiting list in patients with BED (Stefano et al., 2006; Perkins et al., 2006, Sysko & Walsh, 2008, Vocks et al., 2009). Patients using self-help modalities did better than controls in reducing days with OBEs and in improving the specific eating disorder psychopathology (Peterson et al., 1998). However, the comparison of guided self-help with standard cognitive behavioral therapy in individual or group format is still outstanding.

In their Cochrane Review Perkins et al. (2006) conclude that “other media for delivering self-help need to be explored too. In particular, approaches using new technologies such as the
Internet need to be researched further, as they are likely to be more interactive and hence may be more attractive to patients than manual-based approaches.” Internet-based self-help programs have been developed and evaluated for other mental disorders. There exist more than 100 efficacy studies for various mental disorders (e.g. Wright et al., 2005). Guided self-help (“minimal contact”) conditions are more effective than pure self-help (Berger & Andersson, 2009). In the field of eating disorders Internet-based programs have been developed for the prevention of eating disorders in high risk populations with preclinical eating disorder symptoms (Jacobi et al. 2005, 2007), for the treatment of patients with bulimia nervosa (Carrard et al., 2006; Liwowsky, Cebulla & Fichter, 2006), and for relapse prevention in patients with bulimia and anorexia nervosa after successful inpatient therapy (in de Zwaan et al., 2009). For patients with BED no Internet-based self-help programs have been evaluated so far.

In German-speaking countries the SALUT BN program is available, an Internet-based program for patients with bulimia nervosa purging type. It involves 2-3 personal face-to-face sessions and weekly e-mail messages exchanged with a coach. As with all self-help programs it follows cognitive-behavioral principles. It was developed in the European Research Program SALUT by the University Hospital of Geneva and the software company NetUnion (Lausanne) in Switzerland (www2.salut-ed.org/demo) and was translated into eight languages. SALUT BN was evaluated in 4 independent studies in Switzerland, Sweden, Spain, and Germany (Carrard et al., 2006; Liwowsky, Cebulla & Fichter, 2006, Nevonen et al., 2006, Rouget et al., 2005). About two thirds of the patients (68.9%) experienced a reduction of binge eating episodes after 4 months that could be maintained over a 6-month follow-up period. More than half of the patients (58.6%) achieved a reduction of self-induced vomiting within the first 4 months with further improvement to 60.8% until the end of the program.

The SALUT BN program was adapted for the treatment of BED and the English version was translated into German by the principal investigators of this study.
STUDY GOALS AND OBJECTIVES

2.1 Primary outcome

The primary objective of the study is to assess the efficacy of an Internet-based guided self-help intervention (GSH-I) in the treatment of adult patients with binge-eating-disorder (BED) compared to individual face-to-face cognitive-behavioral therapy (CBT) which is considered state-of-the-art therapy for BED. The primary outcome is the difference in the number of days with objective binge eating episodes (OBEs) over the past 28 days between baseline (T0) and end of treatment after 4 months (20 sessions or up to 20 e-mails) (T2). The number of days with OBEs will be assessed with the Eating Disorder Examination (EDE) interview that specifically refers to the last 28 days.

2.2 Secondary outcomes

Secondary outcomes are changes in eating disorder psychopathology (subscales of the EDE and the DEBQ), depressive symptoms (BDI II), mental comorbidity (SCID-I), quality of life (IWQoL), self-esteem (RSE), physical activity (IPAQ), and body weight between T0 and T1 and between T0 and T2.

Additional treatment objectives are the investigation of differential treatment effects of both treatment arms and of moderators and mediators for treatment response. Moderators include mental comorbidity, personality characteristics (e.g. impulsivity) and the expectation of treatment success. Mediator variables include rapid treatment response regarding the reduction of OBEs and weight-related concerns as measured with the EDE interview at midtreatment and with individual items of the EDE-Q on a weekly basis (12 items on binge eating and eating disorder psychopathology). Also the mediating role of the therapeutic alliance (WAI-S) will be investigated.

Maintenance of treatment response will be investigated 6 months after treatment completion (6-month follow-up).

Audiotaped CBT treatment sessions and printed e-mails (GSH-I) will be analyzed by independent raters using qualitative content analysis.
3 STUDY DESCRIPTION

3.1 Study design

Multicenter, randomized, controlled non-inferiority trial with two parallel arms and blinded assessment of the main outcome variable comparing GSH-I and CBT.

3.2 Trial sites and number of patients

The study will be conducted at 6 trial sites. Participating centers will be the Departments of Psychosomatic Medicine and Psychotherapy of the Universities of Bochum, Erlangen-Nuremberg, Heidelberg, and Tübingen and the Institutes of Clinical Psychology of the Universities of Freiburg and Marburg. A sample size of at least 70 participants per treatment group finishing the study is required. With an expected dropout rate of 20% of study participants, 175 participants need to be included into the study. Each trial site agrees to include 30 patients.

Each trial site will be required to report the number of patients assessed for eligibility to the main study center in Erlangen once a month. Reasons for exclusions must be given for each non-eligible patient. For accomplishing this task a screening form will be made available to the trial sites allowing the transfer of anonymous data to the main study center (Erlangen).

3.3 Blinding and randomization

Neither the therapists/coaches nor the patients will be blind to the treatment arm. The primary outcome variable (see 2.1) and the secondary outcome variables (see 2.2); however, will be assessed at 4 measurement time points from independent assessors who will be blind to treatment allocation.

The randomization procedure will be explained in 5.2. Randomization will be performed centrally by the Coordination Center for Clinical Trials (KKS) in Marburg. Randomization will be done according to the „Dynamic Balanced Design“ (Signorini et al., 1993). After intensive discussion we decided against demographic or psychopathological stratification criteria.

3.4 Expected study duration

The duration of the study per patient amounts to 10 months (+ max. 6 weeks). Longer therapy intervals can occur due to factors such as illness or vacation. Treatment will start within 2 weeks after the baseline assessment (T0) in both treatment arms. Participants will receive 20 individual face-to-face treatment sessions with a therapist in the CBT condition and up to 20 e-mail contacts with a coach over a period of 4 months in the GSH-I condition. The follow-up period will be 6 months.

The recruitment of the 175 patients will be conducted over a period of 22 months starting immediately after the initiation visits at each trial site.

The total study duration will be 42 months (preparation: 6 months, patient recruitment, treatment and follow-up: 32 months, data analyses: 4 months)
3.5 Early termination of study

3.5.1 Early termination at a trial site

The study can be terminated at a trial site if

- the trial site fails to adhere to the requirements set out in the study protocol, even after having been reminded twice (e.g. not enough therapists available, low adherence with study interventions).

- the trial site forwards insufficient data of unsatisfactory quality to the KKS Marburg or if protocol violations occur due to action or failure of the local study coordinator (e.g. CRFs are not filled out correctly, data are not collected at the planned measurement points, data are not forwarded to the KKS)

- the trial site is unable to enroll an adequate number of patients

The principal investigators after consulting with the biostatistician can decide about the exclusion of a trial site. The local ethics committee of the trial site must be notified.

3.5.2 Early termination of entire study

The study will be terminated prematurely if one of the following events occurs:

- New evidence-based findings that suggest alterations in accepted clinical practice and make the continuation the study interventions unwise.

- The necessary logistics can no longer be provided.

- If serious adverse events (SAE) occur, a causality assessment will immediately be done. If there is a reasonable suspected causal relationship to the study treatments or procedures and if the SAE occurs frequently, the study arm or the entire study can be terminated prematurely. The principal investigators together with the DSMB decide about an early termination of the study.

- If patient enrollment is insufficient, new trial sites will be included. If patient enrollment remains inadequate the study will be terminated.

The principal investigators after consulting with the biostatistician can terminate the study. The DSMB has advisory capacity. The local ethics committees must be notified by the trial centers.
4 STUY POPULATION

4.1 Inclusion criteria

• Diagnostic criteria for BED according to DSM-IV or subsyndromal BED (patients can lack one diagnostic criterion, e.g. frequency of less than 2 days with objective binge eating episodes (OBEs), no marked distress, presence of only 2 instead of 3 of the 5 associated criteria, or duration of BED less than 6 months)(see Friederich et al., 2007).

• Age $\geq$ 18 years

• $27 < \text{BMI} < 40 \text{ kg/m}^2$

• Internet access available (at home, Internet cafe, at the trial site)

4.2 Exclusion criteria

• Current bulimia nervosa

• Current substance abuse

• Current suicidal ideation

• Psychotic disorder

• Delusional disorder

• Manic episode

• Ongoing psychotherapy

• Serious unstable medical problems or conditions that influence weight or eating (for example, type 1 diabetes mellitus or thyroid problems)

• Pregnancy or lactation

• Participation in other treatment study

• Insufficient computer skills
5 METHODOLOGY

5.1 Patient information and consent

Information about the study will be provided to the patient in a personal communication avoiding coercion. The patient will be given 24 hours for consideration and decision. It will explicitly be pointed out to the patients that there is a difference between study dropout and treatment dropout and that treatment dropout allows for continued assessments. Informed consent must be given in written form. One copy of the signed consent form is filed in the CRF another copy will be handed to the patient. Only after the patient gave written informed consent the baseline assessment (T0) can be conducted.

5.2 Inclusion into the study

In order to check in- and exclusion criteria assessors will conduct a detailed screening interview with the patient. To standardize this process, a checklist will be made available to all trial sites by the main study center in Erlangen. If the inclusion criteria are fulfilled and if no exclusion criteria are present (see 4.2) patients will be informed about study details (5.1) and will be asked to give their written informed consent. This will be followed by the comprehensive baseline assessment (T0). In addition, individuals who are eligible and who gave written informed consent to participate will be randomized. Eligible patients will be reported to the KKS by fax using a randomization form that needs to be completed and signed. To ensure the concealment of allocation, randomization will be performed centrally by fax by the Coordination Center for Clinical Trials (KKS) in Marburg. The randomization form can be faxed to the KKS at the following times:

Monday through Thursday: 8:00 - 16:00; Friday: 8:00 - 14:00
Koordinierungscentrum für Klinische Studien (KKS)
Philips-Universität Marburg
Karl-v.-Frisch-Str. 4
D-35043 Marburg
Fax: 06421 – 28 66517 (66516)

The time of information of the trial site about the randomization result by the KKS defines the time point of inclusion into the study (ITT population). Treatment should start no later than 2 weeks after inclusion.

5.3 Description of study interventions

Therapy will be given over a period of 4 months each (with a maximum of 6 additional weeks). Each therapist will be responsible for both treatments, as a coach in the GSH-I arm and as a therapist in the CBT arm. Prior to start of treatment therapists will receive training for the GSH-I as well as for the CBT program. The first training sessions will take place before study start. To keep high quality standards, trainings will be offered 3 additional times and in addition throughout the study if needed.
5.3.1 Frequency of therapy sessions/e-mail contacts

<table>
<thead>
<tr>
<th></th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Month 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GSH-I</strong></td>
<td>Duration: 4 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of contact</td>
<td>One face-to-face contact with patient</td>
<td>One weekly e-mail contact with patient</td>
<td>One weekly e-mail contact with patient</td>
<td>One face-to-face contact with patient</td>
</tr>
<tr>
<td></td>
<td>One weekly e-mail contact with patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time flow of the intervention modules</td>
<td>Modules 1-3</td>
<td>Modules 3-6</td>
<td>Modules 6-9</td>
<td>Modules 9-11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Month 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CBT</strong></td>
<td>Duration: 4 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of contact</td>
<td>Twice weekly face-to-face sessions with patient</td>
<td>One weekly face-to-face sessions with patient</td>
<td>One weekly face-to-face sessions with patient</td>
<td>One weekly face-to-face sessions with patient</td>
</tr>
<tr>
<td>Time flow of the intervention phases</td>
<td>Phase 1-2</td>
<td>Phase 2</td>
<td>Phase 2</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>

5.3.2 Internet-based guided self-help (GSH-I)

For this intervention, the Self-Help Guide (Copyright NetUnion & University Hospital of Geneva (HUG)) will be used. The program can be accessed from the patients' home. Patients who do not have internet access at their homes can get access at the trial site. Also the coaches get internet access to monitor their patients' progress. Coaches and participants meet in person twice before the beginning and after the end of treatment. During the first face-to-face session, the coaches explain the program's rational to ensure the correct use of the internet program. Throughout the duration of the treatment (4 months) there will be one message exchange per week between the coach and the patient ("guided self-help") with the goal to provide support and encouragement and to answer upcoming questions. The messages are not considered as a means to perform "psychotherapy by e-mail". The structure and content of the messages written by the coach will follow standardized guidelines and adherence will be supervised by the trial site in Marburg with the help of a checklist.

All assessments (interviews, questionnaires, T0-T3) will be conducted at the respective trial sites also in patients who are randomized to the GSH-I arm.

The internet program consists of 11 modules. Each module combines psychoeducation, behavioral interventions and exercises that participants can complete directly in the program and that will allow to recognize the maintaining factors of the eating disorder. One of the most important exercises is the completion of a diary. Based on these diaries automated feedback will be generated by the program and will inform the participants about the course of their behaviors.
<table>
<thead>
<tr>
<th>Modules</th>
<th>Key exercises/examples</th>
</tr>
</thead>
</table>
| **Module 1:** Preparing for change (motivation module) | • Understanding the mechanisms that perpetuate the eating problem  
• Looking at self-esteem, mental attitude, and interpersonal relationships  
• Advantages and disadvantages of the current behavior  
• Imagining the future after successfully finishing the program  
• Conditions for change |
| **Module 2:** Observing yourself | • My food diary  
• Food diary summary  
• Sabine’s food diary |
| **Module 3:** Understanding and trusting yourself | • The possibility of eating for pleasure  
• Food- and emotion-related triggers for compulsive eating |
| **Module 4:** Finding your own rhythm (goal: a healthy meal pattern) | • Eating regularly and according to my own rhythm  
• Finding my own preferences  
• Giving yourself time |
| **Module 5:** Building up your strategies | • How to prevent compulsive eating  
• Building my own strategy list |
| **Module 6:** Physical activities | • How to get started?  
• What is an “activity break”? |
| **Module 7:** Identifying and solving your problems | • Learning how to solve a problem in separate steps |
| **Module 8:** Self-assertion | • Making a place for yourself in the world  
• Using new assertiveness techniques |
| **Module 9:** Handling your emotions | • Automatic thoughts that trigger these emotions |
| **Module 10:** Changing the way you think | • Becoming more aware of certain cognitive distortions  
• Changing automatic thoughts into realistic thoughts  
• Applying these techniques to thoughts concerning food and your figure |
| **Module 11:** Continuing on your way (relapse prevention) | • Remembering what you have learned and preventing relapses  
• Using some tools in case of a misstep |

---

**SALUT BED**  
Guided Online Self-help Program  
for binge eating disorder

Copyright © 2000-2007 English paper version  

**5.3.3 Modular cognitive-behavioral therapy (CBT) for BED**

For this individual intervention, an existing German manual by Hilbert and Tuschen-Caffier (in press) will be used. Each therapist will receive a copy of the manual. All CBT sessions will be audiotaped and one of four consecutive audiotapes of each participant will be randomly chosen.
(20%) and checked with regard to manual adherence at the trial site in Marburg with the help of a checklist. Feedback will be given to the therapists.

CBT comprises 20 individual sessions and will last 4 months. Participants will receive therapy twice weekly for the first month (sessions 1-8) and once weekly from month 2 to month 4 (sessions 8-20). The treatment sessions will be held at the respective trial sites. As mentioned before treatment duration can be extended up to 6 weeks due to vacation or illnesses.

If a session is canceled, a substitute session will be scheduled, if possible, during the same week. If a patient does not show up without excuse the session will not be replaced and this will be documented in the CRF. Fifty percent of the budgeted cost per session will be available for two sessions that were canceled without replacement.

<table>
<thead>
<tr>
<th>Therapeutic goals</th>
<th>Therapeutic interventions and techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial treatment phase (sessions 1-3)</td>
<td>- motivational enhancement</td>
</tr>
<tr>
<td></td>
<td>- psychoeducation</td>
</tr>
<tr>
<td></td>
<td>- self-monitoring of food intake</td>
</tr>
<tr>
<td></td>
<td>- development of an individual maintenance model</td>
</tr>
<tr>
<td></td>
<td>- goal-setting</td>
</tr>
<tr>
<td></td>
<td>- cognitive interventions for motivation</td>
</tr>
<tr>
<td>Intensive treatment phase (sessions 4-17)</td>
<td>- normalizing eating behavior</td>
</tr>
<tr>
<td></td>
<td>- identification and modification of dysfunctional thoughts and cognitive schemata</td>
</tr>
<tr>
<td></td>
<td>- acquisition of new skills</td>
</tr>
<tr>
<td></td>
<td>- establishment of regular physical activity</td>
</tr>
<tr>
<td></td>
<td><strong>Eating Behavior Module:</strong></td>
</tr>
<tr>
<td></td>
<td>- nutritional management</td>
</tr>
<tr>
<td></td>
<td>- hunger and satiety perception training</td>
</tr>
<tr>
<td></td>
<td>- stimulus control</td>
</tr>
<tr>
<td></td>
<td>- cue exposure</td>
</tr>
<tr>
<td></td>
<td>- hedonics exercise</td>
</tr>
<tr>
<td></td>
<td>- cognitive interventions for negative schemata related to eating behavior</td>
</tr>
<tr>
<td></td>
<td><strong>Body Image Module:</strong></td>
</tr>
<tr>
<td></td>
<td>- body image diary</td>
</tr>
<tr>
<td></td>
<td>- body image exposure</td>
</tr>
<tr>
<td></td>
<td>- exposure to avoided body-related situations</td>
</tr>
<tr>
<td></td>
<td>- shaping regular physical activity</td>
</tr>
<tr>
<td></td>
<td>- cognitive interventions for negative body-related schemata</td>
</tr>
<tr>
<td></td>
<td><strong>Stress Module:</strong></td>
</tr>
<tr>
<td></td>
<td>- stimulus and response control</td>
</tr>
<tr>
<td></td>
<td>- stress management techniques</td>
</tr>
<tr>
<td></td>
<td>- affect regulation techniques</td>
</tr>
<tr>
<td></td>
<td>- interpersonal problem solving</td>
</tr>
<tr>
<td></td>
<td>- social competence training</td>
</tr>
<tr>
<td></td>
<td>- cognitive interventions for further relevant negative schemata</td>
</tr>
<tr>
<td></td>
<td><strong>General techniques used in all modules:</strong></td>
</tr>
<tr>
<td></td>
<td>- psychoeducation</td>
</tr>
<tr>
<td></td>
<td>- self-reinforcement</td>
</tr>
<tr>
<td></td>
<td>- homework, self-monitoring</td>
</tr>
<tr>
<td></td>
<td>- development of realistic expectations concerning potential setbacks of binge eating</td>
</tr>
<tr>
<td></td>
<td>- developing of relapse prevention strategies</td>
</tr>
<tr>
<td>Self-management phase (sessions 18-20)</td>
<td>- patients become their own therapist</td>
</tr>
<tr>
<td></td>
<td>- maintaining progress in the future</td>
</tr>
<tr>
<td></td>
<td>- relapse prevention</td>
</tr>
</tbody>
</table>
5.4 Handling of unexpected physical or mental emergencies

If during treatment the therapists in the CBT condition or the coaches in the GSH-I condition notice a severe deterioration of the mental state of their patient, temporary inpatient treatment should be considered. Special attention needs to be given to the occurrence of suicidal tendencies. If a hospital admission is not considered necessary, two extra outpatient appointments in addition to the study treatment can be offered for crisis intervention. However, the inpatient or additional outpatient treatment must not be conducted by the therapist or coach. Inpatient treatment for mental reasons of more than 1 week and more than two additional outpatient sessions will result in treatment dropout.

5.5 Assessment instruments and follow-up

5.5.1 Routine assessment points

The number of days with OBEs over the past 28 days will be assessed for each patient at baseline (T0), at midtreatment after 10 sessions or 2 months (T1, ± 2 weeks), at the end of treatment after 20 sessions or 4 months (T2, ± 2 weeks), and at follow-up 6 months after T2 (T3, ± 4 weeks) in both treatment arms.

5.5.2 Special assessment points

See Study Schedule on page 8

5.5.3 Description of assessment instruments

Body Mass Index (BMI)

Body height will be measured at baseline (T0), body weight will be measured with a standardized scale at T0, T1, T2, and T3 (it has to be taken into account that the scale used is adequate for obese individuals).

Eating disorder psychopathology

a. Eating Disorder Examination-Interview (EDE-I; Fairburn & Beglin, 1994; German: Hilbert et al., 2007). The EDE-I comprises 6 diagnostic items and 22 items that are summarized to 4 subscales: Restraint, Eating Concerns, Weight Concerns, and Shape Concerns. The EDE has good psychometric properties (internal consistency, retest-reliability, convergent and discriminant validity).

b. Eating Disorder Examination-Questionnaire (EDE-Q, Fairburn & Beglin, 2004; German: Hilbert und Tuschen-Caffier, 2006) represents the questionnaire version of the EDE-I. 12 selected items will be used weekly from T0 to T1, and bi-weekly from T1 to T2 to investigate their importance as mediators of treatment response.

c. Dutch Eating Behavior Questionnaire (DEBQ; Grunert, 1989) was developed to characterize the eating behavior in obese individuals. It consists of 33 Items to be answered on a 5-point scale: Restraint Eating, Emotional Eating, and External Eating. The instrument shows acceptable psychometric properties including internal consistency, retest-reliability, convergent,
factorial and discriminant validity as well as sensitivity to change. Also, reference values are available (Tuschen-Caffier et al., 2005).

d. Eating Hedonics Questionnaire (EHQ; Mitchell et al., 1999) measures hedonic aspects of binge eating episodes and other eating behavior and consists of 9 Items to be answered on a 5-point scale. There is evidence for good discriminant validity. The German version is currently validated by our working group.

Mental comorbidity
Structured Clinical Interview for DSM-IV-Diagnoses (SCID-I; German: Wittchen, Zaudig & Fydrich, 1997) is a structured expert interview for the diagnosis of current and lifetime mental disorders according to DSM-IV criteria. It has well-established intrarater-reliability and validity values. The following modules will be used: affective disorders, anxiety disorders, somatoform disorders, substance use disorders, impulse control disorders.

Depressive symptoms
Beck Depression Inventory (BDI-II; German: Hautzinger, Keller & Kühner, 2006) is a self-report instrument to evaluate the severity of depressive symptoms. It consists of 21 items, which are scored on a 4-point scale. The instrument shows good psychometric properties including internal consistency, convergent and discriminant validity as well as sensitivity to change. Norm values are available.

Self-esteem
Rosenberg Self-Esteem Scale (RSE; Ferring & Filipp, 1996, Collani & Herzberg, 2003) assesses self-esteem on 10 items to be answered on a 4-point scale. The RSE has been shown to have good internal consistency, convergent and discriminant validity and sensitivity to change.

Quality of life
a. Impact of Weight on Quality of Life-Lite (IWQoL-Lite; Kolotkin & Crosby, 2002) is a 31-item, self-report, obesity-specific measure of health-related quality of life (HRQoL) that consists of a total score and scores on each of five subscales - Physical Function, Self-esteem, Sexual Life, Public Distress, and Work. It exhibits strong psychometric properties with good internal consistency, retest-reliability, convergent and discriminant validity and sensitivity to change First results of the validation of the German version support these findings (Müller et al., in preparation).

b. The Clinical Impairment Assessment Questionnaire (CIA, Bohn & Fairburn, 2008), this self-report scale is comprised of 16 items that are rated on a 4-point scale and was developed to evaluate psychosocial impairment due to an eating disorder.

Personality characteristics
a. Adult Temperament Questionnaire (ATQ, Rothbart, 1989, German: Wiltink et al., 2006) consists of 77 items measuring 4 dimensions: Negative Affect, Extraversion, Orienting Sensitivity, and Effortful Control. Regulative temperament was measured by means of the 19-item Effortful Control subscale of the ATQ. The scale is divided into three subscales: inhibitory control, attentional control, and activation control. Participants reported on the extent to which effortful control generally characterize their interactions with the environment.

b. Barratt Impulsiveness Scale-11 (BIS-11; Patton, Stanford & Barratt, 1995; German: Preuss et al., 2008) is a self-administered questionnaire with 30 items, which are scored on a 4-point scale that assesses impulsivity as a multidimensional construct. The scale contains three
subscales representing attentional impulsivity, motor impulsivity, and non-planning impulsivity. The total score has good internal consistency and convergent and discriminant validity.

c. **Reactive temperament** will be measured by means of the Behavioral Inhibition system and Behavioral activation system scales (BIS/BAS; Carver & White, 1994; German: Strobel et al., 2001). The BIS/BAS scales consist of 24 items to be rated on a 4-point scale. The BIS scale measures worry concerning potential punishment in the future and avoidance tendencies and the BAS scale measures enthusiasm in the pursuit of potentially rewarding outcomes and approach tendencies. The BAS scale consists of the three subscales: reward responsiveness, drive and fun seeking.

**Others**

a. **Socio-demographic data**

b. **Reason for participation**: 6 items will evaluate to what degree the patients perceive „control over binge eating“ or „weight reduction“ as the main reason for participation.

c. **Treatment expectations**: 3 items will assess the expectations patients have towards each treatment arm (suitability, expected success, motivation).

d. **Working Alliance Inventory-Short Form** (WAI-S, Busseri & Tyler, 2003) consists of 12 items and assesses key aspects of the therapeutic alliance: agreement on the tasks of therapy, agreement on the goals of therapy, and development of an affective bond. The WAI-S demonstrated good psychometric properties. Der WAI-S has already been used in Internet-based treatment programs (Knaevelsrud & Maercker, 2006). The questionnaire will be given weekly from T0 to T1 and bi-weekly from T1 to T2.

e. **International Physical Activity Questionnaire** (IPAQ; Ainsworth et al., 2000, 2006). The short version of the IPAQ consists of 7 questions measuring the degree of light, moderate, and vigorous physical activity (PA) during the previous seven days. The IPAQ is an internationally and widely used self-report measure for PA determination with good psychometric values.

### 5.6 Protocol violations, treatment dropout, study dropout, and dropout

Every deviation from the study protocol (protocol violation) needs to be documented in the Case Report Form (CRF).

Patients can withdraw their consent to participate in the study at any time without giving a reason. Attrition of the patient can be a consequence of several protocol violations (compare 5.6.1). It has to be differentiated between dropping out of treatment and dropping out of the entire study.

In case of study dropout the patient will be asked to give reasons for the decision to withdraw from the study. These reasons will be documented and forwarded to the KKS in Marburg.

In case of treatment dropout the patient will be explicitly asked if he/she also want to withdraw from further data collection. If the patient wants to also withdraw from further data collection, the patient is a study dropout. If the patient only wants to withdraw from the treatment, data...
collection will proceed as planned. As an exception data collection can be conducted in writing or over the phone. This needs to be explicitly labeled as such in the CRF.

5.6.1 Definition of protocol violations

- Screening failure (patient is randomized despite missing inclusion criteria or the existence of exclusion criteria)
- Withdrawal of consent (study dropout)
- Dropping out of treatment (treatment dropout)
- Less than 15 CBT sessions (≥ 5 sessions = treatment acceptor; ≥ 15 sessions = treatment completer)
- Treatment gaps of > 4 consecutive weeks
- Mental deterioration (e.g. acute suicidal ideation, severe self-injury, severe depressive disorder) necessitating inpatient treatment.
- General: inpatient treatment for mental reasons of more than 1 week and inpatient treatment for physical reasons of more than 2 weeks.
- More than 2 additional outpatient sessions for crisis intervention due to mental reasons.

5.6.2 Definition of dropout

A patient is considered a dropout if the main outcome variable is not available (missing value). Calculation of the main outcome variable requires EDE interviews at baseline and at the end of treatment in order to be able to calculate the difference in number of days with OBEs over the last 28 days.
SAFETY ISSUES

6.1 Benefits, risks, and side effects

Study participation is associated with expected benefits; however it is also associated with time and effort and possible risks and side effects.

Participation in the study requires lengthy and comprehensive diagnostic procedures. Standard treatment offered by psychotherapists in private practice on the other hand is usually associated with an extensive search and long waiting periods.

Treatment duration in the study is limited to 20 sessions and 4 months, respectively, whereas duration of standard treatment in clinical practice can be adapted to the individual needs of the patient.

If a patient is randomized to Internet-based self-help he/she will receive 2 face-to-face contacts with a coach and a once weekly e-mail exchange. The patients can work through the program at their own pace; however, the program requires a high level of personal initiative and motivation of the patients.

The expected benefit of both treatment arms is the putatively better treatment outcome, since both study treatments offer a highly structured program with a strong focus on symptom change which is usually not offered by psychotherapists in private practice. However, standard treatment in private practice offers the opportunity to personalize the treatment.

One advantage of participating in the study is the immediate start of treatment without delay. In private practice patients are usually faced with a waiting period of at least 6 months.

6.2 Adverse events (AE)

6.2.1 Definition

Adverse events are all unfavorable signs, symptoms, or diseases whether or not considered related to the treatment. These include events that require inpatient treatment or exert an influence on eating behavior and weight.

6.2.1 Documentation, reporting, and therapeutic measures

When an adverse event occurs (between 2 treatment sessions or reported in e-mail messages) the local study coordinator at the trial site needs to be informed by the study physician or study psychologist who is treating the patient. Together they need to decide how to proceed. The adverse event has to be documented in the CRF.

6.3 Serious adverse events (SAE)

6.1.1 Definition

Adverse events are considered to be serious if they
• are life-threatening (e.g., acute suicidal ideation)
• result in death
• result in persistent or significant disability/incapacity

(Definition according to ICH-Guidelines E2A, IIB)

6.1.2 Documentation and reporting

Serious adverse events are subject to expedited reporting. The trial site has to complete a SAE form and sent it to the main study center in Erlangen within 24 hours (Tel.: 09131/8545927, Mobil: 0173/8645092, Fax: 09131/8534153). The main study center will inform the members of the DSMB. The main study center is responsible for proper conduct.

The local ethics committee of the trial site that reported the SAE needs to be informed after consultation with the main study center in Erlangen.
7 BIOMETRICAL/STATISTICAL ASPECTS OF THE STUDY

In this chapter the definitions for the statistical analyses will be given.

7.1 Endpoints of the study

7.1.1 Primary endpoint

Primary endpoint for the statistical analysis is the difference in the number of days with OBEs over the last 28 days between baseline (T0) and the end of treatment after 4 months (20 sessions or 20 e-mails) (T2). This variable will be defined as $\Delta$ and will be used as quantitative value in the analyses.

The definitions of dropouts are described in 5.6.2.

7.1.2 Secondary endpoints

Secondary endpoints are changes in BMI, eating disorder psychopathology (subscales of EDE, DEBQ), depressive symptoms (BDI II), mental comorbidity (SCID I), quality of life (IWQoL), self-esteem (RSE), physical activity (IPAQ), and weight.

Additional treatment objectives are the investigation of differential treatment effects of both treatment arms and moderators and mediators for treatment response. Moderators include mental comorbidity, personality characteristics (e.g. impulsivity) and the expectation of treatment success. Mediator variables include rapid treatment response regarding the reduction of OBEs and weight-related concerns as measured with the EDE interview at midtreatment and with individual items of the EDE-Q on a weekly basis (12 items on binge eating and eating disorder psychopathology). Also the mediating role of the therapeutic alliance (WAI-S) will be investigated.

Maintenance of treatment response will be investigated 6 months after treatment completion (6-month follow-up).

Audiotaped CBT treatment sessions and e-mails (GSH-I) will be analyzed by independent raters using qualitative content analysis.

7.2 Statistical modelling of the main research question

7.2.1 Statistical hypotheses – main research question

We expect non-inferiority of the GSH-I intervention toward CBT regarding the reduction in number of days with OBE episodes. In statistical terminology this is a typical non-inferiority approach with one-sided equivalence proof. As non-inferiority margin ($\delta$) one day has been agreed upon (see 7.5) in favor of CBT which was seen as non-relevant difference. Thus, the main research question can be statistically described as follows: ($H_0$) $\Delta_{\text{GSH-I}} \leq \Delta_{\text{KVT}} - \delta$ with the alternative hypothesis of ($H_1$) $\Delta_{\text{GSH-I}} \geq \Delta_{\text{KVT}} - \delta$. The non-inferiority of GSH-I to CBT as reference treatment can be hence shown, if the upper boundary of the corresponding 96% CI of the difference between $\Delta$ in CBT and GSH-I ($\Delta_{\text{CBT}} - \Delta_{\text{GSH-I}}$) is less than 1 day.
7.2.2 Statistical hypotheses – additional research questions

It is expected that patients in both treatment arms (CBT und GSH-I) will not differ significantly with regard to the secondary end points. If we will follow the framework for non-inferiority (7.2.1) also for secondary endpoints depends on the exact research questions put forward for each secondary outcome measure.

7.3 Statistical methods

The standard method in non-inferiority trials for the analysis of quantitative outcomes is a one-sided t-test to compare both therapy groups - if their distributions can be assumed to follow approximately a Gaussian distribution. For the statistical significance level one sets $\alpha = 5\%$. In case of indications of unequal variances between both groups Welch’s variant of the t-test can be applied. In case that the normality assumption may not be justified for the variables to be analyzed one can apply a one-sided non-parametric test to compare two independents samples (often denotes in the literature as Mann-Whitney-Test).

Primary and also secondary outcomes will also be analyzed using the regression approach of linear hierarchical models (random coefficient model), in order to gain additional possibilities to statistically control for possible center or moderator effects. Should there be discrepancies between a simple statistical two-sample test and the application of the regression approach, further analysis should be discussed with the DSMB.

The data sets to be analyzed will be prepared following both the intention-to-treat principle as well as the per-protocol approach. Statistical analyses will be based on both data sets. For non-inferiority hypotheses, the intention-to-treat principle could be less conservative (i.e, it could lead too often to a significant result in favor of non-inferiority). As a consequence of this particular situation in non-inferiority trials, the typical preference for intention-to-treat in classical superiority studies is not given in this case and should be treated with care.

Following the test-oriented approach, leading to a decision with respect to the possible non-inferiority of GSH-I, in another step of the statistical analysis methods for point and interval estimates for the difference in primary and secondary outcomes between both therapy groups will be applied. Interval estimates will be reported via 95% confidence intervals.

7.4 Interim and final analyses

There are no interim statistical analyses planned. Once a month those responsible for data management and randomization will give an update about recruitment (and eventually dropout rate). All further statistical analyses will be conducted after the data base has been closed.

7.5 Estimation of the effect size of the main endpoint

The non-inferiority trial seeks to determine whether GSH-I is not worse than CBT by more than an acceptable amount. The effect size of interest refers to the difference in the number of days
with OBEs over a 28-day period in each treatment arm. Of special importance is the
determination of the magnitude of difference of this main endpoint between treatment arms
which can be considered acceptable.

Given a lack of research supporting an evidence-based non-inferiority margin, in-depth study of
the relevant literature and intensive discussions with international clinical experts were carried
out. A difference of one day with OBEs of Δ CBT minus Δ GSH-I was considered as non-
relevant difference. Thus, we specified a pre-stated non-inferiority margin (δ) of one OBE day in
favor of CBT.

7.6 Sample size calculation

For sample size calculation in this non-inferiority trial several assumptions were made: the
significance level was set at α = 5%, we aimed at a statistical power of 80%, and we defined a
non-inferiority margin (δ) of one day for the main endpoint between study arms (see 7.5). Based
on the results of previous studies we assumed a standard deviation of 2.37 days in both groups
for the number of binge eating days over a 28 day time period. Based on these assumptions a
sample size of at least 70 participants per group is required.

Allowing for a dropout rate of 20% of study participants from T0 to T2, 175 participants need to
be recruited overall. The assumed dropout rate is based on the results of as recent meta-
analysis in this area (Sysko & Walsh, 2008), showing that 78-87.5% of participants complete a
trial as planned.
8 ASSOCIATED RESEARCH PROJECTS

1. Molecular genetics, metabolomics and epigenetics (Hebebrand, Essen; Frielings, Hannover).
   Also supported by the BMBF grant

2. Diagnostic validity of binge eating disorder (BED) (Hilbert, Marburg; de Zwaan, Erlangen).
   Submission to the DFG

3. Assessing cost-effectiveness of treatments in cooperation with Prof. König (Leipzig):
   - To estimate costs, the overall health resource utilization as well as productivity loss
     will be operationalized using the Client Sociodemographic and Service Receipt
     Inventory (CSSRI; Chisholm et al., 2000). Assessments will be conducted at T0, T2,
     and T3.
9 ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the Declaration of Helsinki (1996). The study protocol will be submitted to the ethics committees of all trial sites. A trial site can start with patient enrollment only after having received approval from the local ethics committee and after having sent the approval letter to the KKS in Marburg.

Amendments to the study protocol must be submitted to all ethics committees and approval must be received. Modifications to the study protocol that need approval must not be implemented without a positive decision of the ethics committees.
10 ORGANISATION

10.1 Documentation

Documentation of data in the CRF

The trial sites will receive a Case Report Form (CRF) for each patient. All data will be documented in the CRF without the patient’s name. Each patient will receive a number. If it is necessary for safety or legal reasons to gain knowledge about the identity of a patient, study coordinators and study physicians/psychologists will treat this with utmost confidentiality. Entries in the CRF must be done with blue or black ball pen to ensure readability on the carbon copies.

All data required in the study protocol must be made available by the trial sites. Missing data must be justified:

| n | d | not done |
| n | v | not available |
| n | z | not applicable |

Corrections should be done by crossing out the wrong CRF entry with a single horizontal line in order to maintain readability. The new correct entry should be written next to it. The new correct entry needs to be signed by an authorized member of the study team with initials and date:

Example:

wrong date

251102
30503
TT MM JJ

23.05.03 TM

All trial sites will receive instructions for the documentation of data in the CRFs during the initiation visit (see monitoring 10.3).

Only certified CRFs may be forwarded to the KKS Marburg since only certified CRFs can be entered into the database. The same procedure applies to completed queries.

10.2 Data management

The database will be set up at the KKS in Marburg. Data entry will be done by employees of the KKS. Data quality management includes automatic data checks, queries, query handling, and audit trail. The trial sites are required to clarify or explain the queries. The data management will follow the SOPs generated by the KKS Marburg.

Some of the questionnaires in the GSH-I group will be given via the internet and will be stored directly on the server of NetUnion in Switzerland. The KKS Marburg regularly receives an export of these data sources and will bring together individual patient-related data.

10.3 Monitoring

As an instrument of quality control and quality assurance, the study will be monitored according to GCP criteria. Each trial site receives a minimum of 3 monitoring visits, including an initiation visit and a close-out visit. The trial site can enroll patients only after the initiation visit. A second visit will be carried out halfway through the study and will be adapted to the course of the study.
at the respective trial site. After the end of the study (completion of data collection) a close-out
visit will take place. The time points for the monitoring visits will be individually scheduled with
the trial sites. The necessary data and documents must be made available to the monitor to
allow for speedy and efficient work according to GCP criteria. A team member who is familiar
with the study must be at the monitor’s disposal during the visit. The local study coordinator
should also be available for a certain time period during the monitoring visit.
11 ADMINISTRATIVE REGULATIONS

11.1 Amendments to the study protocol

If amendments to the study influence the safety of the participants or the scope and scientific quality of the clinical trial, they have to be submitted to the ethics committees of all participating trial sites. A copy of the approval of the ethics committees constitutes an integral part of the study protocol and must be forwarded to the KKS.

11.2 Budget and insurance

The study is funded by a grant from the German Federal Ministry of Education and Research (BMBF, project number 01GV0601). A patient insurance is not required for psychotherapy trials.

11.3 Handling of data and storage of study documents

Data security and safety regulations require that all patient-related medical data are stored in a pseudonymized manner, with a 4 digit patient identification number without mentioning the patient's name or address. All electronically stored data are secured by a password and data transfer will be done in an encrypted way.

All data and documents relevant to the study will be stored at each trial site for at least 10 years after the end of the study. This relates to written and to electronic material.

11.4 Publication agreement

The publication rights stay with the principal investigators who will confer with the respective local study coordinators at the trial sites. Written publications concerning study results must mention all trial sites and at least one researcher from each trial site as a co-author. The publication of the main outcome paper will include one person as co-author from each trial site that contributed more than 5% of analyzable patients to the study. After consultation with the principal investigators, researchers from each trial sites can publish on specific and agreed upon topics.

(see also cooperation treaty of EDNET)
12 APPROVAL AND SIGNATURES

Approval of the protocol

“I approve the study protocol in its final version.”

Date: ________________________________

Principal investigator: ________________________________

Date: ________________________________

Biostatistician: ________________________________

Approval of the protocol (trial sites)

“I confirm that I have read and understood all parts of the final study protocol. I commit myself to make sure that all patients enrolled at our trial site will be treated, observed and documented according to the requirements of the study protocol.”

Date: ________________________________

Local study coordinator: ________________________________

Signature: ________________________________
13 References


RELEVANT GUIDELINES

AMENDMENTS

There are 3 amendments to the study protocol which were submitted to and approved by the ethics committees of all trial sites.

AMENDMENT 1 (March 11, 2011)

1. Trial site
The co-PI Anja Hilbert started a new position in Fribourg/Switzerland. The Department of Psychology at the University Fribourg was added as a trial site.

2. Exclusion criteria (study protocol 4.2)
Only a “current” manic episode is an exclusion criterion

3. Specification of measurement points (see study schedule on page 8 and study protocol 5.5.1)
A figure was created to better depict the measurement points in both treatment conditions.

4. Assessment instruments (see study schedule on page 8 and study protocol 5.5.3)
The following modifications concerning assessment instruments were realized before study start. This did not substantially prolong the assessment procedure per patient.
- Self-report on socio-demographic data, weight history, and treatment history.
- Eating Disorder Examination - Questionnaire (EDE-Q, Fairburn & Beglin, 2004; German: Hilbert und Tuschen-Caffier, 2006). Besides item 1-12 also items 19-28 will be used.
- The Barrett Impulsiveness Scale will be dropped.
- The Eating Hedonics Questionnaire (EHQ) will be dropped.
- As additional personality inventory the NEO-FFI according to Costa & McCrae (Borkenau & Ostendorf, 1993) will be used. The multidimensional personality inventory comprises the dimensions Neuroticism; Extraversion, Openness, Agreeableness, and Conscientiousness.
The presence of adult ADHD will be screened by using 2 instruments. Recent results point towards a significant association between ADHD, obesity and binge eating in adulthood.

- Wender-Utah-Rating-Scale short version (WURS-K; Rösler et al., 2008) for the retrospective assessment of ADHD symptomatology in childhood.
- Self-report scale to assess ADHD symptoms in adulthood (ADHS-SB; Rösler et al., 2008)

At follow-up and after treatment dropout an additional short follow-up interview will be used with the goal to assess health care utilization (e.g. psychotherapy) since the last visit.

5. Internet-based guided self-help (study protocol 5.3.2)
In case of vacation or illness (no internet access) there can be deviations from the weekly e-mail messages between patient and coach.
Adherence to the content and structure of the e-mails will be supervised at the trial site in Erlangen (instead of Marburg) with the help of a checklist.

6. CBT treatment (study protocol 5.3.3)
In order to specify and standardize the CBT treatment a written guideline was developed by Anja Hilbert.
For content reasons it will be possible to conduct 100-minute sessions, specifically for special interventions such as mirror confrontation. In order to reach a total of 20 50-minute sessions treatment needs then to be tapered off with one session every other week during the last month of treatment.

7. Reporting of serious adverse events (study protocol 6.1.2)
According to information of the Center for Clinical Studies (CCS) in Erlangen expedited reporting of SAE to the main study center in Erlangen, the DSMB, and the ethics committee is necessary only for serious events that are considered related to the study treatment and procedures. Thus, we will change the reporting requirements and modify the forms already available in the CRF.

8. Reimbursement of patients
After treatment dropout the willingness to participate in further assessments appears to be low.
In order to avoid missing data we will reimburse the patients for their time and effort by using the following graduated pricing system depending on the completeness of the measurements. In addition, all patients will be reimbursed for participation at the 6-month follow-up assessment point. The maximum reimbursement per assessment point can be 50 Euros.

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main outcome variable (number of OBEs over the last 28 days)</td>
<td>10€</td>
</tr>
<tr>
<td>EDE-Interview</td>
<td>20 €</td>
</tr>
<tr>
<td>EDE-Interview and SCID-Interview</td>
<td>30 €</td>
</tr>
<tr>
<td>Questionnaires completed</td>
<td>20 €</td>
</tr>
</tbody>
</table>
### Revised study schedule: measurement points and assessment instruments including modifications outlined in amendment 1 and 2

<table>
<thead>
<tr>
<th>Assessment Instrument</th>
<th>Baseline T0 prior to randomization</th>
<th>Midtreatment T1 after 10 sessions or 2 months after randomization</th>
<th>End of treatment T2 after 20 sessions or 4 months after randomization</th>
<th>Follow-up T3 6 months after T2</th>
<th>Long-term follow-up T4 up to 5-years after T2</th>
<th>Weekly until T1, bi-weekly until T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-report for socio-economic data, treatment history and weight history</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight, Body Mass Index (BMI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eating Disorder Examination - Interview (EDE)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch Eating Behavior Questionnaire (DEBQ)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structured Clinical Interview for DSM IV (SCID-I)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beck Depression Inventory II (BDI II)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenberg Self-esteem Scale (RSE)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impact of Weight on Quality of Life (IWQOL-Lite)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Impairment Assessment Questionnaire (CIA)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Activity (IPAQ)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eating Disorder Examination – Q (12 items)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working Alliance Inventory - Short Form (WAI-S)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personality dimensions (ATQ, NEO-FFI, BIS/BAS)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening for ADHD (ADHS-SB, WURS-k)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feedback forms</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health care utilization (CSSRI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal reasons for participation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment expectations</td>
<td>X**</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short Follow-up interview</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
AMENDMENT 2 (July 1, 2011)

Longer-term follow-ups (see study schedule on page 8 and study protocol 5.5.1)

Approval for longer-term follow-up assessments up to 5-years after the end of treatment was applied for. Variables to be assessed at longer-term follow-up assessments are depicted in the study schedule of amendment 1 as T4.

Longer-term follow-ups were no included in the original study protocol because the funding period of the BMBF was limited to 3 years. Longer-term follow-ups are important to evaluate maintenance of change

AMENDMENT 3 (October 8, 2012)

1. Per-protocol treatment completion (study protocol 5.6.1)

Based on recent published study results (Wilson et al., 2010, Carrard et al., 2011) per protocol treatment completion will be defined as attendance at 12 of 20 CBT treatment session (≥ 60% of treatment time). For GSH-I attendance will be counted if a participant has logged in until week 10 (time between activation of the program and last login).

2. Longer-term follow-up (T4)

An additional 1.5-year follow-up assessment was funded by the BMBF and will now be conducted. The funding letter was received on September 24, 2012.
Statistical Analysis Plan

INTERBED: Internet-based guided Self-help for Overweight and Obese patients with Binge-Eating Disorder

A Multi-Center, Randomized Controlled Trial

Andreas Mayr
Institut für Medizininformatik, Biometrie und Epidemiologie
Friedrich-Alexander Universität Erlangen-Nürnberg
22/05/2014

Responsibilities

- Principal Investigators:
  - Prof. Dr. Martina de Zwaan
  - Prof. Dr. Anja Hilbert

- Statistical Analysis
  - Prof. Dr. Olaf Gefeller
  - Dr. Andreas Mayr

- Coordination and Monitoring:
  - Dipl.-Psych. Frauke Schmid
- Data management and randomization

[Signatures]
1. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BED</td>
<td>Binge eating disorder</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>GSH-I</td>
<td>Internet-based guided self-help</td>
</tr>
<tr>
<td>CBT</td>
<td>Cognitive-behavioural therapy</td>
</tr>
<tr>
<td>OBEs</td>
<td>Objective binge eating episodes</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent to treat principle</td>
</tr>
<tr>
<td>FAS</td>
<td>Full analysis set</td>
</tr>
<tr>
<td>PPS</td>
<td>Per protocol set</td>
</tr>
<tr>
<td>SAF</td>
<td>Safety analysis set</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
</tbody>
</table>

2. General remarks

The aim of this statistical analysis plan is to further specify the planned analysis of the INTERBED study. The general framework for the analysis (including the specification of the non-inferiority margin) was adapted from the study protocol.

This document was written prior to study conclusion without further knowledge of any outcome data.

3. Study design

The underlying design of the INTEBED study is given as follows: The study is a multi-center, randomized, non-inferiority trial with two parallel arms. Patients suffer from binge eating disorder (BED) and have body mass index (BMI) between 27 and
40 kg/m². A total of 178 patients were randomized at 7 centers in Germany and Switzerland.

3.1. Randomization

Individuals who met the respective inclusion criteria and who gave written informed consent to participate were randomized. There were no stratification criteria. To ensure the concealment of allocation, randomization was performed centrally via fax by the Coordination Center for Clinical Trials (KKS) in Marburg. Eligibility assessment, obtaining informed consents, and enrolling the participants in the study was done by the respective study centers.

3.2. Blinding

Treatment and assessment were separated. Therapists and coaches are not involved in assessing treatment outcome and assessors are not allowed to hold treatment sessions or write e-mails. The statistician who will conduct the statistical analyses was not involved in randomization. Treatment allocation is not disclosed to the statistician until all data checks will be completed.

3.3. Time points of measurements

\[
\begin{align*}
T0 & \quad \text{Baseline: Beginning of treatment; first treatment session of CBT patients,} \\
& \quad \text{first face-to-face session for GSH-I patients; activation of Internet program.} \\
T1 & \quad \text{Mid treatment: CBT: 10^{th} session, GSH-I 2 months} \\
T2 & \quad \text{End of treatment: CBT: 20^{th} session, GSH-I 4 months} \\
T3 & \quad \text{Follow up: 6 months after T2}
\end{align*}
\]
T4 Follow up: 12 months after T3

4. Primary aim of the analysis

The main aim of the analysis is to investigate the efficacy of an Internet-based guided self-help program (GSH-I) compared to the reference treatment individual cognitive-behavioral therapy (CBT). The study was designed to test the non-inferiority of GSH-I compared to CBT.

The primary outcome variable is difference in the number of binge eating days over the past 28 days compared to baseline (T0). The main confirmatory analysis will be based on the evaluation of the primary outcome after four months of treatment (T2). Additionally, maintenance of outcome was assessed six (T3) and 18 (T4) months after the end of treatment and will be evaluated in a longitudinal analysis, including also the mid-treatment measurement (T1).

Secondary outcome measures include the specific eating disorder psychopathology, general psychopathology, body weight, quality of life and self-esteem. For the secondary outcome measures, we do not assume to find any differences between the two therapies and will hence follow a standard explorative.

5. Endpoints and hypotheses

5.1. Primary endpoint

The primary outcome $\Delta$ is the difference in the number of days with OBEs over the past 28 days between baseline (randomization, T0) and the end of treatment (T2):

$$\Delta := \text{number of days with OBEs (T0)} - \text{number of days with OBEs (T2)}$$

The main instrument to assess treatment efficacy is hence the difference between $\Delta$ in both treatment groups: Estimators and confidence intervals (CIs) for $\Delta$ (also for the other time points of measurement) will be reported.

The study is designed as a non-inferiority trial with a non-inferiority margin of 1 day with OBEs (d) in favor of CBT. Given a lack of research supporting an evidence-
based non-inferiority margin, this margin of 1 day has been agreed upon in discussions with clinical experts during the planning of the study (for details see the study protocol).

The one-sided null hypothesis tested with a significance level of 2.5% in the confirmatory analysis of the primary endpoint therefore is

- \((H_0) \ \Delta \text{GSH-I} \leq \Delta \text{CBT-d}\)

with the alternative hypothesis of

- \((H_1) \ \Delta \text{GSH-I} > \Delta \text{CBT-d}\).

The non-inferiority of GSH-I compared to CBT as reference treatment can be hence shown, if the upper boundary of the corresponding 95% CI of the difference between \(\Delta\) in CBT and GSH-I (\(\Delta \text{CBT} - \Delta \text{GSH-I}\)) is less than 1 day.

If non-inferiority was shown, we will subsequently test GSH-I for superiority: Superiority of GSH-I is shown if the upper boundary of the corresponding 95% CI is also less than 0. For details on those different scenarios of observed treatment differences in non-inferiority trials, see the corresponding explanations in the extension of the CONSORT 2010 statement [1].

Note that the non-inferiority margin was defined in the study protocol for the assessment of the primary endpoint at T2. However, we will also analyse the maintenance of treatment effect in a longitudinal analysis of the primary endpoint, based on the measurements from T1 to T4.

5.2. Secondary Endpoints

For the secondary endpoints we do not follow the framework for non-inferiority and do not suspect a superiority of any of the treatments. We will therefore consider an explorative analysis based on the null hypothesis of no difference between the two therapies.

The (two-sided) null hypotheses tested with a significance level of 5% for the explorative analysis of secondary endpoints is hence

- \((H_0) \ \text{outcome GSH-I} = \text{outcome CBT}\)

with the alternative hypotheses

- \((H_1) \ \text{outcome GSH-I} \neq \text{outcome CBT}\).
5.2.1 Categorical binge-eating endpoints

Consistent with previous research [2], following categorical endpoints regarding binge eating will be determined throughout the study:

- Recovered: No OBEs in the past 28 days.
- Remitted: Fewer than 4 days with OBEs in the past 28 days.
- Improved: Being at or below a comparative level of the global EDE score.

5.2.2 Secondary clinical outcomes

Additional clinical secondary outcome measures are the weight of the patient assessed using the body mass index (BMI), associated eating-related psychopathology measured using the EDE subscales (restraint, eating concerns, shape and weight concerns), psychiatric comorbidity (number of diagnoses or any/none) assessed using the Structured Clinical Interview for DSM-IV diagnoses (SCID-I), severity of depression measured using the Beck Depression Inventory II (BDI-II), and self-esteem measured using the Rosenberg Self-Esteem Scale (RSE). Quality of life is measured using the Impact of Weight on Quality of Life Scale-Lite (IWQOL-Lite) and the Clinical Impairment Assessment (CIA).

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>EDE</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>SCID-I</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>BDI-II</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>RSE</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>IWQOL</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>CIA</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Table 1: Assessment of secondary outcome measures

BMI = Body mass index, EDE = Eating Disorder Examination, SCID-I = Structured Clinical Interview for DSM-IV, axis I diagnoses, BDI-II = Beck Depression Inventory, RSE = Rosenberg Self-Esteem Scale, IWQOL = Impact of Weight on Quality of Life-Lite,
CIA=Clinical Impairment Assessment.

6. Statistical Analysis

6.1. Data sets

- Safety analysis set (SAF): Contains all randomized patients with at least one treatment session. The SAF is the basis for the safety analysis.

- Full analysis set (FAS): Contains all randomised patients with sufficient information at base-line (T0) and at least one post-baseline measurement.

The FAS is the basis for the analysis following a modified intent-to-treat approach. The intention-to-treat principle implies that the primary analysis should include all randomised subjects. In practice this ideal is difficult to achieve: The term 'full analysis set' is used to describe the analysis set which is as complete as possible and as close as possible to the intention-to-treat ideal of including all randomised subjects (compare to the ICH E9 Guidelines [3]). In our case, were the main outcome measure (primary endpoint \(\Delta\)) is based on the difference in OBEs from T2 to T0, we additionally need at least one post baseline measurement in order to make any meaningful assessment.

In our case, patients are eliminated from this set, if

- they did not fulfil the most important inclusion criteria at baseline (severe screening failure).

- the items necessary to assess the primary endpoint at T0 (baseline) are missing.

- they do not have any data regarding the primary endpoint post randomization due to drop-out in the initial study phase (i.e., T1, T2, T3 and T4 missing).

- Per-protocol set (PPS): Contains all patients of the FAS which have been treated according to the protocol. The PPS is the basis for the confirmatory analysis following the per-protocol approach.

Patients are excluded, if
they did not receive sufficient treatment: less than 12 sessions for the CBT group or less than 10 weeks of using the Internet-based guided self-help (measured by time between creation of account and last login or last E-mail contact with coach) until the assessment of T2.

the items necessary to assess the primary endpoint are missing at T2 (end of treatment), the assessment at T2 did not take place between 10 and 26 weeks after randomization (as defined in the study protocol) or more than 8 weeks after end of treatment. If T2 is missing (or was not assessed in the ranges described above) but T1 took place at least 10 weeks after randomization this measurement is considered as T2 if the patient did receive sufficient treatment up to this point (following the definition from the point above).

they did receive new medication during treatment (between T0 and T2) which affects OBEs.

they did receive more than 1 week inpatient psychiatric treatment or more than 2 weeks inpatient treatment for somatic symptoms between T0 and T2.

they did receive more than 2 times out-patient treatment for acute crisis intervention (regarding psychiatric symptoms) between T0 and T2.

It is obvious, that the ‘sufficient treatment’ criterion (as defined in the study protocol) is easier to fulfill for patients in the GSH-I group, as they are not effectively controlled if they did use the available treatment sufficiently. For patients in the GSH-I group, it could be enough to be logged in once around 10 weeks after the account is created (which, however, is unlikely). We accept this inequality in the PPS definition for both groups as it can be considered conservative to exclude fewer patients with GSH-I due to insufficient treatment than with the reference treatment CBT.

For the non-inferiority hypothesis, the per-protocol approach is primarily employed to avoid a potential bias toward equivalence resulting from (modified) intent-to-treat in this specific setting [1]. Additionally, the same analysis is repeated on the FAS (following the intention-to-treat principle) for sensitivity reasons.
6.2. Data cleaning and imputation of missing items

Data management, validation and checks for plausibility are not part of this statistical analysis plan, as this is part of the responsibility of the KKS Marburg.

Missing items in psychological scores (as most secondary outcome measures) will be treated as specified in the corresponding manual or based on literature describing the practical usage of the score.

For the PPS data set no imputation of the primary endpoint (number of binge eating days) is planned. However, in case that T2 is missing and T1 took place at least 10 weeks after T0, this observation is considered as T2 if the patient did receive sufficient treatment up to this point.

For the FAS set, following the modified ITT principle, a missing primary endpoint at T2 can be imputed by the last valid observation at T1 (last observation carried forward) if this is necessary for the statistical analysis (i.e., for the analysis of change scores for the cross-sectional analysis at T2). This procedure can be considered conservative under the null hypothesis that CBT is more effective than GSH-I and that more patients from the GSH-I group are lost than from the control group. However, if in a graphical analysis severe differences between T1 and T2 are found, alternatively a regression based (multiple) imputation of T2 given T1, T0 and treatment will be considered.

However, this statistical analysis plan will also provide statistical methodology which is relatively robust for missing outcomes at specific time points (hierarchical longitudinal modelling). With these approaches, also the FAS will be analysed without imputation of the primary endpoint.

For the secondary endpoints, the decision if imputation of missing values is necessary for the cross-sectional analysis will be made based on the completeness of the corresponding variables. This holds also true for variables that are included as possible confounders in regression models for the primary endpoint.

6.3 Descriptive analysis

Descriptive analyses will be carried out both for the complete data set as well as both study arms separately. For continuous measures mean values, standard
deviation, median values, quartiles, minimum and maximum will be reported. For dichotomous or categorical variables, we will report absolute numbers of patients as well as proportions/percentages. Graphical analysis will report the evolution of recover/remitter/improver rates, BEDs or the BMI of patients from both groups throughout the study.

6.4. Analysis of primary endpoint

6.4.1. Confirmatory non-inferiority analysis (cross-sectional)

The statistical analysis of the primary endpoint Δ (number of days with OBEs in the last 28 days before T0 – number of days with OBEs in the last 28 days before T2) aims at testing for non-inferiority of the GSH-I intervention compared to CBT, taking a non-inferiority margin of 1 day with OBEs into account. The analysis will be carried out both on the PPS and FAS in order to avoid a possible bias from the ITT principle in this specific setting.

The study protocol proposes the two-sample t-test (which was used for the sample size computation) or the non-parametric Mann-Whitney Wilcoxon test (if the outcome does not asymptotically follow a normal distribution). However, in order to adjust for possible group differences at baseline, we will consider multivariable regression analysis for the confirmatory analysis.

The outcome variable $Y_i$ is the difference of binge days $\Delta$ of patient $i$ while the grouping variable (treatment coded as 1 for CBT and 0 for GSH-I) will serve as predictor. Additionally, relevant influential variables from baseline are included in the model ($x_i^T \beta$) to adjust for possible group differences (e.g., BMI, OBEs at baseline, BDI and EDE total score). The definite decision on the included variables will be based on graphical analysis of group differences.

The model can be then written as

$$Y_i = \beta_0 + \beta_1 \cdot \text{treatment}_i + x_i^T \beta + \varepsilon_i$$

where $\beta_0$ denotes the intercept and $\varepsilon_i$ is an error term.

The coefficient for the treatment variable ($\beta_1$) represents an estimate for $\Delta$ CBT – $\Delta$ GSH-I. A two-sided 95% confidence interval (CI) is computed for $\beta_1$. If the upper boundary of the CI is below the non-inferiority margin of one day, non-inferiority of
GSH-I compared to the reference treatment CBT has been shown with significance level of 2.5%. Following the extension of the CONSORT 2010 statement for non-inferiority trials [1], we will additionally provide a figure relating the CI to the non-inferiority margin.

If the distribution of the error term ε does not asymptotically follow a normal distribution (which could lead to a bias in the estimated CIs) non-parametric CIs are computed based on resampling techniques (e.g., bootstrapping). The definite decision on the distribution of the error term, however, can only be made after fitting the model (based on graphical model diagnostics on the residuals).

6.4.2. Explorative longitudinal analysis of the primary endpoint

To evaluate the maintenance of treatment effect, we will carry out an exploratory longitudinal and multivariable regression analysis. As outcome variable we choose the difference Δ of OBE days within the past 28 days in order to maintain the same interpretation as in the confirmatory analysis of the primary outcome at T2: While it could be also possible to directly model the number of OBEs from T0 to T4 via regression models for count data [4], this approach would have the disadvantage that the treatment effect could no longer be related to the non-inferiority margin of 1 day (due to the log-link of count-data models which leads to multiplicative effects of coefficients in the additive predictor). To avoid this drawback, for the longitudinal analysis we therefore also take the difference Δ of OBE days towards baseline (T0) throughout the study (T1 to T4) into account.

The outcome variable $Y_{ij}$ hence represents the difference of binge days $\Delta_{ij}$ for patient $i$ at time point $j$, $j \in \{1,2,3,4\}$. To adjust for the repeated measurements (and the resulting dependence between observations of a single patient) we will include patient-specific random effects $\theta_i$ in the model. This longitudinal modelling approach builds up a design matrix with one row for each measurement instead for each patient. A missing outcome (e.g., at the follow-up measurements T3 or T4) therefore does not lead to the deletion of the patient as with standard change-score analysis.

The model can be then written as

$$Y_{ij} = \theta_i + \beta_{1j} \cdot \text{treatment}_i \cdot \text{time}_j + \beta_{2j} \cdot \text{time}_j + x_i^T \beta + \epsilon_{ij}$$
where $\theta_i$ is the subject specific random intercept, time$_j$ represents the time point $j \in \{1, 2, 3, 4\}$ and treatment$_i \cdot$ time$_j$ is the treatment effect at different time points (treatment is coded as 1 for CBT and 0 for GSH-I). For the time variable, categories for each time point (via different indicator variables) are built. As a result, the estimated treatment effect, represented by $\beta_{1j}$, will consist of different coefficients for each time point (T1, T2, T3 and T4). The term $x_{ij}^T \beta$ represents additional subject-specific, time-constant effects (including possible predictor variables that were assessed pre-treatment, e.g., OBEs at baseline, BMI, BDI and EDE total score.

Two-sided 95% CIs for the treatment effect $\beta_{1j}$, are computed for the different time-points. Additionally, Likelihood ratio tests can be applied to test for an overall treatment effect over all different time points.

### 6.5. Explorative analysis of secondary endpoints

The explorative analysis of secondary endpoints will follow a two-step approach, similar to the one of the primary endpoint. First, a cross-sectional regression analysis will assess post-treatment differences at T2 while adjusting for the corresponding values at baseline. In a second step, we will also analyse the complete data set with all measurements from T1 to T4 based on a longitudinal regression analysis.

#### 6.5.1 Cross-sectional analysis at T2

The cross-sectional analysis for the secondary endpoints will be based on a multivariable regression model, similar to the one of the confirmatory analysis of the primary endpoint.

The response variable $Y_i$ is the corresponding secondary outcome for patient $i$. The grouping variable (treatment coded as 1 for CBT and 0 for GSH-I) will serve as predictor. Additionally, the corresponding baseline measurement (T0) and other relevant influential variables from baseline are included in the model ($x_{i}^T \beta$) to adjust for possible group differences (e.g., age, OBEs, EDE total score, BDI).
The model can be then written as

\[ Y_i = \beta_0 + \beta_1 \cdot treatment_i + x_i^T \beta + \varepsilon_i \]

where \( \beta_0 \) denotes the intercept and \( \varepsilon_i \) is an error term. The coefficient for the \( treatment \) variable (\( \beta_1 \)) hence represents an estimate for the difference between the two treatment groups. This estimate for \( \beta_1 \) and 95% CIs or corresponding tests comparing \( \beta_1 \) to zero are reported.

Graphical analysis of the outcome variable and model diagnostics will be used to determine the applied response distribution for the regression model, as well as to check for the distributional assumptions of the error term \( \varepsilon_i \) (residual diagnostics). In case of the categorical binge-eating endpoints we will apply generalized linear models via the log odds ratios.

### 6.5.2 Longitudinal analysis for T1 to T4

Similar to the primary endpoint, we will also carry out an explorative longitudinal analysis of the secondary endpoints, taking the measurement from T1 to T4 to account.

The outcome variable \( Y_{ij} \) now represents the secondary outcome of patient \( i \) at time point \( j, j \in \{1,2,3,4\} \). To adjust for the longitudinal data structure, we will include patient-specific random effects \( \theta_i \) in the model.

The model can be written as

\[ Y_{ij} = \theta_i + \beta_{1j} \cdot treatment_i \cdot time_j + \beta_{2j} \cdot time_j + x_{ij}^T \beta + \varepsilon_{ij} \]

where \( \theta_i \) is the subject specific random intercept, \( time_j \) represents the time point \( j \in \{1,2,3,4\} \) and \( treatment_i \cdot time_j \) is the treatment effect at different time points. The term \( x_{ij}^T \beta \) represents additional subject-specific, time-constant effects from baseline (e.g., age, OBEs, EDE total score, BDI and the corresponding outcome at T0).

For the categorical and binary outcomes, marginal models with a similar structure based on generalized estimation equations can be considered if the generalized linear mixed effect model approach does not converge (for a similar approach see [2]).

Two-sided 95% CIs for the treatment effect \( \beta_{1j} \) are computed for the different time-
points. Additionally, Likelihood ratio tests can be applied to test for an overall treatment effect over all time points.

6.6. Sensitivity analyses

For sensitivity reasons the confirmatory analyses will be carried out and reported both for the PPS and FAS data set.

Furthermore, statistical models for primary and secondary endpoints will be re-fitted including a center-specific random intercept to adjust for possible center effects. If imputation of the primary or secondary outcomes was necessary for the FAS set, for sensitivity reasons also differing imputation approaches like regression based multiple imputation or baseline value carried forward (for secondary outcome measures) will be considered to analyse the impact of the imputation scheme.

6.7. Safety analysis

The occurrence of adverse events during or after treatment will be analysed for both treatment groups based on the SAF set. Categorization of adverse events (regarding seriousness) will be done by a team of clinical experts including the principal investigators of the study. Descriptive analysis will be based on the number and type of adverse events, as well as the time to occurrence.

6.8. Analysis of practicality of treatment and compliance

Further analysis will focus on the practicality of the two treatments regarding also the compliance of patients: Descriptive analysis will be based on the time to drop-out, the number of missing treatment sessions and the average time spent on the treatment (regarding the log-In times and time between e-mail contact for the GSH-I and the average treatment session times for CBT). The satisfaction of patient with the treatment will be assessed via feedback questionnaires. For GSH-I, the number of e-mails and the number of completed modules will be analysed.

6.9. Analysis of cost-effectiveness

In an associated analysis, which is not part of this statistical analysis plan, the cost-effectiveness of treatment is assessed by calculating the direct and indirect costs of
both treatment conditions.

6.10. Statistical Software

All statistical analysis will be carried out using SAS and the open source statistical programming environment R.

6.11. Tables and Figures

Table 1: Baseline characteristics (Descriptive, both groups and complete sample)

Table 2: Results cross-sectional analysis (Primary + secondary endpoints)

Table 3: Results longitudinal analysis (Primary + secondary endpoints)

Table 4: Compliance, practicability (Descriptive)

Table 5: AEs and SAEs (Descriptive)

Figure 1: CONSORT flow diagram

Figure 2: OBEs from T0 to T4 (both groups)

Figure 3: Results confirmatory analysis + non-inferiority margin (CIs of treatment effect based on FAS and PPS)

Figure 4: Recovery and remission rates (based on categorical binge eating outcomes for both groups from T0 to T4)
References


3. STATISTICAL PRINCIPLES FOR CLINICAL TRIALS E9, I.H.T. GUIDELINE, Editor. 1998.