Supplementary Online Content

Axelsson E, Andersson E, Ljótsson B, Björkander D, Hedman-Lagerlöf M, Hedman-Lagerlöf E. Effect of internet vs face-to-face cognitive behavior therapy for health anxiety: a randomized noninferiority clinical trial. *JAMA Psychiatry*. Published online May 13, 2020. doi:10.1001/jamapsychiatry.2020.0940

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Operationalization of Eligibility Criteria

Eligibility criterion	Operationalization
Principal diagnosis of DSM-5 somatic symptom disorder or illness anxiety disorder.	Clinical diagnosis based on the Health Preoccupation Diagnostic Interview (HPDI)[1], as used in conjunction with the Mini International Neuropsychiatric Interview (MINI)[2], in the context of a psychiatric interview led by a psychologist under supervision. This assessment was aided by an online self-report screening that included the Health Anxiety Inventory (HAI),[3] Illness Attitude Scales (IAS)[4], and the 14-item Whiteley Index (WI) with a dichotomous response format ("yes/no")[5].
At least 18 years old	Self-reported age of at least 18 years on a self-rated online screening questionnaire, as well as during the eligibility interview. The patient was also required to report his or her national personal identity number[6], which is linked to age, and to pass an identification check at the first appointment.
Resident of Stockholm, Sweden	Self-reported resident of Stockholm on a self-rated online questionnaire, as well as during the eligibility interview. The patient was also required to report his or her national personal identity number[6], which was matched against the national civil registry, and to pass an identification check at the first appointment.
No severe depression	No clinical diagnosis of severe depression based on the MINI and the DSM-5 severity criteria (i.e., considerably more symptoms than necessary for a diagnosis, symptoms seriously distressing and unmanageable and symptoms markedly interfere with social and occupational functioning) in the context of a psychiatric interview led by a psychologist under supervision. This assessment was aided by an online screening that included the Montgomery-Åsberg Depression Rating Scale – Self rated (MADRS-S).[7]
No suicidal ideation	Not recurrent thoughts of suicide, as based on clinical judgement aided by an unpublished structured clinical interview and an online self-report screening that included the MADRS-S item 9, rated from 0: "I have a normal appetite for life" to 6: "I am convinced that my only way out is to die, and I think a lot about how to best go about taking my own life".
No bipolar disorder or psychosis, current or previous	Neither (i) a clinical diagnosis of bipolar disorder based on the MINI in the context of a psychiatric interview led by a psychologist under supervision nor (ii) a self-reported pre-established diagnosis of bipolar disorder or psychosis based on the question: "Have you ever received a psychiatric diagnosis by a psychologist or doctor?" and the discussion of medication and electronic medical records.
No personality disorder likely to severely interfere with treatment	No personality disorder deemed likely to interfere with treatment to the degree that cognitive behavior therapy was not suitable. The patient's psychiatric history was surveyed based on the question: "Have you ever received a psychiatric diagnosis by a psychologist or doctor?" and the discussion of medication and electronic medical records. A personality disorder was not in and of itself sufficient to be excluded, but it was also necessary for the patient to exhibit a highly inappropriate pattern of cognition, emotion, and behavior such that treatment in the study was not deemed to be feasible.

Eligibility criterion	**Operationalization**
No alcohol or substance use disorder for the past 6 months	No clinical diagnosis (i.e., alcohol or substance use disorder) based on the MINI in the context of a psychiatric interview led by a psychologist under supervision. This assessment was aided by the Alcohol Use Disorders Identification Test (AUDIT)[8] and the Drug Use Disorders Identification Test (DUDIT).[9]
No serious somatic condition	Any somatic condition that required immediate or extensive care to the degree that cognitive behavior therapy was not suitable. The following questions were routinely asked during the eligibility interview: “Do you have an established serious disease, such as cancer or HIV, that is likely to make it difficult for you to complete your treatment?” and “Do you have – or have you ever had – a medical condition out of the ordinary?”. As is routinely done in the primary care clinic, the patient’s general practitioner was consulted whenever further medical evaluation was deemed necessary.
If on antidepressant, stable dose of this medication for at least 2 months	No or stable (≥2 months) self-reported medication with antidepressants (i.e., medication deemed likely to influence the outcome of the study), as based on (i) a self-rated online screening questionnaire (main item: “Has your dose of medication been stable, i.e., the same for the past 2 months?”) and (ii) the discussion of medications during the eligibility interview. The interviewer described the purpose of the trial, emphasized the importance of stable medication and all study patients agreed to keep their medication with antidepressants constant over the 12-week main phase of the trial.
No other psychological treatment for health anxiety still in progress	No self-reported ongoing psychological treatment for health anxiety, as based on the eligibility interview (main items: “Have you ever attended another psychological treatment for health anxiety?”, “Do you plan to undergo another psychological treatment for health anxiety that risks running at the same time with your participation in this study?”). The interviewer described the purpose of the trial, underscored the importance of focusing on the treatment of the trial and all study patients agreed not to undergo another psychological treatment for health anxiety over the 12-week main phase of the trial.
Not undergone cognitive behavior therapy for health anxiety during the past 12 months	No cognitive behavior therapy (CBT) for health anxiety in the 12 months preceding the start date of Internet-delivered or face-to-face therapy in the present trial. We classified interventions as CBT for health anxiety if they (i) were at least 6 sessions long, (ii) included either cognitive restructuring techniques, exposure-based techniques (including response prevention) or both and (iii) focused on reducing health anxiety.

eTable 2. Treatment Protocol, Cognitive Behavior Therapy for Health Anxiety

Module/ Session	Main theme	Description	Homework exercises	ICBT	FTF-CBT
1	Introduction to CBT and health anxiety	The patient is introduced to the treatment format and concept of health anxiety. Daily self-monitoring is introduced with the behavior diary in which the patient is encouraged to register health anxiety behaviors to increase awareness of key areas to address in treatment and enable the adaption of exposure and response prevention. A daily 10-minute mindfulness exercise is also introduced to reduce covert avoidance and develop a more open stance towards exposure.	Behavior diary (WS), Daily mindfulness exercise	19 pages	80 min + 11 pages
2	The CBT model of health anxiety	The cognitive-behavioural model of health anxiety is described in greater detail and related to the patient's presenting problem. It is described how triggers for health anxiety lead to unwanted emotional responses that provoke hypervigilance to bodily processes and intensify symptoms. Common behaviors such as excessive symptom-checking and frequent doctor visits may reduce or prevent anxiety in the short term but maintain health anxiety over time.[10]	Behavior diary, Daily mindfulness exercise, Idiosyncratic CBT model (WS)	16 pages	50 min + 9 pages
3	Interoceptive exposure	Exposure is introduced based on a habituation rationale. Interoceptive exposure, i.e., exposure to bodily processes and physical symptoms, is introduced to reduce unwanted emotional responses.[11] The patient is encouraged to work through pre-defined interoceptive exercises and continue working with these until habituation is achieved.	Behavior diary, Daily mindfulness exercise, Interoceptive exposure (WS)	11 pages	50 min + 6 pages
4	Response prevention	Tailor-made systematic response prevention is introduced based on the behavior diary. The patient is encouraged to decide on a clear goal for each behavior by, e.g., deciding on a maximum rate to reduce the frequency of the behavior ("I will check my pulse no more than 5 times per day") or deciding on a minimum time to wait from the urge to perform a behavior ("When I get the urge to do so, I will wait at least 30 minutes before I inspect my skin in the mirror"). The patient works with	Daily mindfulness exercise, Response prevention (WS)	10 pages	50 min + 5 pages

		and continuously revises the goals for response prevention over the remainder of the treatment.			
Module/ Session	**Main theme**	**Description**	**Homework exercises**	**ICBT**	**FTF-CBT**
5	Exposure in vivo	Exposure to real-world situations and phenomena is introduced and the patient is encouraged to plan and conduct at least one exposure exercise each day (in vivo or other) for the remainder of the treatment. The choice of exercises is aided by the behavior diary and common examples in the treatment texts. Common exposure exercises include reading about feared illnesses and watching films about other people with serious diseases.	Daily mindfulness exercise, Response prevention, Exposure in vivo (WS)	12 pages	50 min + 8 pages
6	Imaginal exposure	The patient is encouraged to write an “illness story” about his or her most feared outcome, i.e., typically about being diagnosed with a serious disease, gradually becoming worse, and ultimately passing away.[12] The patient is encouraged to repeatedly read the text to determine whether it can be used for exposure and, as with all exposure exercises, continue working with it until it is no longer relevant. The patient is encouraged to adopt a non-reactive stance to feared thoughts.	Response prevention, Exposure in vivo, Imaginal exposure (WS)	9 pages	50 min + 4 pages
7	Continued imaginal exposure and the fear of death	The work with daily exposure and response prevention is continued and expanded. The patient is encouraged to expand on the “illness story” if this is still relevant. In the face-to-face treatment patients are encouraged to read their story aloud. If deemed necessary, additional exposure exercises to address the fear of death (e.g., by reading obituaries or writing a legally binding will) are also planned.	Response prevention, Various forms of exposure (WS)	7 pages	50 min + 0 pages
8	Common obstacles to exposure	The work with daily exposure and response prevention is continued and expanded. The treatment segment focuses on common obstacles to successful exposure, such as finding time and planning for exposure, as well as determining ways to approach those situations and outcomes most feared by the patient.	Response prevention, Various forms of exposure	9 pages	50 min + 0 pages

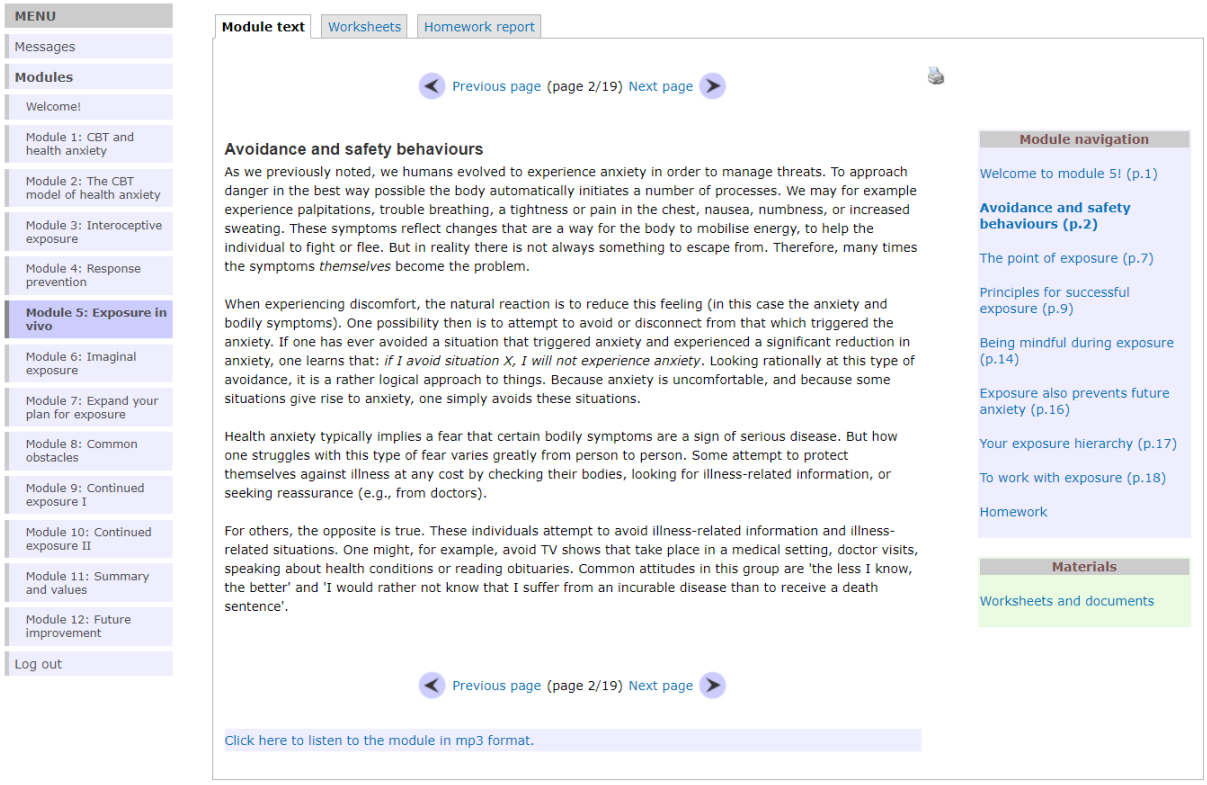
Module/ Session	Main theme	Description	Homework exercises	ICBT	FTF-CBT
9	Continued exposure and response prevention	The work with daily exposure and response prevention is continued and expanded. The patient is encouraged to work through as many interoceptive, in vivo and imaginal exposure exercises as possible.	Response prevention, Various forms of exposure	4 pages	50 min + 0 pages
10	Continued exposure and response prevention	The work with daily exposure and response prevention is continued and expanded. The patient is encouraged to work through as many interoceptive, in vivo and imaginal exposure exercises as possible.	Response prevention, Various forms of exposure	2 pages	50 min + 0 pages
11	Summary and values	The work with daily exposure and response prevention is continued and expanded. The patient is encouraged to prepare and save a written summary of the treatment, especially the core treatment principles in order to remember them. A brief values exercise is also introduced to emphasize the implications of avoidance on health-related quality of life, and the potential benefits of exposure and response prevention.	Response prevention, Various forms of exposure, Written summary (WS), Values exercise (WS)	6 pages	50 min + 0 pages
12	Continued improvement and health-care utilization	The final treatment segment focuses on producing a long-term plan for relapse prevention. Patients are encouraged to continue working with exposure and response prevention after treatment termination. They are also encouraged to prepare and save a written long-term plan for health-care seeking.	Response prevention, Various forms of exposure, Plan for relapse prevention (WS), Plan for health-care seeking (WS)	8 pages	50 min + 0 pages

"Pages" refer to A4 pages of text, i.e., text presented on the web-based online platform of the Internet-delivered treatment and text presented in the form of homework booklets in the face-to-face treatment. FTF-CBT, individual face-to-face cognitive behavior therapy; ICBT, therapist-guided Internet-delivered cognitive behavior therapy; WS, introduction of new work sheet (equivalent over treatments).

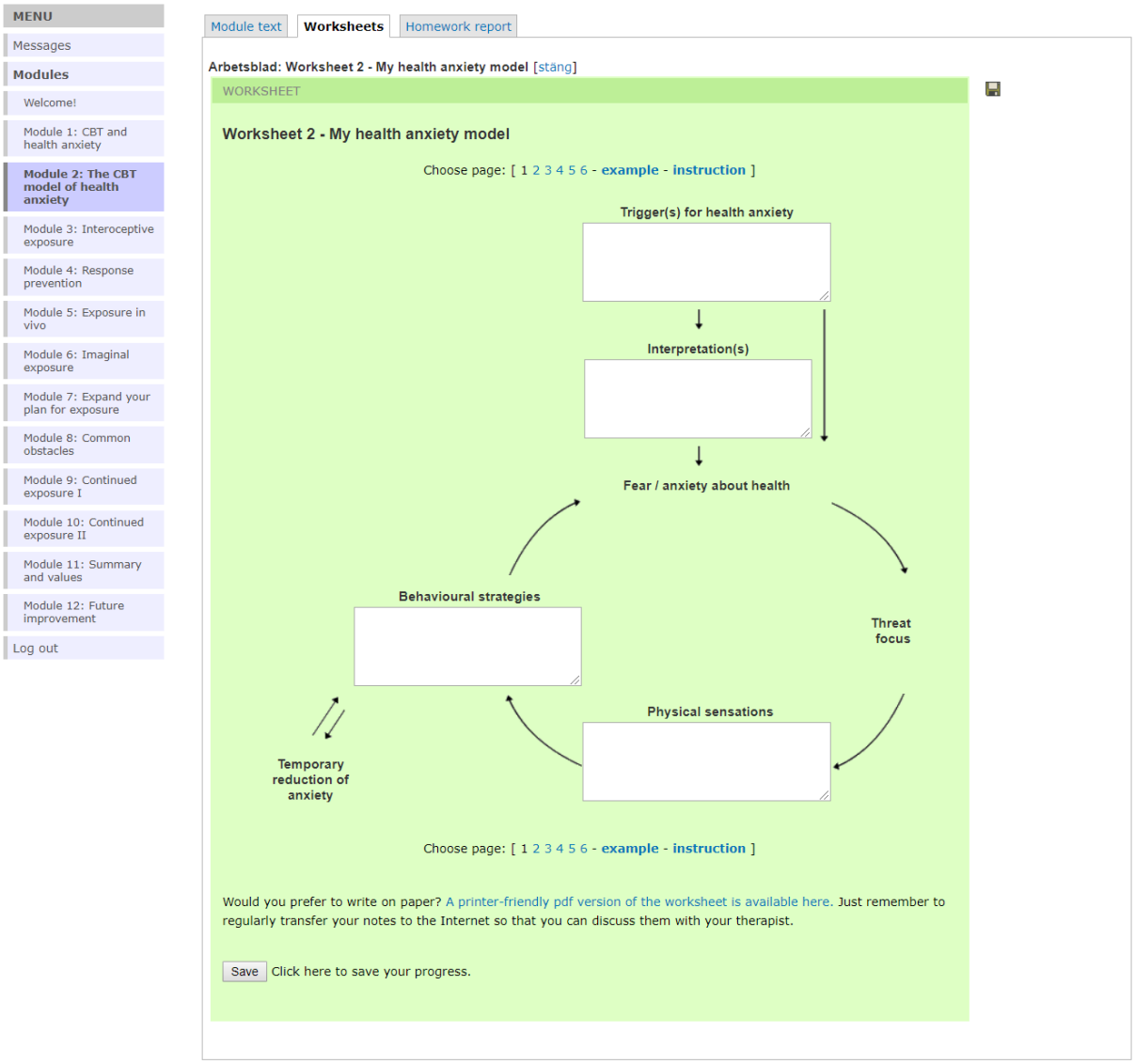
eAppendix 1. Detailed Description of Internet-Delivered Cognitive Behavior Therapy

We delivered Internet-based cognitive behavior therapy (ICBT) in a manner typical of routine clinical practice.[13,14] Patients accessed their treatment using a password-protected personal account on the online study platform, which employed 128-bit encrypted traffic. During the 12-week treatment period, patients were free to log in to their treatment at any time, at any place and with any device capable of running a web browser. The treatment content was presented in text format (eFigure 1), with interactive work sheets (eFigure 2) and simple web graphics on an online platform similar to the one used at the largest ICBT provider in Sweden (i.e., the Internet psychiatry unit in Stockholm). All psychoeducational components, exercises, strategies, and treatment themes were equivalent to those of the face-to-face treatment (eTable 2). Each week, patients in ICBT were encouraged to work through a segment of the treatment ("module"), which meant that the patient was expected to read the equivalent of approximately 5–15 A4 pages of text, either on screen or as a print-out on paper. There was also the possibility to listen to the content in the form of an audio book (i.e., downloadable mp3 files). The idea was that the text would contain all information necessary for the patient to work with the same strategies and conduct the same behavioral changes as in conventional face-to-face CBT. The 12 modules were completed in succession about one module per week. Based on the text, and to some degree the instructions of the therapist, the patient was encouraged to complete daily homework exercises and, at the end of each module, to answer a list of questions intended for reflection and feedback to the therapist (eFigure 3). After each module, the therapist reviewed these responses, gave written feedback by email-like messages, and opened the subsequent treatment module so it could be accessed by the patient. The patient was also able to write to the therapist at any time and expect a reply within two workdays. Therapists were the same five psychologists that worked with face-to-face CBT at the primary care clinic (eTable 3).

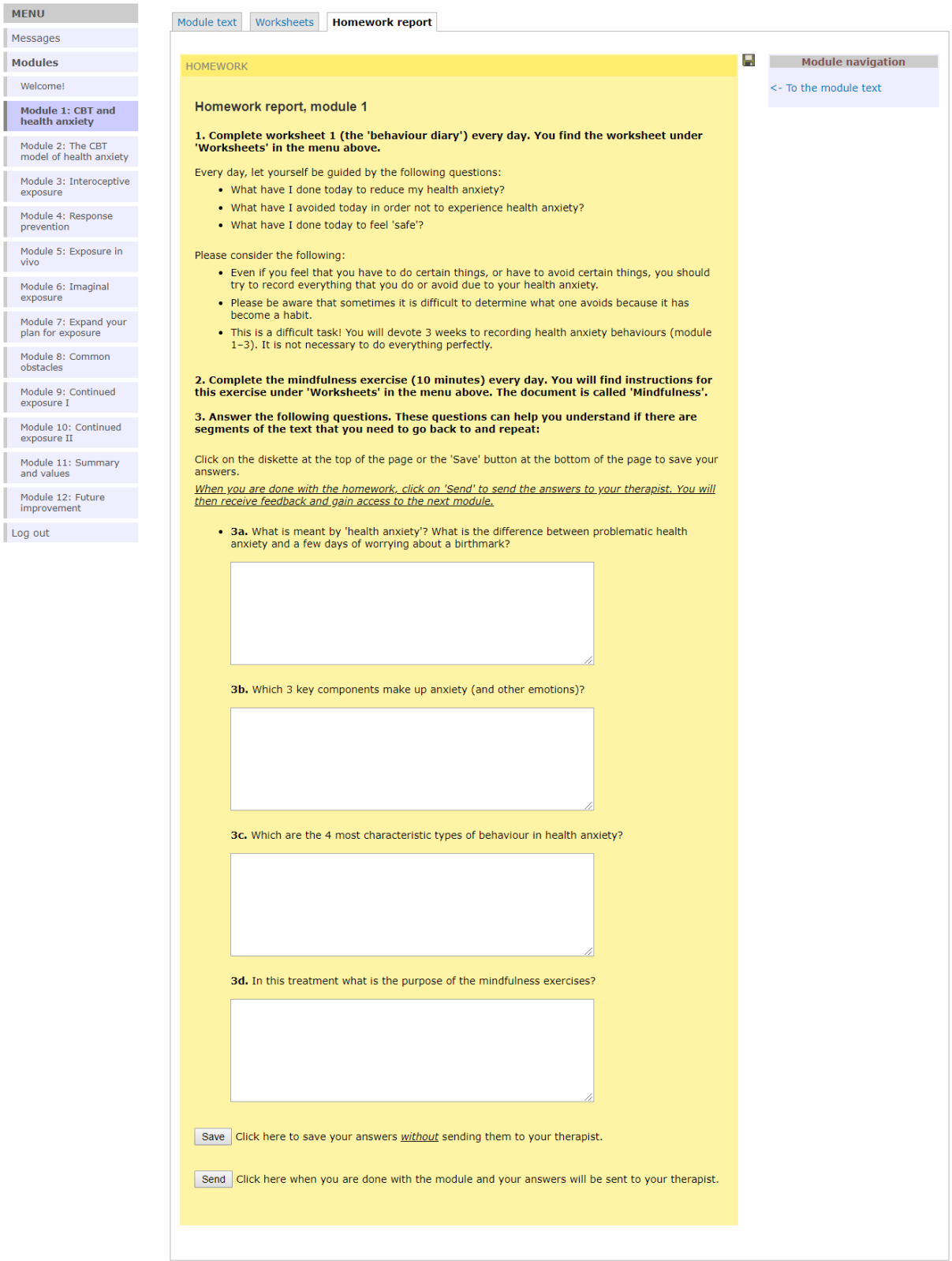
eFigure 1. Online Treatment Platform, Text-Based Main View



eFigure 2. Online Treatment Platform, Interactive Work Sheet



eFigure 3. Online Treatment Platform, Homework Report



eAppendix 2. Detailed Description of Face-to-Face Cognitive Behavior Therapy

We delivered individual face-to-face cognitive behavior therapy in accordance with a structured manual (available from the authors on request), which was based on a cognitive-behavioral model of health anxiety.[10,15,16] Patients had scheduled individual appointments with their therapist about once a week for 12 weeks at Gustavsberg primary care clinic of Stockholm, Sweden. The first appointment was scheduled to be approximately 80 minutes long and the subsequent to be about 50 minutes, although the therapists were instructed to allow for shorter sessions when all necessary components had been conveyed and if the shorter visits did not compromise the quality of the treatment. If the patient cancelled or failed to attend an appointment, the therapist was instructed to schedule a new and additional appointment (i.e., more than one session per week). In such cases the therapist typically contacted the patient by telephone to book a new appointment. However, no treatment content was delivered this way. Each session was scripted in the manual, but the treatment strategies were also adapted to meet the needs and preferences of the individual patient (as based on functional analysis[10]). Adherence to the protocol was ensured through the manualized treatment content, regular supervision, the use of ready-made in-session checklists and session-by-session audio recordings (10% rated for adherence and competence, see the main text). The treatment content was equivalent to that of ICBT (eTable 2), but mostly conveyed orally by the therapist to the patient in the consulting room, sometimes aided by the use of a whiteboard. Homework was also assisted by the use of written material and paper-and-pencil worksheets. The patient was encouraged to work with daily homework exercises, and from the second appointment, each session began with the review of homework from the previous appointment. As in ICBT, the main focus of the treatment was exposure.[10] Therapists were the same five psychologists that worked with ICBT at the primary care clinic (eTable 3), where other forms of evidence-based face-to-face CBT had been delivered previously.[17]

eTable 3. Detailed Description of Therapists

		Patients treated		Years of prior experience		Allegiance (i.e., wanted outcome)		Expectancy (i.e., expected outcome)	
Therapist	**Profession**	**ICBT**	**FTF-CBT**	**ICBT**	**FTF-CBT**	**T1**	**T2**	**T1**	**T2**
A	Psychologist	53	53	1.50	1.50	Non-inferiority	Non-inferiority	Non-inferiority	FTF-CBT superior
B	Psychologist	25	25	0.25	1.25	None	None	Non-inferiority	Non-inferiority
C	Psychologist	19	19	0.25	3.00	Non-inferiority	ICBT superior	None	None
D	Psychologist	3	3	0.00	13.00	None	No data	None	No data
E	Psychologist*	2	2	0.50	1.00	Non-inferiority	Non-inferiority	Non-inferiority	None

FTF-CBT, Individual face-to-face cognitive behavior therapy; ICBT, Therapist-guided Internet-delivered cognitive behavior therapy; T1, First assessment when the therapist began work in the study; T2, Follow-up assessment when the therapist had worked with both treatments for at least 6 weeks. *Resident psychologist.

eTable 4. Properties of Key Outcome Measures

Measure	Internal consistency[a]	Dimensionality[b]	Test-retest reliability[c]	Previous use in clinical trials
Primary outcome				
18-item Health Anxiety Inventory (HAI)[3]	Good (α=0.86)	2 factors (*r*=.58): main + negative consequences	Excellent (ICC=0.92)	Extensive, e.g., [18-23]
Secondary outcomes				
Beck Anxiety Inventory (BAI)[24]	Excellent (α=0.90)	1 factor	No trial-specific data, but adequate in other studies.[24-26]	Extensive, e.g., [18,19,27-30]
Montgomery-Åsberg Depression Rating Scale – Self-rated (MADRS-S)[7]	Good (α=0.84)	1 factor	Good (ICC=0.77)	Extensive, e.g., [31-36]
Sheehan Disability Scale (SDS)[37]	Good (α=0.83)	1 factor	No trial-specific data, but adequate in other studies.[38,39]	Extensive, e.g., [40-45]

a Estimated based on baseline data.
b Estimated based on baseline data and explorative factor analysis (principal axis factoring with promax rotation; Kaiser-Meyer-Olkin values >0.70, Bartlett's test *P*s<.001).
c Estimated based on the subsample of patients that completed the screening and baseline assessments within 14 days (n=54). ICC, two-way mixed-effects model absolute agreement intraclass correlation coefficient.

eAppendix 3. Statistical Analysis (continued)

As is stated in the main article, we decided on the noninferiority margin of 2.25 points on the HAI, ca 0.3 *d*, based on expert consensus and previous knowledge about the typical preference of clinicians and patients in terms of minimally important differences,[46] and documented between-group effects of CBT on health anxiety when compared to waiting-lists and treatment-as-usual controls.[47] Based on the noninferiority margin and data from a previous trial of CBT for health anxiety,[48] we conducted Monte Carlo simulations to determine the target sample size. The simulations indicated that, given a true zero effect size and the expected pattern of data loss, a sample size of 200 would be required for 80% power to confirm noninferiority over the treatment period. All power and primary analyses were done by an independent statistician. See the preregistered protocol for details.

The primary analysis was based on 13 weekly measurement points and a mixed-effects linear regression model (observations at level 1 and patients at level 2) with random intercept and slope (time) fit by means of restricted maximum likelihood, and a one-sided test (α=.05) of the coefficient for the time*group interaction. This multivariable model also included the simple effect of time and group, and had residual errors based on three terms: the random intercepts indexed by patient, the random slopes indexed by patient, and the irreducible error (epsilon). We considered ICBT to be noninferior to its face-to-face CBT comparator if the upper bound of the one-sided confidence interval for the time*group interaction coefficient was lower than the critical noninferiority margin. This analysis was conducted within both intention-to-treat and per-protocol frameworks, where the latter sensitivity analysis was based on data from treatment completers only. Combining intention-to-treat and per-protocol tests enables a stronger test of noninferiority than an intention-to-treat test alone, given that the intention-to-treat approach may indicate noninferiority simply due to poor adherence to the study protocol.[49,50] Patients were classified as completers if they initiated at least 6 modules in ICBT or attended at least 6 face-to-face CBT sessions. This was because at module or session 6, all types of exposure exercises (interoceptive, *in vivo*, imaginal, and response prevention) had been introduced to the patient. In moderator analyses, we also added patient treatment preference (0="strong preference for conventional CBT" to 5="strong preference for ICBT"), path of recruitment (routine care vs. not routine care), and baseline health anxiety as covariates to the intention-to-treat model. These variables were added as simple effects, interactions with time, and interactions with group, and we tested moderation based on the coefficient for the three-way interaction with time and group. Using analogous models, as is sometimes recommended for trials without a non-active control group,[51] we also tested for within-group dose-response relationships between the number of completed ICBT modules, or face-to-face CBT sessions, and change in health anxiety.

Patients with a HAI score reduction larger than 7.74 points (i.e., a reliable change index >1.96)[52] were classified as responders, those who had a resulting HAI score below 23.55 points were classified as in remission, and those who met criteria for both response and remission were classified as clinically significantly improved. We analyzed most nominal data using the χ^2 test. To enable intention-to-treat analysis of secondary symptom outcomes, data were imputed separately for each treatment group using multiple imputation by chained equations (20 samples). We calculated standardized effect sizes for continuous measures in terms of Cohen's *d* with face-to-face CBT as the comparator, based on the group*time coefficient divided by the pooled observed endpoint standard deviation. Analyses were conducted in R 3.4.4 and Stata/MP 14.2.

eAppendix 4. Aug 2016 Revision of Primary Analysis

We originally powered this trial for a post-treatment mean difference test of non-inferiority, which was estimated to require a sample size of 308 for sufficient power. On Aug 31, 2016, when 126 patients had been randomized and prior to all data analyses, we revised this choice of primary analysis as considerably higher power would be achieved (a sample size of 200 would be sufficient) if analyses were instead based on linear mixed effects models and all 13 weekly assessments of health anxiety. See the protocol for details: https://ki.se/en/cns/erik-hedmans-research-group

eTable 5. Weekly Data Completion Rates, Primary Outcome (2386 Data Points)

	Week	0[a]	1	2	3	4	5	6	7	8	9	10	11	12[a]
ICBT	n	102	101	96	94	90	90	90	89	88	87	84	83	97
	%	100%	99%	94%	92%	88%	88%	88%	87%	86%	85%	82%	81%	95%
FTF	n	102	95	97	90	94	93	89	87	85	88	89	89	97
	%	100%	93%	95%	88%	92%	91%	87%	85%	83%	86%	87%	87%	95%

FTF, individual face-to-face cognitive behavior therapy; ICBT, therapist-guided Internet-delivered cognitive behavior therapy.

a Week 0 is the baseline assessment and week 12 is the post-treatment assessment.

eAppendix 5. Treatment Fidelity: Sensitivity Analysis and the Online Treatment

In addition to the primary measure of treatment fidelity (adherence and competence), as a sensitivity analysis, the assessors also made global session ratings of therapist adherence and competence from 0 (“very poor”) to 5 (“excellent”). The outcome of the sensitivity analysis was similar to the primary analysis of adherence and competence in that both were rated high. Specifically, the mean face-to-face therapist adherence was rated 4.2 (SD=0.8) and competence was rated 4.3 (SD=0.7), i.e., both were rated good to excellent. ICBT competency and adherence were not assessed for three reasons. First, in this noninferiority trial our focus was on ensuring treatment fidelity of face-to-face CBT because this was the gold standard comparator and benchmark for ICBT. Second, there is no consensus on what constitutes therapist competency in ICBT. Third, the role of the therapist is different in ICBT, in which most of the treatment content is conveyed through the treatment text rather than messages from the therapist. This structured format ensures that the treatment does not change or deviate from the protocol.

eTable 6. Somatic Conditions Reported at Baseline

Current			Previous	
Condition	n		Condition	n
allergy (severe)	1		abnormal cervical cells	2
alpha-1 antitrypsin deficiency	1		acute spondylitis	1
asthma	1		anaphylaxis	1
atopic dermatitis	1		atrial fibrillation	1
cancer (anal), treated	1		benign heart defect, unspecified	1
cancer (bladder), treated	1		benign paroxysmal positional vertigo	2
cancer (polyps, unspecified)	1		benign stomach tumour	1
cerebral palsy	1		cancer (bladder)	1
chronic fatigue syndrome	1		cancer (breast)	4
coronary artery disease	1		cancer (kidney)	1
factor V Leiden	1		cancer (lymphoma)	1
heart valve disease	1		cancer (polyps, unspecified)	1
hypertension	8		cancer (thyroid)	1
hypothyroidism	12		cataract	1
IgA nephropathy	1		cholelithiasis	2
irritable bowel syndrome	5		heart rhythm disorder (extra pathway)	2
low white blood cell count	1		heart valve disease	1
lung damage, unspecified	1		hyperthyroidism	3
migraine (severe)	2		infection, severe, unspecified	1
osteoarthritis	4		infectious mononucleosis	1
osteoporosis	2		kidney damage, unspecified	1
pituitary cyst	1		molar pregnancy	1
precursor to malignant melanoma	1		myocarditis	1
prostatitis (chronic)	2		pneumothorax	1
psoriasis	1		retinal detachment	1
scoliosis	1		sepsis	1
sleep apnea	1		spinal disc herniation	1
spinal disc herniation	2		thrombus, unspecified	1
tinnitus	1		urolithiasis	1
type 1 diabetes	1		uterine infection	1
type 2 diabetes	1			
ulcerative colitis	1			

eTable 7. Observed Means and Standard Deviations

	Measure				ICBT			FTF-CBT		
Outcome	Abbreviation	Items	Scoring	Assessment	M	SD	n	M	SD	n
Health anxiety	HAI	18	0-54	Baseline	33.9	6.5	102	34.2	6.4	102
Health anxiety	HAI	18	0-54	Post-treatment	21.0	8.5	97	20.4	8.7	97
Health anxiety	HAI	18	0-54	6 months	19.6	8.2	90	18.9	9.1	91
Health anxiety	HAI	18	0-54	12 months	20.7	9.3	92	18.0	8.5	90
Health anxiety	HAI	14	0-42	Baseline	27.6	5.1	102	28.1	4.8	102
Health anxiety	HAI	14	0-42	Post-treatment	16.5	6.8	97	16.4	7.1	97
Health anxiety	HAI	14	0-42	6 months	15.4	6.4	90	15.1	7.2	91
Health anxiety	HAI	14	0-42	12 months	16.1	7.5	92	14.4	6.7	90
General anxiety	BAI	21	0-63	Baseline	19.4	8.9	102	20.3	10.5	102
General anxiety	BAI	21	0-63	Post-treatment	11.2	7.6	97	11.0	8.6	97
General anxiety	BAI	21	0-63	6 months	11.4	8.2	90	10.8	6.7	91
General anxiety	BAI	21	0-63	12 months	11.8	8.7	92	9.7	7.7	89
Depression	MADRS-S	9	0-54	Baseline	13.7	6.9	102	14.7	7.0	102
Depression	MADRS-S	9	0-54	Post-treatment	8.2	6.1	97	7.6	6.5	97
Depression	MADRS-S	9	0-54	6 months	7.6	6.4	90	6.6	5.7	91
Depression	MADRS-S	9	0-54	12 months	7.6	6.3	92	5.9	5.0	89
Disability	SDS	3	0-30	Baseline	11.4	7.5	102	11.6	6.8	102
Disability	SDS	3	0-30	Post-treatment	6.5	6.1	97	6.4	5.7	97
Disability	SDS	3	0-30	6 months	6.1	7.1	90	4.8	5.0	91
Disability	SDS	3	0-30	12 months	5.1	6.1	92	4.9	5.6	89
Health anxiety	IAS	29[a]	0-108	Baseline	67.5	11.3	102	69.4	11.6	102
Health anxiety	IAS	29[a]	0-108	Post-treatment	43.9	15.6	97	44.0	15.9	97
Health anxiety	IAS	29[a]	0-108	6 months	42.5	16.3	90	41.5	16.8	91
Health anxiety	IAS	29[a]	0-108	12 months	43.4	17.5	92	39.9	16.6	89
Health anxiety	WI (yes/no)	14	0-14	Baseline	10.5	2.0	102	10.8	2.0	102
Health anxiety	WI (yes/no)	14	0-14	Post-treatment	6.7	3.2	97	6.8	3.5	97
Health anxiety	WI (yes/no)	14	0-14	6 months	6.3	3.2	90	6.1	3.5	91
Health anxiety	WI (yes/no)	14	0-14	12 months	6.2	3.5	92	5.3	3.5	89
Anxiety sensitivity	ASI	16	0-64	Baseline	25.2	10.7	102	24.4	10.3	102
Anxiety sensitivity	ASI	16	0-64	Post-treatment	14.5	9.6	97	13.1	7.9	97
Anxiety sensitivity	ASI	16	0-64	6 months	14.9	11.3	90	12.7	9.0	91
Anxiety sensitivity	ASI	16	0-64	12 months	14.7	10.8	92	11.5	8.4	89
Sleep disturbance	ISI	5[b]	0-28	Baseline	8.9	5.0	102	9.3	6.0	102

Sleep disturbance	ISI	5[b]	0-28	Post-treatment	5.8	4.6	97	5.5	4.8	97
Sleep disturbance	ISI	5[b]	0-28	6 months	5.9	5.2	90	5.2	4.7	91
Sleep disturbance	ISI	5[b]	0-28	12 months	5.7	4.7	92	4.8	4.7	89
Alcohol use	AUDIT	10	0-40	Baseline	4.4	3.4	102	3.8	3.0	102
Alcohol use	AUDIT	10	0-40	Post-treatment	4.4	3.3	97	3.8	3.1	97
Alcohol use	AUDIT	10	0-40	6 months	4.0	3.0	90	4.0	3.4	91
Alcohol use	AUDIT	10	0-40	12 months	4.2	3.6	92	3.8	3.3	89
Disability	WHODAS 2	15[c]	12-60	Baseline	21.1	6.3	81	21.1	6.6	80
Disability	WHODAS 2	15[c]	12-60	Post-treatment	16.3	5.1	81	15.8	5.1	83

Abbreviations. ASI, Anxiety Sensitivity Index; AUDIT, Alcohol Use Disorders Identification Test; BAI, Beck Anxiety Inventory; HAI, Health Anxiety Inventory; IAS, Illness Attitude Scales; ISI, Insomnia Severity Index; MADRS-S, Montgomery-Åsberg Depression Rating Scale – Self rated; SDS, Sheehan Disability Scale; WHODAS 2, self-report World Health Organization Disability Assessment Schedule 2.0; WI (yes/no), Whiteley Index (yes/no-item version).

[a] Only 27 items (not items 22 or 26) are used for the sum scale.

[b] Item 1 has 3 subitems, which implies that 7 responses are given.

[c] Only 12 items (not items 13-15) are used for the sum scale.

eTable 8. Change in Additional Secondary Outcomes From Baseline

	ICBT	FTF-CBT	Difference: ICBT - FTF-CBT	
	B (95% CI)	B (95% CI)	B (95% CI)	*d*[a] (95% CI)
Health anxiety (Illness Attitude Scales[4])				
Post-treatment	-23.0 (-26.2 to -19.9)	-25.0 (-28.3 to -21.8)	2.0 (-2.6 to 6.5)	0.13 (-0.16 to 0.42)
6 months	-23.3 (-26.5 to -20.2)	-27.0 (-30.1 to -23.9)	3.7 (-0.8 to 8.1)	0.22 (-0.05 to 0.49)
12 months	-23.6 (-27.5 to -19.7)	-29.0 (-32.8 to -25.1)	5.4 (-0.2 to 10.9)	0.31 (-0.01 to 0.64)
Health anxiety (14-item yes/no Whiteley Index[5])				
Post-treatment	-3.7 (-4.3 to -3.1)	-3.9 (-4.5 to -3.3)	0.2 (-0.7 to 1.1)	0.05 (-0.22 to 0.32)
6 months	-3.9 (-4.5 to -3.3)	-4.6 (-5.1 to -4.0)	0.7 (-0.2 to 1.5)	0.19 (-0.05 to 0.44)
12 months	-4.1 (-4.9 to -3.3)	-5.3 (-6.0 to -4.5)	1.1 (0.1 to 2.2)	0.33 (0.02 to 0.63)
Anxiety sensitivity (Anxiety Sensitivity Index[53])				
Post-treatment	-10.2 (-12.5 to -8.0)	-11.1 (-13.3 to -8.8)	0.8 (-2.3 to 3.9)	0.09 (-0.26 to 0.45)
6 months	-10.0 (-12.2 to -7.9)	-11.9 (-14.0 to -9.8)	1.9 (-1.1 to 4.9)	0.18 (-0.11 to 0.48)
12 months	-9.8 (-12.2 to -7.4)	-12.7 (-15.2 to -10.3)	2.9 (-0.5 to 6.4)	0.30 (-0.05 to 0.66)
Sleep problems (Insomnia Severity Index[54])				
Post-treatment	-2.9 (-4.0 to -1.8)	-3.7 (-4.8 to -2.7)	0.8 (-0.7 to 2.3)	0.17 (-0.15 to 0.50)
6 months	-2.9 (-3.9 to -1.9)	-4.1 (-5.1 to -3.1)	1.2 (-0.2 to 2.6)	0.24 (-0.04 to 0.52)
12 months	-3.0 (-4.1 to -1.8)	-4.5 (-5.6 to -3.4)	1.5 (0.0 to 3.1)	0.32 (-0.01 to 0.65)
Alcohol use (Alcohol Use Disorders Identification Test[8])				
Post-treatment	-0.1 (-0.5 to 0.4)	0.0 (-0.5 to 0.5)	-0.1 (-0.8 to 0.6)	-0.03 (-0.24 to 0.19)
6 months	-0.1 (-0.5 to 0.3)	0.0 (-0.4 to 0.5)	-0.1 (-0.8 to 0.5)	-0.05 (-0.24 to 0.15)
12 months	-0.1 (-0.6 to 0.3)	0.1 (-0.5 to 0.6)	-0.2 (-0.9 to 0.5)	-0.06 (-0.27 to 0.15)
Functional impairment (12-item self-report World Health Organization Disability Assessment Schedule 2.0[55])[b]				
Post-treatment	-4.6 (-6.1 to -3.2)	-5.2 (-6.8 to -3.6)	0.6 (-1.5 to 2.7)	0.11 (-0.30 to 0.52)

Note. Intention-to-treat estimates based on piecewise linear mixed effects models with a spline at the post-treatment assessment, fitted on data with missing values imputed separately for each treatment group using multiple imputation by chained equations. Differences represent the coefficient for the time*group interaction. We also administered a few additional scales that are available on request. Note that due to administrative error ClinicalTrials lists the Quality of Life Inventory (QOLI) as an outcome despite this never being used. Similarly, the original protocol lists the Obsessive Compulsive Inventory – Revised (OCI-R), the Yale-Brown Obsessive-Compulsive Inventory Scale (Y-BOCS), and the Peters et al. Delusions Inventory (PDI-21) but these were never administered. FTF-CBT, individual face-to-face cognitive behavior therapy; ICBT, Internet-delivered cognitive behavior therapy.

[a] Cohen's *d* effect sizes calculated as the model-implied mean difference divided by the pooled observed endpoint standard deviation.

[b] This outcome was scored 12-60[56] and had relatively high missing rates (baseline data available: ICBT 81/102, FTF-CBT 80/102; post-treatment data available: ICBT 81/102, FTF-CBT 83/102) because a translated Swedish version first became available when about one fifth of the clinical trial had been completed.

eAppendix 6. Satisfaction With Treatment

At the post-treatment assessment, we measured treatment satisfaction using the Client Satisfaction Questionnaire.[57] Patients in face-to-face CBT had significantly higher satisfaction though the difference was small (ICBT: M=25.5, SD=5.0, n=96; face-to-face CBT: M=27.1, SD=4.2, n=97; difference: -1.7 [-3.1 to -0.4]).

eAppendix 7. Criteria for Response, Remission, and Clinically Significant Improvement

Responder and remission rates were based on the reliable change index and clinically significant improvement as operationalized by Jacobson and Truax.[52] The test-retest reliability of the HAI (*r*=.81, as based on data from a subsample [n=39] of individuals with health anxiety who completed the HAI two times within 14 days at baseline in a previous trial[58]), and HAI norm data from healthy controls (M=12.41 [SD=6.81])[59] was used to determine whether patients were reliably improved to a clinically significant degree. Patients with a HAI score reduction larger than 7.74 points (i.e., a reliable change index >1.96)[52] were classified as responders; those with a HAI score below 23.55 points were classified as in remission; and those who met criteria for both response and remission were classified as clinically significantly improved. See eTable 9-14.

eTable 9. Response Rates, Total Sample

	Observed only					Modelled, Intention-to-Treat			
Post-treatment	**n**	**%**	**RR**	**95% CI**		**n**	**%**	**RR**	**95% CI**
ICBT	75	77%	1.04	0.89; 1.22		78	76%	1.04	0.89; 1.22
FTF-CBT	72	74%				75	74%		
6-month follow-up									
ICBT	72	80%	0.98	0.85; 1.13		78	76%	0.98	0.84; 1.13
FTF-CBT	74	81%				80	78%		
12-month follow-up									
ICBT	64	70%	0.86	0.73; 1.01		70	69%	0.86	0.73; 1.02
FTF-CBT	73	81%				81	79%		

Modelled estimates are based on single imputation of missing values, based on fitted values from linear mixed effects models. FTF-CBT, individual face-to-face cognitive behavior therapy; ICBT, therapist-guided Internet-delivered cognitive behavior therapy; RR, risk ratio.

eTable 10. Response Rates, Per Protocol

	Observed only					Modelled			
Post-treatment	**n**	**%**	**RR**	**95% CI**		**n**	**%**	**RR**	**95% CI**
ICBT	64	80%	1.05	0.89; 1.23		64	79%	1.04	0.88; 1.22
FTF-CBT	68	76%				70	76%		
6-month follow-up									
ICBT	63	80%	0.99	0.85, 1.15		64	79%	1.00	0.85; 1.16
FTF-CBT	68	81%				73	79%		
12-month follow-up									
ICBT	56	71%	0.89	0.74; 1.06		57	70%	0.89	0.74; 1.06
FTF-CBT	67	80%				73	79%		

Modelled estimates are based on single imputation of missing values, based on fitted values from linear mixed effects models. FTF-CBT, individual face-to-face cognitive behavior therapy; ICBT, therapist-guided Internet-delivered cognitive behavior therapy; RR, risk ratio.

eTable 11. Remission Rates, Total Sample

	Observed only					Modelled, Intention-to-Treat			
Post-treatment	**n**	**%**	**RR**	**95% CI**		**n**	**%**	**RR**	**95% CI**
ICBT	61	63%	0.91	0.74; 1.12		62	61%	0.91	0.74; 1.12
FTF-CBT	67	69%				68	67%		
6-month follow-up									
ICBT	60	67%	0.92	0.76; 1.12		64	63%	0.90	0.74; 1.10
FTF-CBT	66	73%				71	70%		
12-month follow-up									
ICBT	57	62%	0.79	0.65; 0.95		61	60%	0.80	0.66; 0.98
FTF-CBT	71	79%				76	75%		

Modelled estimates are based on single imputation of missing values, based on fitted values from linear mixed effects models. FTF-CBT, individual face-to-face cognitive behavior therapy; ICBT, therapist-guided Internet-delivered cognitive behavior therapy; RR, risk ratio.

eTable 12. Remission Rates, Per Protocol

	Observed only					Modelled			
Post-treatment	**n**	**%**	**RR**	**95% CI**		**n**	**%**	**RR**	**95% CI**
ICBT	51	64%	0.89	0.72; 1.09		51	63%	0.91	0.73; 1.12
FTF-CBT	64	72%				64	70%		
6-month follow-up									
ICBT	52	66%	0.92	0.75; 1.14		52	64%	0.92	0.75; 1.14
FTF-CBT	60	71%				64	70%		
12-month follow-up									
ICBT	50	63%	0.82	0.67; 1.00		50	62%	0.84	0.68; 1.03
FTF-CBT	65	77%				68	74%		

Modelled estimates are based on single imputation of missing values, based on fitted values from linear mixed effects models. FTF-CBT, individual face-to-face cognitive behavior therapy; ICBT, therapist-guided Internet-delivered cognitive behavior therapy; RR, risk ratio.

eTable 13. Clinically Significant Improvement, Total Sample

	Observed only					Modelled, Intention-to-Treat			
	n	%	RR	95% CI		n	%	RR	95% CI
Post-treatment									
ICBT	57	59%	0.98	0.78; 1.24		58	57 %	0.98	0.78; 1.25
FTF-CBT	58	60%				59	58 %		
6-month follow-up									
ICBT	55	61%	0.90	0.72; 1.11		58	57 %	0.87	0.69; 1.08
FTF-CBT	62	68%				67	66 %		
12-month follow-up									
ICBT	50	54%	0.75	0.60; 0.94		54	53 %	0.77	0.62; 0.97
FTF-CBT	65	72%				70	69 %		

Modelled estimates are based on single imputation of missing values, based on fitted values from linear mixed effects models. FTF-CBT, individual face-to-face cognitive behavior therapy; ICBT, therapist-guided Internet-delivered cognitive behavior therapy; RR, risk ratio.

eTable 14. Clinically Significant Improvement, Per Protocol

	Observed only					Modelled			
	n	%	RR	95% CI		n	%	RR	95% CI
Post-treatment									
ICBT	47	59%	0.95	0.74; 1.22		47	58 %	0.97	0.76; 1.25
FTF-CBT	55	62%				55	60 %		
6-month follow-up									
ICBT	47	59%	0.89	0.70; 1.13		47	58 %	0.89	0.70; 1.13
FTF-CBT	56	67%				60	65 %		
12-month follow-up									
ICBT	45	57%	0.81	0.64; 1.03		45	56 %	0.82	0.65; 1.05
FTF-CBT	59	70%				62	67 %		

Modelled estimates are based on single imputation of missing values, based on fitted values from linear mixed effects models. FTF-CBT, individual face-to-face cognitive behavior therapy; ICBT, therapist-guided Internet-delivered cognitive behavior therapy; RR, risk ratio.

eTable 15. Crude (Observed) Monthly Costs at Baseline and Post-Treatment

	Baseline assessment		Post-treatment assessment	
	ICBT (n=102)	FTF-CBT (n=102)	ICBT (n=97)	FTF-CBT (n=97)
Direct medical costs	597 (641), 402	706 (852), 472	253 (404), 30	303 (460), 241
Health care visits	589 (639), 402	697 (849), 468	245 (401), 0	286 (448), 241
Medication	8 (12), 2	9 (28), 3	8 (12), 0	17 (71), 2
Direct non-medical costs	138 (246), 48	183 (282), 84	78 (163), 10	110 (169), 20
Indirect costs	782 (1375), 191	1084 (1943), 404	612 (1283), 23	461 (1113), 8
Unemployment	205 (929), 0	278 (1037), 0	391 (1257), 0	214 (931), 0
Sick leave	329 (1020), 0	385 (1618), 0	95 (324), 0	159 (614), 0
Work cutback	179 (282), 0	364 (776), 0	95 (230), 0	71 (270), 0
Domestic	70 (266), 16	57 (131), 23	31 (96), 0	17 (30), 0
Gross total costs	1517 (1671), 886	1972 (2167), 1328	943 (1354), 439	875 (1323), 378

Mean (SD), median. All costs are converted from the Swedish krona to the US Dollar based on the exchange rate of Jan 1, 2017. Medical costs are based on official listings of costs in the publicly funded Swedish healthcare system. FTF-CBT, individual face-to-face cognitive behavior therapy; ICBT, therapist-guided Internet-delivered cognitive behavior therapy.

eTable 16. Crude (Observed) Monthly Costs at the 6- and 12-Month Follow-Up

	6-month follow-up		12-month follow-up	
	ICBT (n=90)	FTF-CBT (n=91)	ICBT (n=92)	FTF-CBT (n=89)
Direct medical costs	220 (380), 50	287 (601), 92	242 (296), 130	285 (409), 19
Health care visits	211 (376), 0	274 (598), 81	235 (294), 130	269 (390), 0
Medication	9 (16), 0	12 (41), 0	7 (12), 0	17 (68), 1
Direct non-medical costs	43 (97), 3	70 (138), 7	72 (138), 7	79 (157), 10
Indirect costs	441 (1104), 1	379 (946), 0	474 (1067), 0	252 (693), 0
Unemployment	268 (1024), 0	181 (847), 0	255 (1004), 0	85 (569), 0
Sick leave	101 (486), 0	121 (428), 0	103 (373), 0	82 (337), 0
Work cutback	57 (138), 0	59 (171), 0	99 (260), 0	64 (224), 0
Domestic	15 (38), 0	19 (42), 0	17 (51), 0	19 (51), 0
Gross total costs	704 (1179), 250	737 (1169), 358	789 (1100), 414	616 (935), 318

Mean (SD), median. All costs are converted from the Swedish krona to the US Dollar based on the exchange rate of Jan 1, 2017. Medical costs are based on official listings of costs in the publicly funded Swedish healthcare system. FTF-CBT, individual face-to-face cognitive behavior therapy; ICBT, therapist-guided Internet-delivered cognitive behavior therapy.

eTable 17. Intervention Costs by Treatment Group

	ICBT (n=102)	FTF-CBT (n=102)
Health care costs		
Therapist costs	454 (257), 427	2069 (595), 2210
Platform overhead costs	16 (9), 15	0 (0), 0
Production loss	747 (470), 708	783 (433), 710
Travelling costs	0 (0), 0	1124 (743), 1096
Total intervention costs	1216 (638), 1205	4133 (1356), 4241

Mean (SD), median. Total intervention costs listed here refer to the full 12-week treatment period. All costs are converted from the Swedish krona to the US Dollar based on the exchange rate of Jan 1, 2017. Medical costs are based on official listings of costs in the publicly funded Swedish healthcare system. FTF-CBT, individual face-to-face cognitive behavior therapy; ICBT, therapist-guided Internet-delivered cognitive behavior therapy.

eAppendix 8. Measurement of Resource Utilization and Health-Related Quality of Life

For health economic analyses, we estimated societal costs using the Trimbos and Institute of Medical Technology Assessment Cost Questionnaire on Costs Associated with Psychiatric Illness (TIC-P)[60]. We estimated quality-adjusted life years (QALYs) using the EuroQoL-5[61] (EQ-5D) with Swedish experience-based utility tariffs.[62] As stated in the main text, data on resource utilization (i.e., the TIC-P) and health-related quality of life (i.e., the EQ-5D) were collected at baseline, post-treatment, and at the 6- and 12-month follow-up.

eAppendix 9. Health Economic Analysis

We conducted health economic analyses to compare ICBT with face-to-face CBT as regards societal net costs in relation to treatment efficacy (i.e., incremental cost-effectiveness ratios [ICERs]), as measured from baseline to the post-treatment assessment and from baseline to the 12-month follow-up. Two types of analysis were conducted: analyses in which clinically significant improvement was the efficacy measure (i.e., cost-effectiveness) and analyses where quality-adjusted life years (QALYs) were the efficacy measure (i.e., cost-utility). Societal net costs included direct medical costs (i.e., health care consumption), direct non-medical costs (e.g., alternative medicine and help from others), indirect costs (e.g., unemployment and sick leave), and intervention costs. Health care costs, in turn, were based on official listings from the publicly funded Swedish healthcare system. Intervention costs were the sum of the cost of (a) therapist time, (b) production loss, (c) travelling and fuel expenditure and (d) online platform overhead costs. Costs of production loss were estimated based on gross earnings (i.e., the human capital approach). Because our analyses did not extend beyond the 12-month follow-up, we deemed it unnecessary to discount costs. All costs were converted from the Swedish krona to the US Dollar based on the exchange rate of Jan 1, 2017, when 1 SEK was equivalent to 0.110 USD.

We modelled cost-effectiveness and cost-utility based on the assumption that costs and effects would change linearly over time, but that the rate of change would be different over the treatment and follow-up periods. (The only exception being intervention costs, see eTable 17, which were added as an additional one-time cost.) To capture the shift in change rate we fitted piecewise linear mixed models (random intercept) with a spline at the post-treatment assessment on our data and calculated the ICER as the difference between the model-implied net ICBT costs minus the net face-to-face CBT costs, divided by the ICBT efficacy minus the face-to-face CBT efficacy, for each specific period. In these linear models, grand mean centered baseline costs were used as a covariate to capture baseline differences in costs (see eTable 15). For sensitivity analyses, we fitted analogous piecewise models on 5000 cluster bootstrapped samples so that the difference in net costs, efficacy and ICER could be calculated for each sample. Results were plotted in cost-effectiveness planes, i.e., with efficacy on the x-axis and costs on the y-axis.

eAppendix 10. Health Economic Point Estimates

The point estimate for the baseline to post-treatment cost-effectiveness ICER was -3854/-0.01=$393 097, or a societal cost of $393 097 per additional patient in clinically significant improvement in face-to-face CBT as compared with ICBT. The corresponding cost-utility point ICER was -3854/0.0015=$-2.5 million, or a societal gain of $2.5 million per additional QALY gained by choosing ICBT over face-to-face CBT. Up to the 12-month follow-up, the cost-effectiveness ICER was -6127/-0.16=$39 057, or a societal cost of $39 057 per additional patient in a clinically significant improvement in face-to-face CBT as compared with ICBT. The point cost-utility ICER was -6127/-0.0095=$643 516, or a societal cost of $643 516 per additional QALY gained by choosing face-to-face CBT over ICBT. These point estimates correspond to the sensitivity analyses presented in Figure 3 of the main article.

eTable 18. Modelled Net Total Costs Per Observation Period

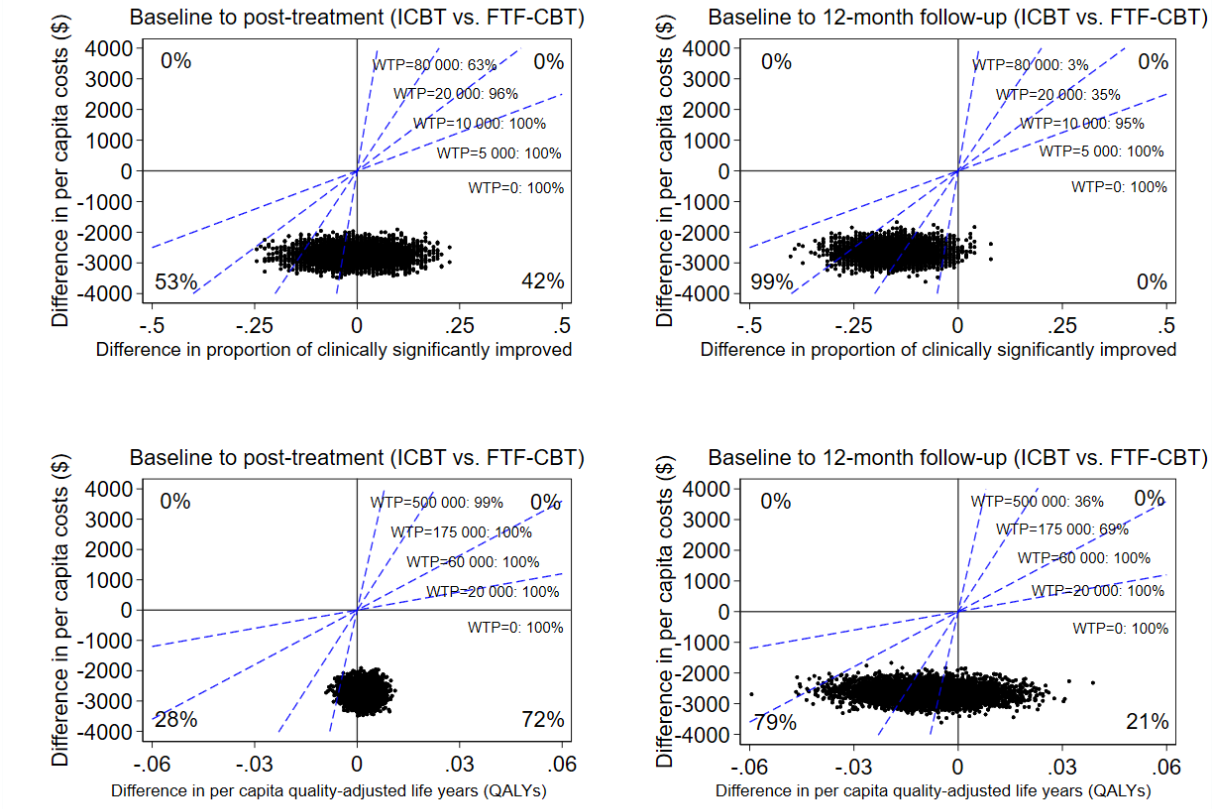
	ICBT (n=102)	FTF-CBT (n=102)
Net total costs		
Baseline to post-treatment	4 355	8 209
Baseline to 12 months	13 113	19 240

Estimates based on linear mixed models with centered gross baseline costs as covariate, and the one-time ICBT vs. FTF-CBT intervention cost. All costs are converted from the Swedish krona to the US Dollar based on the exchange rate of Jan 1, 2017. FTF-CBT, individual face-to-face cognitive behavior therapy; ICBT, therapist-guided Internet-delivered cognitive behavior therapy

eAppendix 11. Health Economy Sensitivity Analysis: Alternative Calculation of Costs

For the main health economic analyses, we based the numerator of the ICER[63] on the model-implied difference in net societal costs of ICBT and face-to-face CBT under the period of interest (baseline to post-treatment, or baseline to 12 months). There is also another common way of calculating costs for the numerator of the ICER. This alternative method, which has been employed in at least one other study of CBT for health anxiety,[64] regards the difference in costs not so much as a difference in societal investment over the observation period, but as a difference in the monthly cost rate that is achieved as an effect of the treatment (in this case: ICBT vs. face-to-face CBT). We calculated this alternative ICER numerator as the sum of (a) the model-implied treatment difference in change of gross total costs and (b) the difference in mean intervention costs. Using this alternative approach, the point estimate difference in costs (ICBT vs. face-to-face CBT) from baseline to post-treatment was $-2701 (as compared with the $-3854 numerator of the main analysis) and $-2606 up to the 12-month follow-up (as compared with the $-6127 numerator of the main analysis). As can be seen in eFigure 4, the distribution of ICERs over the cost-effectiveness plane mirrored the main health economic analyses in that ICBT had lower net costs, and cost-effectiveness depended on the time frame and societal willingness to pay.

eFigure 4. Cost-Effectiveness and Cost-Utility, Alternative Calculation of Costs



eAppendix 12. Measurement of Adverse Events

To collect information about adverse events at post-treatment we prompted patients to complete an online questionnaire consistent with previous clinical trials for health anxiety.[48,58] Patients were encouraged to report up to three adverse events or unwanted effects that they believed to be related to their participation in the study. Responses were given in free-text fields. Patients rated how much they were affected by these adverse events on a five-point scale from 0 ("did not affect me at all") to 4 ("affected me very negatively"). Patients also rated how much their adverse events affected them at post-treatment. Four patients in ICBT and nine in face-to-face CBT rated at least one of their adverse events as having affecting them "very negatively", and the average rating was more negative in face-to-face CBT (M=3, SD=1.1) than in ICBT (M=2, SD=1.2; *P*=.015). All adverse events were classified by type, by a person that was blind to treatment group.

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