Statistical analysis plan

Cost-effectiveness of internet-delivered exposure therapy versus healthy lifestyle promotion for distress related to persistent somatic symptoms: secondary analysis of a randomized controlled trial in primary care

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Background

Persistent somatic symptoms are associated with clinical levels of distress and dysfunctional behavioral patterns throughout the healthcare system. Exposure therapy and healthy lifestyle promotion have been found to reduce somatic symptom burden and symptom preoccupation. Little is known, however, about the cost-effectiveness of these two treatment strategies.

Aim of this study

The primary aim of this study is to evaluate the cost-effectiveness of exposure therapy versus healthy lifestyle promotion as treatments for individuals with persistent somatic symptoms, as assessed and treated in primary care.

A secondary aim is also to compare the resource utilization, primarily the average healthcare consumption, of individuals with persistent physical symptoms to that of healthy volunteers.

Hypotheses

For the primary analyses of cost-effectiveness, we hypothesize that, assuming common rules of thumb for willingness to pay (a primary test focusing on 20 000, and sensitivity analyses based on 10 000 and 50 000 GBP per QALY [1]), exposure therapy is (probably, i.e., as based on probabilistic sensitivity analyses) cost-effective compared to healthy lifestyle promotion, regardless of whether the focus is on societal or exclusively healthcare costs, and regardless of whether the outcome is overall somatic symptom burden, symptom preoccupation, or quality-adjusted life years (QALYs). The hypothesis of superiority in terms of cost-effectiveness was formulated in the protocol submitted for ethical application before the trial data collection.

For the secondary comparison with healthy volunteers, we hypothesize that, on average, patients who seek care for distress related to persistent somatic symptoms utilize more health care resources, and report higher overall costs, than healthy volunteers.

Methods

Overall design

This will be a cost-effectiveness evaluation based on a randomized controlled trial of online exposure therapy versus online healthy lifestyle promotion for individuals with distress related to persistent somatic symptoms (N=161). The study will also incorporate reference data pertaining to resource utilization in healthy volunteers (N=160). Results will be reported in accordance with CHEERS 2022 [2].

Measurement

All questionnaires are administered online via a simple web interface, with black text on white background and radio buttons to indicate responses. Somatic symptom burden is

measured using the Patient Health Questionnaire 15 (PHQ-15) [3]. Symptom preoccupation is measured using the Somatic Symptom Disorder B-criteria scale 12 (SSD-12) [4]. Health-related quality of life, used for utility scores, is measured using the EuroQol-5D (EQ-5D-3L) [5]. Data on resource use including healthcare use are collected using the Trimbos/iMTA questionnaire for costs associated with psychiatric illness (TIC-P) [6]. All questionnaires are administered at the pre- and post-treatment assessment. The PHQ-15 and SSD-12 are also administered each week during treatment, resulting in 11 assessments over the main phase. In this trial, there is also follow-up data 6 and 12 months after treatment on all aforementioned outcomes (PHQ-15, SSD-12, EQ-5D-3L, TIC-P) for the exposure arm but not for the healthy lifestyle promotion participants who were crossed over after the post-treatment assessment.

Statistical analysis plan

Because the healthy lifestyle promotion group was crossed over to exposure therapy after the post-treatment assessment, the main analysis of cost-effectiveness is based on data collected over the pre- to post-treatment main phase of the trial. Dichotomous efficacy outcomes other than quality-adjusted life years (QALYs) will be based on the minimal clinically important difference (MID) which is 3 for the PHQ-15 [7], and 3 for the SSD-12 [8]. Utility scores will be derived from the EQ-5D-3L on the basis of Swedish experience-based norms [9].

Resource use will be determined primarily on the basis of the TIC-P, which is scored in terms of frequencies (e.g., the number visits with a general practitioner) that can be multiplied by tariffs to estimate costs. Healthcare tariffs are derived from official listings for the publicly funded Swedish health care system, medication costs from market prices, and costs due to productivity loss are estimated based on lost gross earnings (the human capital approach) [10] with incomes estimated on the basis of gender and educational attainment, which is matched to national averages (Statistics Sweden). As to intervention costs, because this is primarily a study of cost-effectiveness, i.e., the difference in costs in relation to the difference in efficacy between two treatment alternatives, we will only model those intervention costs that differ between the two treatment alternatives. More specifically, we will model salaries based on therapist time devoted to each therapy, but we will not model the cost for the development of clinic procedures, infrastructure including maintenance and IT security, therapist education, or supervision, as these are all assumed to be identical, or nearly similar, over the two therapies.

Variable distributions are investigated, and descriptive statistics are tabulated to characterize the sample. Differences in costs between the clinical trial participants and healthy volunteers are tested for within a generalized linear model framework. Dichotomous efficacy outcomes first reported in the primary publication, and change in utility and costs over the course of the trial (including treatment difference over the pre-post main phase), is then evaluated using bootstrapped linear mixed effects regression models. In cost-effectiveness analysis, even when distributions are skewed, the mean is often of primary concern for policy decisions.

Cost-effectiveness analyses will be conducted both from a societal and healthcare perspective. Whereas the societal perspective is often regarded as the gold standard for assessing the total impact of health states, the healthcare perspective can be more important for policy makers in the healthcare system specifically. The time perspective modelled in this study will be 1 year following baseline, which is a common approach, that we believe strikes a balance between an unreasonably pure focus on the treatment period itself, and a timeframe so long that the relative effect and cost of the treatments becomes mere speculation. Due to the relatively short time horizon, costs will not be adjusted for inflation or discounted. Efficacy outcomes based

on the MID are adequate here even though these do not give any indication of deterioration or negative effects, because such outcomes were highly similar over the therapies in this trial.

Table 1. Overview of planned cost-effectiveness analyses

Efficacy outcome	**Extrapolation from post-treatment to 1 year after baseline**		**Main (observed) phase only**
	Societal perspective on costs	**Healthcare perspective on costs**	**Societal perspective on costs**
Total sample			
MID on the PHQ-15	Primary analysis	Secondary analysis	Secondary analysis
MID on the SSD-12	Secondary analysis	Secondary analysis	Secondary analysis
QALYs based on the EQ-5D-3L	Secondary analysis	Secondary analysis	Secondary analysis
PHQ-15-1w≥15 or SSD-12-1w≥25			
MID on the PHQ-15	Secondary analysis		
MID on the SSD-12	Secondary analysis		
QALYs based on the EQ-5D-3L	Secondary analysis		

MID, minimal important difference; PHQ-15, Patient Health Questionnaire 15; SSD-12, Somatic Symptom Disorder B criteria scale 12; TIC-P, Trimbos/iMTA questionnaire for costs associated with psychiatric illness.

The cost-effectiveness analyses will focus on the incremental cost-effectiveness ratio (ICER) which stands for the difference in mean cost between two treatment options, divided by the difference in mean efficacy. In the main tests costs and effects will be extrapolated, and assumed to remain stable from the post-treatment assessment onwards (Table 1). Because a positive ICER can result either from the numerator and denominator both being positive, or from both being negative, and a negative ICER can be the result of either the numerator of the denominator being negative, the numerator and denominator will also be reported separately for each ICER point estimate [11]. An intention-to-treat analysis is achieved through the use of linear mixed effects regression models to derive the numerator and denominator for the ICER (notably, all 161 participants of the trial completed the pre-treatment assessment). In probabilistic sensitivity analyses, each ICER will be bootstrapped (1000 samples), and ICERs derived from linear mixed effects models on the resulting samples will be used to construct cost-effectiveness planes.

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