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**Which patients benefit specifically from short-term psychodynamic psychotherapy (STPP) for depression?
Study protocol of a systematic review and meta-analysis of individual participant data.**

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Complete List of Authors:	Driessen, Ellen; Vrije Universiteit Amsterdam, Department of Clinical, Neuro and Developmental Psychology Abbass, Allan; DALHOUSIE UNIVERSITY, PSYCHIATRY Barber, Jacques P.; Adelphi University Connolly Gibbons, Mary Beth Dekker, Jack; Arkin Mental Health Care, Department of Research; Vrije Universiteit Amsterdam, Department of Clinical Psychology Fokkema, Marjolein Fonagy, Peter Hollon, Steven Jansma, Elise; Vrije Universiteit Amsterdam de Maat, Saskia; Arkin Town, Joel; Dalhousie University Department of Psychiatry Twisk, Jos; VU, Medisch Centrum Van, Henricus; Arkin Weitz, Erica; Vrije Universiteit Amsterdam, Department of Clinical, Neuro and Developmental Psychology Cuijpers, Pim; VU University Amsterdam, Department of Clinical Psychology
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Manuscripts

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3 1 **Which patients benefit specifically from short-term psychodynamic**
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5 2 **psychotherapy (STPP) for depression? Study protocol of a systematic review and**
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7 3 **meta-analysis of individual participant data.**
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11
12 5 Ellen Driessen ^{1*} e.driessen@vu.nl
13
14 6 Allan A. Abbass ² allan.abbass@dal.ca
15
16 7 Jacques P. Barber ³ jbarber@adelphi.edu
17
18 8 Mary Beth Connolly Gibbons ⁴ gibbonsm@mail.med.upenn.edu
19
20 9 Jack J. M. Dekker ⁵ jack.dekker@arkin.nl
21
22 10 Marjolein Fokkema ⁶ m.fokkema@fsw.leidenuniv.nl
23
24 11 Peter Fonagy ⁷ p.fonagy@ucl.ac.uk
25
26 12 Steven D. Hollon ⁸ steven.d.hollon@vanderbilt.edu
27
28 13 Elise P. Jansma ⁹ i.jansma@vu.nl
29
30 14 Saskia C. M. de Maat ¹⁰ saskia.demaat@gmail.com
31
32 15 Joel M. Town ² joel.town@dal.ca
33
34 16 Jos W. R. Twisk ^{11, 12} jwr.twisk@vumc.nl
35
36 17 Henricus L. Van ¹⁰ rien.van@arkin.nl
37
38 18 Erica Weitz ¹ e.weitz@vu.nl
39
40 19 Pim Cuijpers ¹ p.cuijpers@vu.nl
41
42
43
44
45
46
47
48
49

20
21 **Affiliations**

22 ¹ Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public
23 Health research institute, Vrije Universiteit Amsterdam, Netherlands

24 ² Centre for Emotions & Health, Dalhousie University, Halifax, NS, Canada

1
2
3 25 ³ Gordon F. Derner School of Psychology, Adelphi University, Garden City, NY, USA

4
5 26 ⁴ Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

6
7 27 ⁵ Department of Research, Arkin Mental Health Care, Amsterdam, Netherlands

8
9 28 ⁶ Department of Methodology and Statistics, Leiden University, Netherlands Research

10
11 29 ⁷ Department of Clinical, Educational and Health Psychology, University College

12
13
14 30 London, UK

15
16 31 ⁸ Department of Psychology, Vanderbilt University, Nashville, TN, USA

17
18 32 ⁹ University Library, Vrije Universiteit Amsterdam, Netherlands

19
20 33 ¹⁰ Dutch Psychoanalytic Institute, Arkin Mental Health Care, Amsterdam, Netherlands

21
22 34 ¹¹ Department of Health Sciences, Vrije Universiteit Amsterdam, Netherlands

23
24 35 ¹² Department of Epidemiology and Biostatistics, VU University Medical Center

25
26 36 Amsterdam, Netherlands

27
28
29 37

30
31 38 * Corresponding author:

32
33 39 Ellen Driessen, Ph.D.

34
35 40 Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public

36
37 41 Health research institute, Vrije Universiteit Amsterdam, Van der Boechorststraat 1, 1081

38
39 42 BT Amsterdam, Netherlands. T: +31 20 598 8973

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44 44 **Word count:** 4984 (excluding title page, abstract, references, figures, and tables)

1
2
3 45 **ABSTRACT**
4
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7
8 47 **Introduction:** Short-term psychodynamic psychotherapy (STPP) is an empirically
9
10 48 supported treatment that is often used to treat depression. However, it is largely unclear
11
12 49 if certain subgroups of depressed patients can benefit specifically from this treatment
13
14 50 method. We describe the protocol for a systematic review and meta-analysis of
15
16 51 individual participant data (IPD) aimed at identifying predictors and moderators of STPP
17
18 52 for depression efficacy.
19
20

21 53 **Method and analysis:** We will conduct a systematic literature search to identify studies
22
23 54 reporting (a) outcomes on standardized measures of (b) depressed (c) adult patients (d)
24
25 55 receiving STPP. We will next invite the authors of these studies to share the participant-
26
27 56 level data of their trials and combine these data to conduct IPD meta-analyses. The
28
29 57 primary outcome for this study is post-treatment efficacy as assessed by a continuous
30
31 58 depression measure. Potential predictors and moderators include all socio-demographic
32
33 59 variables, clinical variables, and psychological patient characteristics that are measured
34
35 60 before the start of treatment and are assessed consistently across studies. One-stage
36
37 61 IPD meta-analyses will be conducted using mixed effects models.
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42 62 **Ethics and dissemination:** IRB approval is not required for this study. We intend to
43
44 63 submit reports of the outcomes of this study for publication to international peer-
45
46 64 reviewed journals in the fields of psychiatry or clinical psychology. We also intend to
47
48 65 present the outcomes at international scientific conferences aimed at psychotherapy
49
50 66 researchers and clinicians. The findings of this study can have important clinical
51
52 67 implications, as they can inform expectations of STPP efficacy for individual patients,
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3 68 and help to make an informed choice concerning the best treatment option for a given
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5 69 patient.

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8 70 **Registration:** PROSPERO (registration number currently being assigned).
9

10 71

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12 72 **Word count abstract:** 265
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14 73

15
16
17 74 **Keywords:** depression, short-term psychodynamic psychotherapy, predictors,
18
19 75 moderators, individual participant data meta-analysis.
20

21 76

22 77 **Strengths and limitations of this study**

- 23
24
25
26 78 • This is the first study that systematically assesses patient characteristics associated
27
28 79 with STPP for depression efficacy.
29
30
31 80 • IPD meta-analysis allows for the examination of predictors and moderators by
32
33 81 maximizing statistical power while protecting against ecological bias that presents
34
35 82 problems when using conventional meta-analysis techniques.
36
37
38 83 • The findings of this study can have important clinical implications, as they can inform
39
40 84 expectations of STPP efficacy for individual patients, and help to make an informed
41
42 85 choice concerning the best treatment option for a given patient.
43
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45 86 • IPD meta-analyses rely on variables previously assessed in individual studies and
46
47 87 available across multiple trials. Thus, it is possible that not all variables of interest
48
49 88 can be examined as potential predictors or moderators.
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90 INTRODUCTION

91 Depression is a highly prevalent and disabling disorder associated with major personal
92 and societal costs.[1] Affecting more than 300 million people worldwide, depression is
93 ranked as the single largest contributor to global disability by the World Health
94 Organization.[2] Given the tremendous burden of disease, there is a great need for
95 effective and efficient treatments for depression. Antidepressant medications and
96 different psychological therapies constitute the predominant treatments for depressive
97 disorders.[3] Concerning psychological treatments, there is a clinical tradition of short-
98 term psychodynamic psychotherapies (STPPs) being used to treat depression.

99 Although STPP is a time-honored therapy for depression, its efficacy in this regard
100 has not been studied as extensively as the efficacy of other psychotherapies, such as
101 cognitive behavioral therapy (CBT).[4-5] For this reason, the efficacy of STPP for
102 depression has been debated.[6] This is reflected in treatment guidelines, which
103 typically have not considered STPP a first-choice therapy for depression.[7-8] In recent
104 years, there has been a change with the publication of a number of large-scale and
105 high-quality studies that support the efficacy of STPP for depression.[e.g.,9-10]
106 However, it remains unclear if certain subgroups of depressed patients can benefit
107 specifically from STPP.

108 Two types of information are relevant to this question: predictors and moderators.
109 Predictors (or prognostic factors) predict outcome to a given treatment and can be used
110 to determine which patients are more likely to respond to STPP relative to other
111 patients. Predictors can inform expectations of STPP efficacy, but are of little use in
112 deciding what treatment to select. On the other hand, moderators (or prescriptive

1
2
3 113 factors) can detect different patterns of outcomes between different treatments for
4
5 114 different types of patients and provide a basis for choosing the best treatment of a given
6
7
8 115 patient.[11]

9
10 116 Some preliminary empirical findings concerning predictors and moderators of STPP
11
12 117 efficacy for depression do exist. With regard to predictors, meta-regression analyses
13
14 118 alongside a 'conventional' meta-analysis - based on results extracted from
15
16
17 119 publications[12] - showed that mean pre-treatment depression scores were positively
18
19 120 associated with pre- to post-treatment depression effect size in STPP. With regard to
20
21 121 moderators, Driessen et al.[13] found STPP to be more efficacious than CBT among
22
23
24 122 depressed patients who showed low baseline comorbid anxiety levels. Furthermore,
25
26 123 Barber et al.[14] reported that STPP was more efficacious than medication or placebo
27
28 124 for ethnic minority males. However, a systematic assessment of which patient
29
30
31 125 characteristics are associated with STPP efficacy is currently lacking.

32
33 126 The main reason why predictors and moderators of STPP for depression have not
34
35 127 yet been examined thoroughly is lack of statistical power in individual clinical trials due
36
37
38 128 to relatively small sample sizes. Prediction and moderation analyses can also be
39
40 129 conducted alongside conventional meta-analyses. However, since these analyses are
41
42 130 usually based on study-level characteristics, they are prone to ecological bias, such that
43
44 131 the association between the study-level characteristics may not be representative of the
45
46
47 132 true relationships in the data at the individual level.[15] Thus, current research methods
48
49 133 (clinical trials and conventional meta-analyses) have been insufficient to answer the
50
51 134 question as to whether certain subgroups of patients can benefit specifically from STPP
52
53
54 135 for depression.

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2
3 136 Individual participant data (IPD) meta-analysis is a relatively new technique to
4
5 137 examine treatment effects by combining participant-level data of multiple trials. IPD
6
7 138 meta-analysis uses the same basic approach as any other well-conducted systematic
8
9
10 139 review and meta-analysis. However, it involves collection of the original data from as
11
12 140 many of the relevant trials worldwide as can be accessed. IPD meta-analysis has
13
14 141 several advantages over conventional meta-analysis, including increased statistical
15
16 142 power to examine predictors and moderators of treatment efficacy.[16] Furthermore,
17
18 143 because predictors and moderators are studied at patient-level, ecological bias can be
19
20 144 circumvented. For these reasons, IPD meta-analysis is currently considered the 'gold
21
22 145 standard' in evidence synthesis[17].
23
24
25

26 146 We describe the study protocol for a systematic review and IPD meta-analysis
27
28 147 concerning predictors and moderators of STPP for depression efficacy. The aim of this
29
30 148 project is to examine which depressed patients benefit specifically from STPP in terms
31
32 149 of depressive symptom reduction when compared to other patients (predictors), and
33
34 150 which patients benefit specifically from STPP when compared to no-treatment
35
36 151 conditions, other psychotherapies, and antidepressant medication (moderators). The
37
38 152 goal of this study is to collect the participant-level data of all trials examining the efficacy
39
40 153 of STPP for depression identified by a systematic literature search, and to combine
41
42 154 these datasets in order to conduct IPD meta-analyses.
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156 **METHODS**

158 **Design**

159 This study is a systematic review and meta-analysis of individual participant data that is
160 registered in the PROSPERO International prospective register of systematic reviews
161 (identification number is currently being assigned). Important protocol amendments will
162 be documented in this register too. The project started December 1st, 2016 and is
163 expected to be completed November 30th, 2018.

165 **Search strategy**

166 We will use an extensive search strategy including six different search methods in order
167 to retrieve as many relevant studies as possible. These searches have already been
168 performed in 2007 and 2014 for two previous conventional meta-analyses concerning
169 the efficacy of STPP for depression[12,18] and will be updated in 2017.

170 First, we will systematically search the bibliographic databases PubMed, PsycINFO
171 (via EBSCO), Embase.com, Web of Science (via Elsevier), and Cochrane's Central
172 Register of Controlled Trials (via Wiley). Search terms will include a wide range of
173 synonyms, both in index terms and free-text words, for 1) psychodynamic
174 psychotherapy (e.g., psychotherapy, psychoanalytic), 2) therapy (e.g., psychotherapy),
175 3) psychodynamic (e.g., dynamic*), and 4) depression (e.g., depressive disorder).

176 These four sets of search terms will be combined as follows: (#1 OR (#2 AND #3)) AND
177 #4. The exact terms for the search in PubMed are presented in Table 1. Complete

178 search terms for all electronic databases are available on request from the
 179 corresponding author. No language or date restrictions will be applied in the searches.

180

181 **Table 1. PubMed search strategy**

Search	PubMed Query 19-06-2017	Items found
#8	Search #7 NOT ("addresses"[Publication Type] OR "biography"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type])	2285
#7	Search #6 AND #4	2350
#6	Search #1 OR #5	39841
#1	Search "Psychoanalytic Therapy"[Mesh] OR "Psychotherapy, Psychodynamic"[Mesh] OR psychodynamic*[tiab] Sort by: Relevance	20177
#5	Search #2 AND #3	21435
#4	Search Depressive disorder[Mesh] OR depression[Mesh] OR ((depress*[tiab] OR melancholia*[tiab] OR dysphoria*[tiab] OR dysthymi*[tiab] OR "seasonal affective disorder"[tiab]) NOT medline[sb])	223737
#3	Search dynamic*[tiab] OR STPP[tiab] OR BDT[tiab] OR DIT[tiab] OR insight*[tiab] OR interpretive[tiab] OR interpretative[tiab] OR analytic*[tiab] OR psychoanalytic*[tiab]	1073217
#2	Search ("Psychotherapy"[Mesh:noexp] OR "Animal Assisted Therapy"[Mesh] OR "Art Therapy"[Mesh] OR "Bibliotherapy"[Mesh] OR "Psychotherapy, Group"[Mesh] OR "Psychotherapy, Brief"[Mesh] OR "Psychotherapy, Multiple"[Mesh] OR "Counseling"[Mesh:NoExp] OR "Directive Counseling"[Mesh:NoExp] OR ((psychotherap*[tiab] OR therap*[tiab] OR counseling[tiab]) NOT medline[sb]))	380901

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2
3 182 Second, in order to identify relevant studies from the so-called 'grey literature', we will
4
5 183 search GLIN, a Dutch electronic database for grey literature, and UMI database
6
7
8 184 ProQuest for digital dissertations. Third, a prospective trial register will be searched for
9
10 185 unpublished ongoing research (<http://www.controlled-trials.com>). The grey literature and
11
12 186 prospective trial register searches will be conducted using the search strategy described
13
14 187 above. Fourth, we will search an Internet database of controlled and comparative
15
16 188 outcome studies on psychological treatments of depression
17
18 189 (<http://www.psychotherapytrials.org>[19]) for studies examining STPP. Fifth, reviews and
19
20 190 meta-analyses concerning the efficacy of psychodynamic treatments for depression or
21
22 191 for psychiatric disorders in general retrieved from the first search method will be
23
24 192 screened for relevant references not located by means of the other search methods.
25
26 193 Sixth, we will contact an email list of researchers in the field of psychodynamic therapy
27
28 194 to ask for ongoing or unpublished studies.
29
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33 195

35 196 **Selection of studies**

36
37 197 We will include studies if they report (a) outcomes on standardized measures of (b)
38
39 198 depressed (c) adult patients (d) receiving STPP. Participants are considered depressed
40
41 199 if they meet specified criteria for major depressive disorder or another mood disorder, or
42
43 200 if they present an elevated score on a standardized measure of depression. Participants
44
45 201 need to be at least 18 years old, and studies concerning older adults (mean age >55)
46
47 202 will be included as well. We will include studies in which STPP (a) is based on
48
49 203 psychoanalytic theories and practices, (b) is time-limited from the onset (i.e. not a
50
51 204 therapy that is brief only in retrospect), and (c) applies verbal techniques (e.g., therapies
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3 205 applying art as expression form are not considered STPP). Studies need to include at
4
5 206 least 10 subjects. Case studies will therefore be excluded. We will also include
6
7 207 naturalistic studies with a heterogeneous study sample, if these studies include more
8
9 208 than 10 participants diagnosed as depressed, as these subgroups also meet the
10
11 209 inclusion criteria specified previously. For these studies, the authors will be contacted
12
13 210 with a request for subgroup data.
14
15

16
17 211 The screening process will consist of three phases. At first, the selection criteria will
18
19 212 be applied to the citations generated from the searches independently by two raters.
20
21 213 Disagreements will be discussed and resolved by consensus. Unless they can be
22
23 214 definitely excluded, titles identified as potentially relevant will be requested in full text.
24
25 215 During the second screening phase, two independent raters will apply the selection
26
27 216 criteria to the full-text papers. Disagreements will be discussed and resolved by
28
29 217 consensus. During the third phase, two expert STPP raters will confirm that the included
30
31 218 papers meet criteria for STPP. Again, disagreements will be discussed and resolved by
32
33 219 consensus. When disagreements cannot be resolved in this way, a third rater will be
34
35 220 consulted.
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41 42 222 **Data collection**

43
44 223 Authors of the included studies will be contacted and invited to contribute the
45
46 224 participant-level data of their studies. Researchers who share their data will be offered
47
48 225 co-authorship for all publications that are based on their study's data (group-
49
50 226 authorship), given that they meet standard criteria for authorship of scientific
51
52 227 publications according to internationally accepted criteria (www.icmje.org). In addition,
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3 228 the collected data will be made available to investigators who contribute data to
4
5 229 examine other research questions in the combined dataset. This strategy has been
6
7
8 230 used in previous IPD meta-analyses concerning depression treatments[20-21] and has
9
10 231 been successful in convincing researchers to share their data.

11
12 232 Contact details of all first authors will be collected from the relevant publications, or if
13
14 233 not reported there, through Internet searches or personal contacts with other
15
16
17 234 researchers. First authors will be contacted by email with a letter of invitation outlining
18
19 235 the project's goals and asking if they would be willing to collaborate by sharing the
20
21 236 participant-level data of their trial. If an author does not respond after three weeks, a
22
23
24 237 second and third email will be sent. In case of non-response to email, a letter will be
25
26 238 sent (again with three attempts). If still no response is received, we will try to contact the
27
28 239 author by telephone. If all these attempts fail, the last, second, third, fourth, etc. author
29
30 240 of the study (in this order) will be contacted in the same way. If none of the authors
31
32 241 respond to these efforts, other ways will be sought to contact one of the authors (e.g.,
33
34 242 via colleagues or anyone who might know them). Study data will be considered
35
36
37 243 unavailable only if all these attempts fail, or in the event that an author indicates that the
38
39 244 participant-level data have not been retained or declines sharing these data.

40
41
42 245 If the author is willing and able to share the individual participant data of his/her trial,
43
44 246 both parties will sign a data sharing agreement. The author will then transfer the
45
46
47 247 participant-level dataset, including all potential predictors and moderators assessed
48
49 248 before the start of treatment, as well as all outcome variables assessed during and after
50
51 249 treatment, both in the STPP condition as well as in any comparison condition included
52
53
54 250 in the study. The author will anonymize the data, so that the dataset is transferred

1
2
3 251 without containing personal information that can lead back to individuals. Data can be
4
5 252 submitted to the project in any format, and will then be converted to Stata.
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8 253

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10 254 **Data integrity check**

11
12 255 After the dataset has been transferred, the file will be checked to examine whether the
13
14 256 data received match the data reported in the publication. For all treatment conditions
15
16 257 included in the study, sample size, number of females, mean age, observed mean pre-
17
18 258 treatment depression scores, observed mean post-treatment score for the primary
19
20 259 depression outcome, and the number of missing cases for the latter will be calculated
21
22 260 from the dataset received and checked against the published article for this purpose.
23
24 261 Discrepancies will be resolved with the authors. In addition, the data will be checked for
25
26 262 invalid, out-of-range, or inconsistent items. Furthermore, we will check the integrity of
27
28 263 the randomization for randomized studies by inspecting the balance of the potential
29
30 264 predictor/moderator variables across treatment arms.
31
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34
35 265 For each study, we will list all predictor/moderator variables that were assessed, as
36
37 266 well as all outcome variables, intermediate, and follow-up assessments. We will also
38
39 267 extract multiple STPP characteristics and study design characteristics (for an overview
40
41 268 see[12]) as well as study validity criteria according to the Cochrane risk of bias
42
43 269 assessment tool[22].
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45
46

47 270 After checking the data, the datasets will be standardized. For this purpose, a copy of
48
49 271 each trial's raw data file will be recoded into a data file that matches the IPD meta-
50
51 272 analysis database in terms of variables. Next, the individual study data files will be
52
53 273 concatenated in one database structured by study and individual participant ID. After all
54
55
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1
2
3 274 data files have been recoded and entered, the data for each study will be checked with
4
5 275 the original data file received for accuracy. A codebook document will be made that
6
7 276 includes the coding of the individual studies as well as the coding of the combined study
8
9 277 database. Coding for the database will be finalized when all data have been received
10
11 278 from the study authors.
12
13
14
15 279

16 17 280 **Measures**

18
19 281 The primary outcome for this study is treatment efficacy as assessed by a continuous
20
21 282 depression outcome measure at post-treatment. We have chosen depressive symptom
22
23 283 status as the main outcome for this study as we consider this to be the primary target of
24
25 284 STPP for depression. We chose continuous symptom level as the primary outcome,
26
27 285 because we expect that the increased variance relative to dichotomous outcomes might
28
29 286 facilitate the search for predictors and moderators. We have chosen post-treatment
30
31 287 assessment as the primary end-point as it is difficult to control additional treatment in
32
33 288 the follow-up period in psychotherapy efficacy studies (e.g.,[23]).
34
35
36

37 289 For each trial, we will identify the primary continuous depression outcome as defined
38
39 290 by the study authors. All instruments explicitly measuring depression qualify in this
40
41 291 regard. Different depression measures have probably been used and, therefore, we will
42
43 292 standardize the depression outcomes by converting the depression scores into Z-
44
45 293 scores. Sensitivity analyses will be conducted using unstandardized scores for each
46
47 294 depression measure that is assessed in the majority of studies included in the meta-
48
49 295 analysis (e.g., Hamilton Depression Rating Scale[24], Beck Depression Inventory[25]).
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3 296 The secondary outcomes for this study are dichotomous depression outcomes for 1)
4
5 297 response (a 50% reduction in symptoms from pre- to post-treatment), and 2) remission
6
7 298 (maximum absolute post-treatment scores reflecting normalization). In addition,
8
9 299 outcome measures other than depression will be collected (e.g., anxiety symptoms,
10
11 300 quality of life, interpersonal functioning). These can be considered tertiary outcomes.
12
13

14 301 Potential predictors and moderators include socio-demographic variables (e.g.,
15
16 302 gender, age, education level, marital status, employment status, ethnicity), clinical
17
18 303 variables (e.g., number of previous depressive episodes, previous exposure to
19
20 304 treatment, comorbid Axis I and II psychopathology, global assessment of functioning),
21
22 305 and psychological patient characteristics (e.g., personality organization, attachment,
23
24 306 interpersonal styles, childhood maltreatment). These are likely assessed differently in
25
26 307 individual studies and will be standardized as well, for instance by converting scores
27
28 308 into Z-scores for continuous variables or by recoding variables into similar categories for
29
30 309 categorical variables. In the latter case, we will consult study authors to confirm
31
32 310 correctness of the recoding.
33
34
35
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37

38 311

39 312 **Missing data**

40 313 All datasets received that contain individual participant data, at least one relevant
41
42 314 outcome measure, and at least one predictor/moderator variable will be considered for
43
44 315 quantitative synthesis. We will examine the possibility of complete-case analyses by
45
46 316 evaluating the extent of missing data as well as the possible reasons for missing data,
47
48 317 and by comparing patients with complete data to patients with missing data. We will
49
50 318 also assess whether the missing data can be considered missing at random.[26] If
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3 319 complete-case analysis is not justifiable and data can be considered missing at random,
4
5 320 we will impute missing data using multiple imputation, which is currently considered to
6
7 321 be the most sophisticated method for handling missing data.[27]
8
9

10 322 We will generate one imputed dataset for each percent of missing data (e.g., when
11
12 323 30% of the data is missing, we will create 30 imputed datasets). We will impute missing
13
14 324 data by means of hierarchical imputation with fully conditional specification (FCS-
15
16 325 GLM),[28] which allows for preserving the heterogeneity across studies, non-normal
17
18 326 distributions of variables, and imputing systematically missing variables. FCS-GLM has
19
20 327 shown to be a reliable procedure with advantageous properties for IPD meta-analyses
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22 328 with limited numbers of studies or studies with small sample sizes.[29] FCS-GLM will be
23
24 329 conducted in R. To ensure congeniality, imputation will be based on all variables that
25
26 330 will be included in the meta-analysis model including their interactions as well as any
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28 331 variables that were identified to be predictive of missing values.[29] If multiple
29
30 332 imputation is pursued, we will conduct sensitivity analyses restricted to complete cases
31
32 333 and compare the results. We will not pursue efforts to combine IPD with aggregate data
33
34 334 from studies for which no IPD is available,[30] since the requisite treatment-covariate
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36 335 interactions are seldom reported in publications.
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44 337 **Data-analysis**

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46 338 We will conduct IPD meta-analyses according to the one-stage approach, because that
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48 339 accounts for the correlation amongst model parameters when modelling interactions,
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50 340 offers the highest degree of flexibility for making the necessary assumptions when
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52 341 detecting treatment-covariate interactions,[31] and provides a more exact likelihood in
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3 342 the case of small studies.[32] We will conduct IPD meta-analyses using mixed models
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5 343 with restricted maximum likelihood to estimate between-study heterogeneity, which is
6
7 344 recommended when there are few studies in the meta-analysis or studies have small
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10 345 sample sizes.[33] Analyses will be conducted in Stata 'mixed'. We will apply the
11
12 346 Kenward-Roger denominator-degrees-of-freedom adjustment for confidence
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14 347 intervals,[34] because it more adequately accounts for uncertainty than the standard
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16
17 348 Dersimonian-Laird estimator when the number of studies is small or when heterogeneity
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19 349 is present.[35] To account for clustering of patients within studies and to preserve
20
21 350 randomization, we will include a random intercept for study and a random slope for
22
23 351 baseline depression. We assume that these random effects will be normally distributed
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25
26 352 and this assumption will be assessed. We will assess heterogeneity by examining the
27
28 353 standard deviation of the predictor or moderator parameter estimates.

30
31 354 Separate analyses will be conducted for the identification of predictors and the
32
33 355 identification of moderators of STPP efficacy. With regard to predictors, IPD from STPP
34
35 356 conditions across all studies will be combined, regardless of study type (randomized
36
37 357 controlled study, non-random comparative study, naturalistic study). For each of the
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39
40 358 potential predictors, a model will be estimated with baseline depression and the
41
42 359 predictor's main effect. A random slope will be added to the predictor to examine if this
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44 360 results in a model improvement. If so, this predictor variable will be included with a
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46
47 361 random slope in subsequent analyses. Next, all predictors will be modeled
48
49 362 simultaneously. Backward selection based on p-value will be conducted until a final
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51 363 prediction model is obtained consisting of statistical significant predictors only. This
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53
54 364 prediction model will be validated in a held-out sample of the data.

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3 365 With regard to moderators, analyses will be conducted separately for each
4
5 366 comparison (e.g., STPP versus control conditions, STPP versus other psychotherapy,
6
7 367 STPP versus antidepressant medication). These analyses will only include IPD from
8
9 368 randomized studies. For each of the potential moderators, a model will be estimated
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11 369 with baseline depression as well as the moderator's main effect and interaction with
12
13 370 treatment. Next, to examine ecological bias, within-study and across-study interaction
14
15 371 effects will be separated.[30] If within-study and across-study interactions differ,
16
17 372 ecological bias may be at play, and only the within-trial interaction will be interpreted in
18
19 373 subsequent analyses. Finally, all significant treatment-covariate interactions, their main
20
21 374 effects, and higher order interactions will be modeled simultaneously. The resulting
22
23 375 prediction model will be validated in a held-out sample of the data.
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28 376 A number of sensitivity analyses will be conducted to examine the robustness of the
29
30 377 findings. To examine the impact of study quality, we will conduct sensitivity analyses
31
32 378 including only studies that score high on all quality criteria. In addition, we will conduct
33
34 379 analyses in which we add the risk of bias items as covariates to the mixed effects
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36 380 models, centered at a value indicating freedom of bias.[36] We will also conduct
37
38 381 sensitivity analyses to control for the effects of additional non-study treatment during the
39
40 382 trial and in the follow-up period by adding collected data in this regard as covariates to
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42 383 the mixed effects models. Finally, we will examine the impact of STPP delivery mode
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44 384 (individual versus group STPP) by adding this variable to the mixed effects models too.
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49 385 Furthermore, to examine possible data availability bias, t-tests and chi-square
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51 386 analyses will be conducted comparing the included studies with studies for which no
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53 387 participant-level data was obtained with regard to the extracted study characteristics.
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3 388 Conventional meta-analysis techniques will be utilized to examine differences in effect
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5 389 sizes between studies that contributed data and studies that did not. We will assess
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7 390 potential publication bias by assessing asymmetry in contour enhanced funnel plots for
8
9 391 meta-analyses including 10 or more trials, as is recommended by Sterne and
10
11 392 colleagues.[37] The confidence in the cumulative body of evidence will be assessed
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13
14 393 according to GRADE.

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17 394 In addition, we will conduct explorative analyses using tree-based statistical learning.
18
19 395 More specifically, we will use the generalized linear mixed effects regression trees
20
21 396 algorithm (glmertree[38]) in R to detect predictors and moderators of continuous and
22
23 397 binary treatment outcomes. These analyses offer several advantages over more
24
25 398 traditional mixed-effects modeling approaches, as they allow for the detection of non-
26
27 399 linear and higher-level interactions, allow for specifying a large number of potential
28
29 400 predictor and moderator variables and involve less stringent assumptions about the
30
31 401 distribution of the data. Furthermore, the result of applying glmertree consists of a
32
33 402 decision tree that graphically depicts the effects of the relevant predictor and moderator
34
35 403 variables. Such a tree can easily be interpreted, and applied in clinical decision-making.
36
37 404 However, it should be noted that such tree-based analyses are exploratory by nature.
38
39 405 We will assess the expected predictive accuracy on new data using *k*-cross
40
41 406 validation[39] and the stability of the resulting decision trees using subsampling
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43 407 methods.[40] The glmertree analyses will be performed using observed, non-imputed
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45 408 data only, as it is currently unclear how to best specify the model for generating imputed
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47 409 data in tree-based analyses for clustered data.
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411 **ETHICS AND DISSEMINATION**

412 IRB approval was not required for this project. IRB approval may be required for the
413 investigators who share their primary data depending on their institution's policies. It is
414 the responsibility of the investigators to obtain IRB approval if their institution's policies
415 require them to do so. We intend to submit reports of the outcomes of this study for
416 publication to international peer-reviewed journals in the fields of psychiatry or clinical
417 psychology. We also intend to present the findings of this study at international scientific
418 conferences aimed at psychotherapy researchers and clinicians.

419

420

421 **DISCUSSION**

422 We described the study protocol of a systematic review and meta-analysis of IPD to
423 examine predictors and moderators of STPP efficacy for depression. The goal of this
424 study is to collect the participant-level data of all studies examining the efficacy of STPP
425 for depression identified by a thorough literature search, and to combine these datasets
426 in order to conduct IPD meta-analyses. The proposed study design allows for the
427 examination of predictors and moderators of STPP efficacy with increased statistical
428 power and can thus help to show which subsets of depressed patients specifically
429 benefit from therapies based on psychoanalytic principles.

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431 **Clinical and scientific relevance**

432 STPPs are underrepresented in current treatment guidelines for depressive disorders,
433 in contrast to how commonly they are utilized in clinical practice. Further high-quality

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3 434 research that extends and disseminates knowledge about the effectiveness of STPP is
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5 435 therefore called for. Research showing whether subsets of depressed patients can
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7 436 specifically benefit from this therapy modality, especially when compared to other
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9 437 treatments, is particularly needed. Knowledge of such moderators can have important
10
11 438 implications for clinical practice, as it can be used to guide treatment selection and
12
13 439 increase the efficiency of treatments for depression by helping patients and clinicians to
14
15 440 make an informed choice concerning the best treatment option for a given patient.
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19 441 Little is known about patient characteristics associated with STPP efficacy, because
20
21 442 clinical trials often have relatively small sample sizes and limited statistical power to
22
23 443 examine predictors and moderators of change. Moreover, prediction and moderation
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25 444 analyses in conventional meta-analyses are often based on study-level aggregates and
26
27 445 are, therefore, prone to ecological bias. By means of individual participant data meta-
28
29 446 analyses these critical limitations can be overcome. IPD meta-analyses have been
30
31 447 utilized more frequently in the medical field, but are newer in the field of psychiatry and
32
33 448 clinical psychology.[41] Although IPD meta-analyses have now been used to examine
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35 449 single moderators of CBT and pharmacotherapy efficacy for depression,[20-21] to date
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37 450 no IPD meta-analysis has been conducted concerning STPP.
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452 **Strengths and limitations**

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47 453 Individual participant data meta-analysis has several advantages over conventional
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49 454 meta-analysis, including increased statistical power to examine predictors and
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51 455 moderators.[16] In addition, by collecting the primary data, access to predictor or
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53 456 moderator variables that might not have been reported in the published articles is
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3 457 gained; increasing the chance that aggregation of these variables across studies is
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5 458 possible. Other advantages of individual participant data meta-analysis over
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7 459 conventional meta-analysis include the possibility to 1) account for missing data at the
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9 460 individual participant level, so that for instance intention-to-treat analyses can be
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11 461 conducted even though the original study reported completers-only analyses, 2) use the
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13 462 same statistical methods for imputing missing data and for conducting statistical
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15 463 analyses, thereby facilitating standardization across studies, 3) standardize outcomes
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17 464 across studies, for instance by using equal cut-off points on a depression outcome
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19 465 measure when the primary studies used different cut-offs, and 4) verify the results
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21 466 presented in the original studies, also by means of more sophisticated statistical
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23 467 techniques that were not available at time of publication in the case of older studies.[42]

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25 468 IPD meta-analyses involve collection of original data from all the relevant trials
26
27 469 worldwide that can be accessed. These data need to be prepared and checked before
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29 470 being included in the meta-analysis, and complex decisions on the data sometimes
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31 471 need to be made in order to ensure the accuracy of the outcomes. Therefore, it takes
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33 472 more time and resources to conduct an IPD meta-analysis than to conduct a
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35 473 conventional meta-analysis based solely on results extracted from published trial
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37 474 reports.[42] However, the IPD approach can improve the quality of both the data and
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39 475 the analyses, and so the reliability of the results. Therefore, it is considered the 'gold
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41 476 standard' of meta-analysis.[17]

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43 477 IPD meta-analyses can also have a number of limitations. First, although IPD meta-
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45 478 analyses are generally considered the most reliable approach to evidence
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47 479 synthesis,[17] this does not mean that they are bias-free and selection bias, publication
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3 480 bias, and data availability bias need to be considered.[43] We do so by performing a
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5 481 systematic literature search that also aims to identify grey literature and unpublished
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7 482 work, and by testing for differences between studies for which IPD was and was not
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9 483 obtained. Second, IPD meta-analyses rely on variables previously assessed in
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11 484 individual studies and available across multiple trials. For this reason, it is possible that
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13 485 not all variables of interest can be examined as potential predictors or moderators.
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15 486 Third, and related, it is necessary to standardize predictor/moderator variables for the
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17 487 analyses, but doing so might involve recoding and possibly omitting important
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19 488 information for some variables. Fourth, although combining multiple trials reduces the
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21 489 possibility that predictors/moderators identified are chance findings in single study
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23 490 samples, generalizability of the findings might still be limited to patients who volunteer to
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25 491 participate in scientific outcome research.
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33 493 **Conclusion**

34
35 494 We described the study protocol for a systematic review and meta-analysis of IPD
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37 495 aimed at examining if certain subgroups of depressed patients can benefit specifically
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39 496 from STPP. We will collect the participant-level data of all studies examining the efficacy
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41 497 of STPP for depression identified by a thorough literature search. We will combine these
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43 498 datasets and conduct IPD meta-analyses to identify predictors and moderators of STPP
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45 499 efficacy. Knowledge of such predictors and moderators can have important implications
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47 500 for clinical practice, as they can, respectively, inform expectations of treatment efficacy
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49 501 for individual patients, and help patients and clinicians to make an informed choice
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51 502 concerning the best treatment option for a given patient.
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503 **AUTHORS' CONTRIBUTIONS**

504 All authors made substantial contributions to the study design or the acquisition of
505 individual participant data. ED, EW, and PC drafted the manuscript. All other authors
506 revised it critically for important intellectual content and approved the final version of this
507 manuscript. ED is the guarantor of the review.

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516 **COMPETING INTERESTS STATEMENT**

517 AAA practices and provides training in methods of STPP and receives royalties from a
518 book he wrote on STPP. JPB has given talks on STPP at workshops and conferences
519 for which organizers often have not paid for travel and accommodations. JPB and JJMD
520 receive royalties from books on STPP they have co-authored. JMT has given talks on
521 STPP at workshops and conferences for which organizers have paid for travel and
522 accommodations. PF declares being Chief Executive of the Anna Freud Centre (UK).
523 He teaches mentalization-based treatment trainings and dynamic-interpersonal therapy
524 trainings in the UK and internationally. He is the Co-PI on The IMPACT Study – The
525 Effectiveness of Psychological Treatment for Depressed Adolescents, and Consultant to

1
2
3 526 the Child and Family Program at the Menninger Department of Psychiatry and
4
5 527 Behavioural Sciences at Baylor College of Medicine, Houston, TX, USA. PF also
6
7 528 receives royalties from books on interpersonal psychotherapy which he has co-authored
8
9
10 529 with others. HLV and SCMdM are trainers and registered supervisors of short-term
11
12 530 psychodynamic supportive psychotherapy. They also receive royalties from books on
13
14 531 STPP they have co-authored. SDH reports no financial conflicts, but acknowledges an
15
16 532 intellectual passion for the cognitive and behavioral interventions for depression. ED,
17
18
19 533 MBCG, MF, JWRT, EW, and PC declare that they have no known conflicts of interest.
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534 **REFERENCES**

- 535 1 Kessler RC. The costs of depression. *Psychiatr Clin North Am* 2012;35:1-14.
- 536 2 World Health Organization. Depression and other common mental disorders. Global
537 health estimates. [http://apps.who.int/iris/bitstream/10665/254610/1/WHO-MSD-
MER-2017.2-eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/254610/1/WHO-MSD-
538 MER-2017.2-eng.pdf?ua=1) (accessed July 2017).
- 539 3 Marcus SC, Olfson M. National trends in the treatment of depression from 1998 to
540 2007. *Arch Gen Psychiatry* 2010;67:1265-73.
- 541 4 Cuijpers P, van Straten A, Andersson G, et al. Psychotherapy for depression in adults:
542 a meta-analysis of comparative outcome studies. *J Consult Clin Psychol*
543 2008;76:909-22.
- 544 5 Thase ME. Comparative effectiveness of psychodynamic psychotherapy and
545 cognitive-behavioral therapy: It's about time, and what's next? *Am J Psychiatry*
546 2013;170:953-56.
- 547 6 Connolly-Gibbons MB, Crits-Christoph P, Hearon B. The empirical status of
548 psychodynamic therapies. *Annu Rev Clin Psychol* 2008;4:93-108.
- 549 7 American Psychiatric Association. Practice guideline for the treatment of patients with
550 major depressive disorder (3rd ed).
551 [http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/md
d.pdf](http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/md
552 d.pdf) (accessed July 2017).
- 553 8 National Institute for Health and Clinical Excellence. Depression: The treatment and
554 management of depression in adults (update). <http://guidance.nice.org.uk/CG90/>
555 (accessed July 2017).

- 1
2
3 556 9 Beutel ME, Weißflog G, Leuteritz K, et al. Efficacy of short-term psychodynamic
4
5 557 psychotherapy (STPP) with depressed breast cancer patients: results of a
6
7 558 randomized controlled multicenter trial. *Ann Oncol* 2014;25:378-84.
- 9
10 559 10 Connolly Gibbons MB, Gallop R, Thompson D, et al. Comparative effectiveness of
11
12 560 cognitive therapy and dynamic psychotherapy for major depressive disorder in a
13
14 561 community mental health setting. *JAMA Psychiatry* 2016;73:904-11.
- 16
17 562 11 Kraemer HC, Wilson GT, Fairburn CG, et al. Mediators and moderators of treatment
18
19 563 effects in randomized clinical trials. *Arch Gen Psychiatry* 2002;59:877-83.
- 21
22 564 12 Driessen E, Hegelmaier LM, Abbass AA, et al. The efficacy of short-term
23
24 565 psychodynamic psychotherapy for depression: a meta-analysis update. *Clin*
25
26 566 *Psychol Rev* 2015;42:1-15.
- 28
29 567 13 Driessen E, Smits N, Dekker JJM, et al. Differential efficacy of cognitive behavioral
30
31 568 therapy and psychodynamic therapy for major depression: a study of prescriptive
32
33 569 factors. *Psychol Med* 2016;46:731-44.
- 35
36 570 14 Barber JP, Barrett MS, Gallop R, et al. Short-term dynamic therapy vs.
37
38 571 pharmacotherapy for major depressive disorder. *J Clin Psychiatry* 2012;73:66-73.
- 39
40 572 15 Fisher DJ, Carpenter JR, Morris TP, et al. Meta-analytical methods to identify who
41
42 573 benefits most from treatments: daft, deluded, or deft approach? *BMJ* 2017;356:j573.
- 44
45 574 16 Lambert PC, Sutton AJ, Abrams KR, et al. A comparison of summary patient-level
46
47 575 covariates in meta-regression with individual patient data meta-analysis. *J Clin*
48
49 576 *Epidemiol* 2002;55:86-94.
- 51
52 577 17 Stewart LA, Parmar MKB. Meta-analysis of the literature or of individual patient data:
53
54 578 is there a difference? *Lancet* 1993;341:418-22.

- 1
2
3 579 18 Driessen E, Cuijpers P, de Maat SCM, et al. The efficacy of short-term
4
5 580 psychodynamic psychotherapy for depression: a meta-analysis. *Clin Psychol Rev*
6
7 581 2010;30:25-36.
8
9
10 582 19 Cuijpers P, van Straten A, Warmerdam L, et al. Psychological treatment of
11
12 583 depression: A meta-analytic database of randomized studies. *BMC Psychiatry*
13
14 584 2008;8:36.
15
16
17 585 20 Cuijpers P, Weitz E, Twisk J, et al. Gender as predictor and moderator of outcome in
18
19 586 cognitive behavior therapy and pharmacotherapy for adult depression: an “individual
20
21 587 patient data” meta-analysis. *Depress Anxiety* 2014;31:941-51.
22
23
24 588 21 Weitz ES, Hollon SD, Twisk J, et al. Baseline depression severity as moderator of
25
26 589 depression outcomes between cognitive behavioral therapy vs pharmacotherapy:
27
28 590 an individual patient data meta-analysis. *JAMA Psychiatry* 2015;72:1102-09.
29
30
31 591 22 Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions
32
33 592 Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available at:
34
35 593 <http://www.cochrane-handbook.org>.
36
37
38 594 23 Driessen E, Van HL, Don FJ, et al. The efficacy of cognitive-behavioral therapy and
39
40 595 psychodynamic therapy in the outpatient treatment of major depression: a
41
42 596 randomized clinical trial. *Am J Psychiatry* 2013;170:1041-50.
43
44
45 597 24 Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*
46
47 598 1960;23:56–62.
48
49 599 25 Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression.
50
51 600 *Arch Gen Psychiatry* 1961;4:561–71.
52
53
54
55
56
57
58
59
60

- 1
2
3 601 26 Sterne JAC, White IA, Carlin JB, et al. Multiple imputation for missing data in
4
5 602 epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393.
6
7
8 603 27 Donders A, van der Heiden G, Stijnen T, et al. Review: a gentle introduction to
9
10 604 imputation of missing values. *J Clin Epidemiol* 2012;59:1087–91.
11
12 605 28 Jolani S, Debray TPA, Koffijberg H, et al. Imputation of systematically missing
13
14 606 predictors in an individual participant data meta-analysis: a generalized approach
15
16 607 using MICE. *Stat Med* 2015;34:1841-63.
17
18
19 608 29 Audigier V, White IR, Jolani S, et al. Multiple imputation for multilevel data with
20
21 609 continuous and binary variables. <https://arxiv.org/abs/1702.00971> (accessed July
22
23 610 2017).
24
25
26 611 30 Riley RD, Lambert PC, Staessen JA, et al. Meta-analysis of continuous outcomes
27
28 612 combining individual patient data and aggregate data. *Stat Med* 2008;27:1870-93.
29
30
31 613 31 Debray TPA, Moons KGM, van Valkenhoef G, et al. Get real in individual participant
32
33 614 data (IPD) meta-analysis: a review of the methodology. *Res Synth Methods* 2015;6:
34
35 615 293-309.
36
37
38 616 32 Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-
39
40 617 stage and two-stage approaches, and why they may differ. *Stat Med* 2017;36:855-
41
42 618 75.
43
44
45 619 33 Higgins JPT, Whitehead A, Turner RM, et al. Meta-analysis of continuous outcome
46
47 620 data from individual patients. *Stat Med* 2001;20:2219-41.
48
49 621 34 Kenward MG, Roger JH. Small sample inference for fixed effects from restricted
50
51 622 maximum likelihood. *Biometrics* 1997;53:983-97.
52
53
54
55
56
57
58
59
60

- 1
2
3 623 35 Cornell JE, Mulrow CD, Localio R, et al. Random-effects meta-analysis of
4
5 624 inconsistent effects: a time for change. *Ann Intern Med* 2014;160:267-70.
6
7
8 625 36 Higgins JPT, Thomspon SG, Spiegelhalter DJ. A re-evaluation of random-effects
9
10 626 meta-analysis. *J R Stat Soc* 2009;172:137-59.
11
12 627 37 Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and
13
14 628 interpreting funnel plot asymmetry in meta-analyses of randomized controlled trials.
15
16 629 *BMJ* 2011;343:d4002.
17
18
19 630 38 Fokkema M, Smits N, Zeileis A, et al. Detecting treatment-subgroup interactions in
20
21 631 clustered data with generalized linear mixed-effects model trees. *Working Papers in*
22
23 632 *Economics and Statistics* No. 2015-10.
24
25
26 633 39 Friedman J, Hastie T, Tibshirani R. *The Elements of Statistical Learning* (2nd Ed.).
27
28 634 Berlin: Springer 2009.
29
30
31 635 40 Philipp M, Zeileis A, Strobl C. A toolkit for stability assessment of tree-based
32
33 636 learners. *Working Papers in Economics and Statistics* No. 2016-11.
34
35
36 637 41 Simmonds M, Stewart G, Stewart L. A decade of individual participant data meta-
37
38 638 analyses: A review of current practice. *Contemp Clin Trials* 2015;45:76-83.
39
40 639 42 Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data:
41
42 640 rationale, conduct, and reporting. *BMJ* 2010;340:c221.
43
44
45 641 43 Ahmed I, Sutton AJ, Riley R. Assessment of publication bias, selection bias, and
46
47 642 unavailable data in meta-analyses using individual participant data: a database
48
49 643 survey. *BMJ* 2011;344:d7762.
50
51
52
53
54
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56
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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	70
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	5-42
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	503-507
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input checked="" type="checkbox"/>	<input type="checkbox"/>	161-162
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	510-513
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	511
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	511-513
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	99-145
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to	<input checked="" type="checkbox"/>	<input type="checkbox"/>	146-154

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		participants, interventions, comparators, and outcomes (PICO)			
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	196-210, 179
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	165-194
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	170-181, Table 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	265-278
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	211-220
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	222-264
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	246-250, 265-269
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	280-300
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	266-269, 377-380
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	313-315
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	337-375
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-	<input checked="" type="checkbox"/>	<input type="checkbox"/>	376--409

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		regression)			
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	376-392
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	392-393

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BMJ Open

Which patients benefit specifically from short-term psychodynamic psychotherapy (STPP) for depression? Study protocol of a systematic review and meta-analysis of individual participant data.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-018900.R1
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Date Submitted by the Author:	16-Oct-2017
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Depression & mood disorders < PSYCHIATRY, Adult psychiatry < PSYCHIATRY, Clinical trials < THERAPEUTICS

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3 1 **Which patients benefit specifically from short-term psychodynamic**
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5 2 **psychotherapy (STPP) for depression? Study protocol of a systematic review and**
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7 3 **meta-analysis of individual participant data.**
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11
12 5 Ellen Driessen ^{1*} e.driessen@vu.nl
13
14 6 Allan A. Abbass ² allan.abbass@dal.ca
15
16 7 Jacques P. Barber ³ jbarber@adelphi.edu
17
18 8 Mary Beth Connolly Gibbons ⁴ gibbonsm@mail.med.upenn.edu
19
20 9 Jack J. M. Dekker ⁵ jack.dekker@arkin.nl
21
22 10 Marjolein Fokkema ⁶ m.fokkema@fsw.leidenuniv.nl
23
24 11 Peter Fonagy ⁷ p.fonagy@ucl.ac.uk
25
26 12 Steven D. Hollon ⁸ steven.d.hollon@vanderbilt.edu
27
28 13 Elise P. Jansma ⁹ i.jansma@vu.nl
29
30 14 Saskia C. M. de Maat ¹⁰ saskia.demaat@gmail.com
31
32 15 Joel M. Town ² joel.town@dal.ca
33
34 16 Jos W. R. Twisk ^{11, 12} jwr.twisk@vumc.nl
35
36 17 Henricus L. Van ¹⁰ rien.van@arkin.nl
37
38 18 Erica Weitz ¹ e.weitz@vu.nl
39
40 19 Pim Cuijpers ¹ p.cuijpers@vu.nl
41
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50

51 21 **Affiliations**

52 22 ¹ Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public
53 23 Health research institute, Vrije Universiteit Amsterdam, Netherlands

54 24 ² Centre for Emotions & Health, Dalhousie University, Halifax, NS, Canada

1
2
3 25 ³ Gordon F. Derner School of Psychology, Adelphi University, Garden City, NY, USA

4
5 26 ⁴ Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

6
7
8 27 ⁵ Department of Research, Arkin Mental Health Care, Amsterdam, Netherlands

9
10 28 ⁶ Department of Methodology and Statistics, Leiden University, Netherlands

11
12 29 ⁷ Department of Clinical, Educational and Health Psychology, University College

13
14
15 30 London, UK

16
17 31 ⁸ Department of Psychology, Vanderbilt University, Nashville, TN, USA

18
19 32 ⁹ University Library, Vrije Universiteit Amsterdam, Netherlands

20
21 33 ¹⁰ Dutch Psychoanalytic Institute, Arkin Mental Health Care, Amsterdam, Netherlands

22
23 34 ¹¹ Department of Health Sciences, Vrije Universiteit Amsterdam, Netherlands

24
25 35 ¹² Department of Epidemiology and Biostatistics, VU University Medical Center

26
27
28 36 Amsterdam, Netherlands

29
30
31 37

32
33 38 * Corresponding author:

34
35 39 Ellen Driessen, Ph.D.

36
37 40 Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public

38
39 41 Health research institute, Vrije Universiteit Amsterdam, Van der Boechorststraat 1, 1081

40
41 42 BT Amsterdam, Netherlands. T: +31 20 598 8973

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46 44 **Word count:** 4925 (excluding title page, abstract, references, figures, and tables)

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2
3 45 **ABSTRACT**
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7
8 47 **Introduction:** Short-term psychodynamic psychotherapy (STPP) is an empirically
9
10 48 supported treatment that is often used to treat depression. However, it is largely unclear
11
12 49 if certain subgroups of depressed patients can benefit specifically from this treatment
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14 50 method. We describe the protocol for a systematic review and meta-analysis of
15
16 51 individual participant data (IPD) aimed at identifying predictors and moderators of STPP
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18 52 for depression efficacy.
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21 53 **Method and analysis:** We will conduct a systematic literature search in multiple
22
23 54 bibliographic databases (PubMed, PsycINFO, Embase.com, Web of Science, and
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25 55 Cochrane's Central Register of Controlled Trials), 'grey literature' databases (GLIN and
26
27 56 UMI ProQuest), and a prospective trial register (<http://www.controlled-trials.com>).
28
29 57 We will include studies reporting (a) outcomes on standardized measures of (b)
30
31 58 depressed (c) adult patients (d) receiving STPP. We will next invite the authors of these
32
33 59 studies to share the participant-level data of their trials and combine these data to
34
35 60 conduct IPD meta-analyses. The primary outcome for this study is post-treatment
36
37 61 efficacy as assessed by a continuous depression measure. Potential predictors and
38
39 62 moderators include all socio-demographic variables, clinical variables, and
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41 63 psychological patient characteristics that are measured before the start of treatment and
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43 64 are assessed consistently across studies. One-stage IPD meta-analyses will be
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45 65 conducted using mixed effects models.
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51 66 **Ethics and dissemination:** IRB approval is not required for this study. We intend to
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53 67 submit reports of the outcomes of this study for publication to international peer-
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3 68 reviewed journals in the fields of psychiatry or clinical psychology. We also intend to
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5 69 present the outcomes at international scientific conferences aimed at psychotherapy
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8 70 researchers and clinicians. The findings of this study can have important clinical
9
10 71 implications, as they can inform expectations of STPP efficacy for individual patients,
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12 72 and help to make an informed choice concerning the best treatment option for a given
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15 73 patient.

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17 74 **Registration:** PROSPERO (registration number: CRD42017056029).
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21 76 **Word count abstract:** 294
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26 78 **Keywords:** depression, short-term psychodynamic psychotherapy, predictors,
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28 79 moderators, individual participant data meta-analysis.
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32 33 81 **Strengths and limitations of this study**

- 34
35 82 • This is the first study that systematically assesses patient characteristics associated
36
37 83 with STPP for depression efficacy.
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40 84 • IPD meta-analysis allows for the examination of predictors and moderators by
41
42 85 maximizing statistical power while protecting against ecological bias that presents
43
44 86 problems when using conventional meta-analysis techniques.
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47 87 • The findings of this study can have important clinical implications, as they can inform
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49 88 expectations of STPP efficacy for individual patients, and help to make an informed
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51 89 choice concerning the best treatment option for a given patient.
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3 90 • IPD meta-analyses rely on variables previously assessed in individual studies and
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5 91 available across multiple trials. Thus, it is possible that not all variables of interest
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8 92 can be examined as potential predictors or moderators.
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- IPD meta-analyses rely on variables previously assessed in individual studies and available across multiple trials. Thus, it is possible that not all variables of interest can be examined as potential predictors or moderators.

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94 INTRODUCTION

95 Depression is a highly prevalent and disabling disorder associated with major personal
96 and societal costs.[1] Affecting more than 300 million people worldwide, depression is
97 ranked as the single largest contributor to global disability by the World Health
98 Organization.[2] Given the tremendous burden of disease, there is a great need for
99 effective and efficient treatments for depression. Antidepressant medications and
100 different psychological therapies constitute the predominant treatments for depressive
101 disorders.[3] Concerning psychological treatments, there is a clinical tradition of short-
102 term psychodynamic psychotherapies (STPPs) being used to treat depression. STPP is
103 an empirically supported treatment for depression.[4] However, it is unlikely that any
104 treatment will work for equally well for all depressed patients[5] and it remains largely
105 unclear if certain subgroups of patients can benefit specifically from STPP.

106 Two types of information are relevant to this question: predictors and moderators.
107 Predictors (or prognostic factors) predict outcome to a given treatment and can be used
108 to determine which patients are more likely to respond to STPP relative to other
109 patients. For instance, if age were found to be a positive predictor of STPP efficacy, this
110 might indicate that older patients would be more likely to benefit from STPP than
111 younger patients. Predictors can inform expectations of STPP efficacy, but are of little
112 use in deciding which treatment to select. On the other hand, moderators (or
113 prescriptive factors) can detect different patterns of outcomes between different
114 treatments for different types of patients and provide a basis for choosing the best
115 treatment for a given patient.[6] For instance, if age were found to be a moderator of
116 STPP efficacy versus antidepressant medication, this might indicate that older patients

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3 117 might benefit more from STPP than from medication, while younger patients might
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5 118 benefit more from medication than from STPP.
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8 119 Some preliminary empirical findings concerning predictors and moderators of STPP
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10 120 efficacy for depression do exist. With regard to predictors, meta-regression analyses
11
12 121 alongside a 'conventional' meta-analysis (based on results extracted from
13
14 122 publications[4]) showed that mean pre-treatment depression scores were positively
15
16 123 associated with pre- to post-treatment depression effect size, although this effect might
17
18 124 not be specific to STPP[7]. With regard to moderators, Driessen et al.[8] found STPP to
19
20 125 be more efficacious than CBT among depressed patients who showed low baseline
21
22 126 comorbid anxiety levels. Furthermore, Barber et al.[9] reported that STPP was more
23
24 127 efficacious than medication or placebo for ethnic minority males. However, a systematic
25
26 128 assessment of which patient characteristics are associated with STPP efficacy is
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28 129 currently lacking.
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33 130 The main reason why predictors and moderators of STPP for depression have not
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35 131 yet been examined thoroughly is lack of statistical power in individual clinical trials due
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37 132 to relatively small sample sizes. Prediction and moderation analyses can also be
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39 133 conducted alongside conventional meta-analyses. However, since these analyses are
40
41 134 usually based on study-level characteristics, they are prone to ecological bias, such that
42
43 135 the association between the study-level characteristics may not be representative of the
44
45 136 true relationships in the data at the individual level.[10] Thus, current research methods
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47 137 (clinical trials and conventional meta-analyses) have been insufficient to answer the
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49 138 question as to whether certain subgroups of patients can benefit specifically from STPP
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51 139 for depression.
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3 140 Individual participant data (IPD) meta-analysis is a relatively new technique to
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5 141 examine treatment effects by combining participant-level data of multiple trials. IPD
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7 142 meta-analysis uses the same basic approach as any other well-conducted systematic
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9 143 review and meta-analysis. However, it involves collection of the original data from as
10
11 144 many of the relevant trials worldwide as can be accessed. IPD meta-analysis has
12
13 145 several advantages over conventional meta-analysis, including increased statistical
14
15 146 power to examine predictors and moderators of treatment efficacy.[11] Furthermore,
16
17 147 because predictors and moderators are studied at patient-level, ecological bias can be
18
19 148 circumvented. For these reasons, IPD meta-analysis is currently considered the 'gold
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21 149 standard' in evidence synthesis[12].
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26 150 We describe the study protocol for a systematic review and IPD meta-analysis
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28 151 concerning predictors and moderators of STPP for depression efficacy. The aim of this
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30 152 project is to examine which depressed patients benefit specifically from STPP in terms
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32 153 of depressive symptom reduction when compared to other patients (predictors), and
33
34 154 which patients benefit specifically from STPP when compared to no-treatment
35
36 155 conditions, other psychotherapies, and antidepressant medication (moderators). The
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38 156 goal of this study is to collect the participant-level data of trials examining the efficacy of
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40 157 STPP for depression identified by a systematic literature search, and to combine these
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42 158 datasets in order to conduct IPD meta-analyses.
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160 **METHODS**

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162 **Design**

163 This study is a systematic review and meta-analysis of individual participant data that is
164 registered in the PROSPERO International prospective register of systematic reviews
165 (registration number: CRD42017056029). Important protocol amendments will be
166 documented in this register too. The project started December 1st, 2016 and is
167 expected to be completed February 28th, 2019.

168

169 **Search strategy**

170 We will use an extensive search strategy including six different search methods in order
171 to retrieve as many relevant studies as possible. These searches have already been
172 performed in 2007 and 2014 for two previous conventional meta-analyses concerning
173 the efficacy of STPP for depression[4,13] and will be updated in 2017.

174 First, we will systematically search the bibliographic databases PubMed, PsycINFO
175 (via EBSCO), Embase.com, Web of Science (via Elsevier), and Cochrane's Central
176 Register of Controlled Trials (via Wiley). Search terms will include a wide range of
177 synonyms, both in index terms and free-text words, for 1) psychodynamic
178 psychotherapy (e.g., psychotherapy, psychoanalytic), 2) therapy (e.g., psychotherapy),
179 3) psychodynamic (e.g., dynamic*), and 4) depression (e.g., depressive disorder).

180 These four sets of search terms will be combined as follows: (#1 OR (#2 AND #3)) AND
181 #4. The exact terms for the search in PubMed are presented in Table 1. Complete

182 search terms for all electronic databases are available on request from the
 183 corresponding author. No language or date restrictions will be applied in the searches.

184

185 **Table 1. PubMed search strategy**

Search	PubMed Query 19-06-2017	Items found
#1	Search "Psychoanalytic Therapy"[Mesh] OR "Psychotherapy, Psychodynamic"[Mesh] OR psychodynamic*[tiab] Sort by: Relevance	20177
#2	Search ("Psychotherapy"[Mesh:noexp] OR "Animal Assisted Therapy"[Mesh] OR "Art Therapy"[Mesh] OR "Bibliotherapy"[Mesh] OR "Psychotherapy, Group"[Mesh] OR "Psychotherapy, Brief"[Mesh] OR "Psychotherapy, Multiple"[Mesh] OR "Counseling"[Mesh:NoExp] OR "Directive Counseling"[Mesh:NoExp] OR ((psychotherap*[tiab] OR therap*[tiab] OR counseling[tiab]) NOT medline[sb]))	380901
#3	Search dynamic*[tiab] OR STPP[tiab] OR BDT[tiab] OR DIT[tiab] OR insight*[tiab] OR interpretive[tiab] OR interpretative[tiab] OR analytic*[tiab] OR psychoanalytic*[tiab]	1073217
#4	Search #2 AND #3	21435
#5	Search #1 OR #4	39841
#6	Search Depressive disorder[Mesh] OR depression[Mesh] OR ((depress*[tiab] OR melancholia*[tiab] OR dysphoria*[tiab] OR dysthymi*[tiab] OR "seasonal affective disorder"[tiab]) NOT medline[sb])	223737
#7	Search #5 AND #6	2350
#8	Search #7 NOT ("addresses"[Publication Type] OR "biography"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type])	2285

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3 186 Second, in order to identify relevant studies from the so-called 'grey literature', we will
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5 187 search GLIN, a Dutch electronic database for grey literature, and UMI database
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7
8 188 ProQuest for digital dissertations. Third, a prospective trial register will be searched for
9
10 189 unpublished ongoing research (<http://www.controlled-trials.com>). The grey literature and
11
12 190 prospective trial register searches will be conducted using the search strategy described
13
14 191 above. Fourth, we will search an Internet database of controlled and comparative
15
16 192 outcome studies on psychological treatments of depression
17
18 193 (<http://www.psychotherapytrials.org>[14]) for studies examining STPP. Fifth, reviews and
19
20 194 meta-analyses concerning the efficacy of psychodynamic treatments for depression or
21
22 195 for psychiatric disorders in general retrieved from the first search method will be
23
24 196 screened for relevant references not located by means of the other search methods.
25
26 197 Sixth, we will contact an email list of researchers in the field of psychodynamic therapy
27
28 198 to ask for ongoing or unpublished studies.
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33 199 34 35 200 **Selection of studies**

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37 201 We will include studies if they report (a) outcomes on standardized measures of (b)
38
39 202 depressed (c) adult patients (d) receiving STPP. Participants are considered depressed
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41 203 if they meet specified criteria for major depressive disorder or another mood disorder as
42
43 204 assessed by means of a semi-structured interview or clinicians' assessment, or if they
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45 205 present an elevated score above the 'no depression' cut-off on a standardized measure
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47 206 of depression. Participants need to be at least 18 years old, and studies concerning
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49 207 older adults (mean age >55) will be included as well. We will include studies in which
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51 208 STPP (a) is based on psychoanalytic theories and practices, (b) is time-limited from the
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3 209 onset (i.e. not a therapy that is brief only in retrospect), and (c) applies verbal
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5 210 techniques (e.g., therapies applying art as expression form are not considered STPP).
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8 211 Studies need to include at least 10 subjects. Case studies will therefore be excluded.
9
10 212 We will also include naturalistic studies with a heterogeneous study sample, if these
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12 213 studies include more than 10 participants diagnosed as depressed, as these subgroups
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14 214 also meet the inclusion criteria specified previously. For these studies, the authors will
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16 215 be contacted with a request for subgroup data.
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19 216 The screening process will consist of three phases. At first, the selection criteria will
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21 217 be applied to the citations generated from the searches independently by two raters.
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23 218 Disagreements will be discussed and resolved by consensus. Unless they can be
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25 219 definitely excluded, titles identified as potentially relevant will be requested in full text.
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27 220 During the second screening phase, two independent raters will apply the selection
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29 221 criteria to the full-text papers. Disagreements will be discussed and resolved by
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31 222 consensus. During the third phase, two expert STPP raters will confirm that the included
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33 223 papers meet criteria for STPP. Again, disagreements will be discussed and resolved by
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35 224 consensus. When disagreements cannot be resolved in this way, a third rater will be
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37 225 consulted.
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44 227 **Data collection**

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46 228 Authors of the included studies will be contacted and invited to contribute the
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48 229 participant-level data of their studies. Researchers who share their data will be offered
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50 230 co-authorship for all publications that are based on their study's data (group-
51
52 231 authorship), given that they meet standard criteria for authorship of scientific
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3 232 publications according to internationally accepted criteria (www.icmje.org). In addition,
4
5 233 the collected data will be made available to investigators who contribute data to
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7
8 234 examine other research questions in the combined dataset. This strategy has been
9
10 235 used in previous IPD meta-analyses concerning depression treatments[15-16] and has
11
12 236 been successful in convincing researchers to share their data.

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14 237 Contact details of all first authors will be collected from the relevant publications, or if
15
16 238 not reported there, through Internet searches or personal contacts with other
17
18
19 239 researchers. First authors will be contacted by email with a letter of invitation outlining
20
21 240 the project's goals and asking if they would be willing to collaborate by sharing the
22
23 241 participant-level data of their trial. If an author does not respond after three weeks, a
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25 242 second and third email will be sent. In case of non-response to email, a letter will be
26
27 243 sent (again with three attempts). If still no response is received, we will try to contact the
28
29 244 author by telephone. If all these attempts fail, the last, second, third, fourth, etc. author
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31 245 of the study (in this order) will be contacted in the same way. If none of the authors
32
33 246 respond to these efforts, other ways will be sought to contact one of the authors (e.g.,
34
35 247 via colleagues or anyone who might know them). Study data will be considered
36
37 248 unavailable only if all these attempts fail, or in the event that an author indicates that the
38
39 249 participant-level data have not been retained or declines sharing these data.

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41 250 If the author is willing and able to share the individual participant data of his/her trial,
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43 251 both parties will sign a data sharing agreement. The author will then transfer the
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45 252 participant-level dataset, including all potential predictors and moderators assessed
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47 253 before the start of treatment, as well as all outcome variables assessed during and after
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49 254 treatment, both in the STPP condition as well as in any comparison condition included
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2
3 255 in the study. The author will anonymize the data, so that the dataset is transferred
4
5 256 without containing personal information that can lead back to individuals. Data can be
6
7
8 257 submitted to the project in any format, and will then be converted to Stata.
9

10 258

11 12 259 **Data integrity check**

13
14 260 After the dataset has been transferred, the file will be checked to examine whether the
15
16
17 261 data received match the data reported in the publication. For all treatment conditions
18
19 262 included in the study, sample size, number of females, mean age, observed mean pre-
20
21 263 treatment depression scores, observed mean post-treatment score for the primary
22
23 264 depression outcome, and the number of missing cases for the latter will be calculated
24
25
26 265 from the dataset received and checked against the published article for this purpose.
27
28 266 Discrepancies will be resolved with the authors. In addition, the data will be checked for
29
30
31 267 invalid, out-of-range, or inconsistent items. Furthermore, we will check the integrity of
32
33 268 the randomization for randomized studies by inspecting the balance of the potential
34
35 269 predictor/moderator variables across treatment arms.

36
37
38 270 For each study, we will list all predictor/moderator variables that were assessed, as
39
40 271 well as all outcome variables, intermediate, and follow-up assessments. We will also
41
42 272 extract multiple STPP characteristics (e.g., number of sessions, treatment format, STPP
43
44 273 mode) and study design characteristics (e.g., therapist training, treatment integrity
45
46
47 274 check, use of a treatment manual; for a complete overview see[4]). Finally, we will
48
49 275 extract study validity criteria according to the Cochrane risk of bias assessment tool[17].

50
51 276 After checking the data, the datasets will be standardized. For this purpose, a copy of
52
53
54 277 each trial's raw data file will be recoded into a data file that matches the IPD meta-

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2
3 278 analysis database in terms of variables. Next, the individual study data files will be
4
5 279 concatenated in one database structured by study and individual participant ID. After all
6
7 280 data files have been recoded and entered, the data for each study will be checked with
8
9 281 the original data file received for accuracy. A codebook document will be made that
10
11 282 includes the coding of the individual studies as well as the coding of the combined study
12
13 283 database. Coding for the database will be finalized when all data have been received
14
15 284 from the study authors.
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286 **Measures**

287 The primary outcome for this study is treatment efficacy as assessed by a continuous
288 depression outcome measure at post-treatment. We have chosen depressive symptom
289 status as the main outcome for this study as we consider this to be the primary target of
290 STPP for depression. We chose continuous symptom level as the primary outcome,
291 because we expect that the increased variance relative to dichotomous outcomes might
292 facilitate the search for predictors and moderators. We have chosen post-treatment
293 assessment as the primary end-point as it is difficult to control additional treatment in
294 the follow-up period in psychotherapy efficacy studies (e.g.,[18]).

295 For each trial, we will identify the primary continuous depression outcome as defined
296 by the study authors. All instruments explicitly measuring depression qualify in this
297 regard. Different depression measures have probably been used and, therefore, we will
298 standardize the depression outcomes by converting the depression scores into Z-
299 scores. Sensitivity analyses will be conducted using unstandardized scores for each

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2
3 300 depression measure that is assessed in the majority of studies included in the meta-
4
5 301 analysis (e.g., Hamilton Depression Rating Scale[19], Beck Depression Inventory[20]).
6

7
8 302 The secondary outcomes for this study are dichotomous depression outcomes for 1)
9
10 303 response (a 50% reduction in symptoms from pre- to post-treatment), and 2) remission
11
12 304 (maximum absolute post-treatment scores reflecting normalization). In addition,
13
14 305 outcome measures other than depression will be collected (e.g., anxiety symptoms,
15
16 306 quality of life, interpersonal functioning). These can be considered tertiary outcomes.
17
18

19 307 Potential predictors and moderators include socio-demographic variables (e.g.,
20
21 308 gender, age, education level, marital status, employment status, ethnicity), clinical
22
23 309 variables (e.g., number of previous depressive episodes, previous exposure to
24
25 310 treatment, comorbid Axis I and II psychopathology, global assessment of functioning),
26
27 311 and psychological patient characteristics (e.g., personality organization, attachment,
28
29 312 interpersonal styles, childhood maltreatment, alexithymia). These are likely assessed
30
31 313 differently in individual studies and will be standardized as well, for instance by
32
33 314 converting scores into Z-scores for continuous variables or by recoding variables into
34
35 315 similar categories for categorical variables. In the latter case, we will consult study
36
37 316 authors to confirm correctness of the recoding.
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42 317

43 44 318 **Missing data**

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46
47 319 All datasets received that contain individual participant data, at least one relevant
48
49 320 outcome measure, and at least one predictor/moderator variable will be considered for
50
51 321 quantitative synthesis. We will examine the possibility of complete-case analyses by
52
53 322 evaluating the extent of missing data as well as the possible reasons for missing data,
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3 323 and by comparing patients with complete data to patients with missing data. We will
4
5 324 also assess whether the missing data can be considered missing at random.[21] If
6
7 325 complete-case analysis is not justifiable and data can be considered missing at random,
8
9 326 we will impute missing data using multiple imputation, which is currently considered to
10
11 327 be the most sophisticated method for handling missing data.[22]

12
13
14 328 We will generate one imputed dataset for each percent of missing data (e.g., when
15
16 329 30% of the data is missing, we will create 30 imputed datasets). We will impute missing
17
18 330 data by means of hierarchical imputation with fully conditional specification (FCS-
19
20 331 GLM),[23] which allows for preserving the heterogeneity across studies, non-normal
21
22 332 distributions of variables, and imputing systematically missing variables. FCS-GLM has
23
24 333 shown to be a reliable procedure with advantageous properties for IPD meta-analyses
25
26 334 with limited numbers of studies or studies with small sample sizes.[24] FCS-GLM will be
27
28 335 conducted in R. To ensure congeniality, imputation will be based on all variables that
29
30 336 will be included in the meta-analysis model including their interactions as well as any
31
32 337 variables that were identified to be predictive of missing values.[24] If multiple
33
34 338 imputation is pursued, we will conduct sensitivity analyses restricted to complete cases
35
36 339 and compare the results. We will not pursue efforts to combine IPD with aggregate data
37
38 340 from studies for which no IPD is available,[25] since the requisite treatment-covariate
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40 341 interactions are seldom reported in publications.

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48 49 343 **Data-analysis**

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51 344 We will conduct IPD meta-analyses according to the one-stage approach, because that
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53 345 accounts for the correlation amongst model parameters when modelling interactions,
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3 346 offers the highest degree of flexibility for making the necessary assumptions when
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5 347 detecting treatment-covariate interactions,[26] and provides a more exact likelihood in
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7 348 the case of small studies.[27] We will conduct IPD meta-analyses using mixed models
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9 349 with restricted maximum likelihood to estimate between-study heterogeneity, which is
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11 350 recommended when there are few studies in the meta-analysis or studies have small
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13 351 sample sizes.[28] Analyses will be conducted in Stata 'mixed'. We will apply the
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15 352 Kenward-Roger denominator-degrees-of-freedom adjustment for confidence
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17 353 intervals,[29] because it more adequately accounts for uncertainty than the standard
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19 354 Dersimonian-Laird estimator when the number of studies is small or when heterogeneity
20
21 355 is present.[30] To account for clustering of patients within studies and to preserve
22
23 356 randomization, we will include a random intercept for study and a random slope for
24
25 357 baseline depression. We assume that these random effects will be normally distributed
26
27 358 and this assumption will be assessed. We will assess heterogeneity by examining the
28
29 359 standard deviation of the predictor or moderator parameter estimates.
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35 360 Separate analyses will be conducted for the identification of predictors and the
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37 361 identification of moderators of STPP efficacy. With regard to predictors, IPD from STPP
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39 362 conditions across all studies will be combined, regardless of study type (randomized
40
41 363 controlled study, non-random comparative study, naturalistic study). For each of the
42
43 364 potential predictors, a model will be estimated with baseline depression and the
44
45 365 predictor's main effect. A random slope will be added to the predictor to examine if this
46
47 366 results in a model improvement. If so, this predictor variable will be included with a
48
49 367 random slope in subsequent analyses. Next, all predictors will be modeled
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51 368 simultaneously. Backward selection based on p-value will be conducted until a final
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3 369 prediction model is obtained consisting of statistical significant predictors only. This
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5 370 prediction model will be validated in a held-out sample of the data.
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8 371 With regard to moderators, analyses will be conducted separately for each
9
10 372 comparison (e.g., STPP versus control conditions, STPP versus other psychotherapy,
11
12 373 STPP versus antidepressant medication). These analyses will only include IPD from
13
14 374 randomized studies. For each of the potential moderators, a model will be estimated
15
16 375 with baseline depression as well as the moderator's main effect and interaction with
17
18 376 treatment. Next, to examine ecological bias, within-study and across-study interaction
19
20 377 effects will be separated.[25] If within-study and across-study interactions differ,
21
22 378 ecological bias may be at play, and only the within-trial interaction will be interpreted in
23
24 379 subsequent analyses. Finally, all significant treatment-covariate interactions, their main
25
26 380 effects, and higher order interactions will be modeled simultaneously. The resulting
27
28 381 prediction model will be validated in a held-out sample of the data.
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33 382 A number of sensitivity analyses will be conducted to examine the robustness of the
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35 383 findings. To examine the impact of study quality, we will conduct sensitivity analyses
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37 384 including only studies that score high on all quality criteria. In addition, we will conduct
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39 385 analyses in which we add the risk of bias items as covariates to the mixed effects
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41 386 models, centered at a value indicating freedom of bias.[31] We will also conduct
42
43 387 sensitivity analyses to control for the effects of additional non-study treatment during the
44
45 388 trial and in the follow-up period by adding collected data in this regard as covariates to
46
47 389 the mixed effects models. Finally, we will examine the impact of STPP characteristics
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49 390 (e.g., STPP type, delivery mode) and study design characteristics (e.g., therapist
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3 391 training, use of a treatment manual) by adding these variables to the mixed effects
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5 392 models too.

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8 393 Furthermore, to examine possible data availability bias, t-tests and chi-square
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10 394 analyses will be conducted comparing the included studies with studies for which no
11
12 395 participant-level data was obtained with regard to the extracted study characteristics.
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14 396 Conventional meta-analysis techniques will be utilized to examine differences in effect
15
16 397 sizes between studies that contributed data and studies that did not. We will assess
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18 398 potential publication bias by assessing asymmetry in contour enhanced funnel plots for
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20 399 meta-analyses including 10 or more trials, as is recommended by Sterne and
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22 400 colleagues.[32] The confidence in the cumulative body of evidence will be assessed
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24 401 according to GRADE.[33]

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28 402 In addition, we will conduct explorative analyses using tree-based statistical learning.
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30 403 More specifically, we will use the generalized linear mixed effects regression trees
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32 404 algorithm (glmertree[34]) in R to detect predictors and moderators of continuous and
33
34 405 binary treatment outcomes. These analyses offer several advantages over more
35
36 406 traditional mixed-effects modeling approaches, as they allow for the detection of non-
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38 407 linear and higher-level interactions, allow for specifying a large number of potential
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40 408 predictor and moderator variables and involve less stringent assumptions about the
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42 409 distribution of the data. Furthermore, the result of applying glmertree consists of a
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44 410 decision tree that graphically depicts the effects of the relevant predictor and moderator
45
46 411 variables. Such a tree can easily be interpreted, and applied in clinical decision-making.
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48 412 However, it should be noted that such tree-based analyses are exploratory in nature.
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50 413 We will assess the expected predictive accuracy on new data using *k*-cross
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3 414 validation[35] and the stability of the resulting decision trees using subsampling
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5 415 methods.[36] The glmertree analyses will be performed using observed, non-imputed
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7 416 data only, as it is currently unclear how to best specify the model for generating imputed
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9 417 data in tree-based analyses for clustered data.
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420 **ETHICS AND DISSEMINATION**

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19 421 IRB approval was not required for this project. IRB approval may be required for the
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21 422 investigators to share their primary data depending on their institution's policies. It is the
22
23 423 responsibility of the investigators to obtain IRB approval if their institution's policies
24
25 424 require them to do so. By signing the data sharing agreement, the authors who share
26
27 425 their data declare that those data were collected and transferred to our research group
28
29 426 according to all applicable local and international laws and regulations, including but not
30
31 427 limited to local IRB approval.
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35 428 We intend to submit reports of the outcomes of this study for publication to
36
37 429 international peer-reviewed journals in the fields of psychiatry or clinical psychology. We
38
39 430 also intend to present the findings of this study at international scientific conferences
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41 431 aimed at psychotherapy researchers and clinicians.
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434 **DISCUSSION**

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51 435 We described the study protocol of a systematic review and meta-analysis of IPD to
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53 436 examine predictors and moderators of STPP efficacy for depression. The goal of this
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3 437 study is to collect the participant-level data of studies examining the efficacy of STPP for
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5 438 depression identified by a thorough literature search, and to combine these datasets in
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8 439 order to conduct IPD meta-analyses. The proposed study design allows for the
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10 440 examination of predictors and moderators of STPP efficacy with increased statistical
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12 441 power and can thus help to show which subsets of depressed patients specifically
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14 442 benefit from therapies based on psychoanalytic principles.
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19 444 **Clinical and scientific relevance**

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21 445 In contrast to how commonly STPPs are utilized in clinical practice, they are
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23
24 446 underrepresented in current treatment guidelines for depressive disorders. Further high-
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26 447 quality research that extends and disseminates knowledge about the effectiveness of
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28 448 STPP is therefore called for. Research showing whether subsets of depressed patients
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30
31 449 can specifically benefit from this therapy modality, especially when compared to other
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33 450 treatments, is particularly needed. Knowledge of such moderators can have important
34
35 451 implications for clinical practice, as it can be used to guide treatment selection and
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37 452 increase the efficiency of treatments for depression by helping patients and clinicians to
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39
40 453 make an informed choice concerning the best treatment option for a given patient.
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42 454 Little is known about patient characteristics associated with STPP efficacy, because
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44 455 clinical trials often have relatively small sample sizes and limited statistical power to
45
46
47 456 examine predictors and moderators of change. Moreover, prediction and moderation
48
49 457 analyses in conventional meta-analyses are often based on study-level aggregates and
50
51 458 are, therefore, prone to ecological bias. By means of individual participant data meta-
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54 459 analyses these critical limitations can be overcome. IPD meta-analyses have been
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3 460 utilized more frequently in the medical field, but are newer in the field of psychiatry and
4
5 461 clinical psychology.[37] Although IPD meta-analyses have now been used to examine
6
7 462 single moderators of CBT and pharmacotherapy efficacy for depression,[20-21] to date
8
9 463 no IPD meta-analysis has been conducted concerning STPP.
10
11
12 464

14 465 **Strengths and limitations**

16 466 Individual participant data meta-analysis has several advantages over conventional
17
18 467 meta-analysis, including increased statistical power to examine predictors and
19
20 468 moderators.[11] In addition, by collecting the primary data, access to predictor or
21
22 469 moderator variables that might not have been reported in the published articles is
23
24 470 gained; increasing the chance that aggregation of these variables across studies is
25
26 471 possible. Other advantages of individual participant data meta-analysis over
27
28 472 conventional meta-analysis include the possibility to 1) account for missing data at the
29
30 473 individual participant level, so that for instance intention-to-treat analyses can be
31
32 474 conducted even though the original study reported completers-only analyses, 2) use the
33
34 475 same statistical methods for imputing missing data and for conducting statistical
35
36 476 analyses, thereby facilitating standardization across studies, 3) standardize outcomes
37
38 477 across studies, for instance by using equal cut-off points on a depression outcome
39
40 478 measure when the primary studies used different cut-offs, and 4) verify the results
41
42 479 presented in the original studies, also by means of more sophisticated statistical
43
44 480 techniques that were not available at time of publication in the case of older studies.[38]

45 481 IPD meta-analyses involve collection of original data from all the relevant trials
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47 482 worldwide that can be accessed. These data need to be prepared and checked before
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3 483 being included in the meta-analysis, and complex decisions on the data sometimes
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5 484 need to be made in order to ensure the accuracy of the outcomes. Therefore, it takes
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8 485 more time and resources to conduct an IPD meta-analysis than to conduct a
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10 486 conventional meta-analysis based solely on results extracted from published trial
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12 487 reports.[38] However, the IPD approach can improve the quality of both the data and
13
14 488 the analyses, and so the reliability of the results. Therefore, it is considered the 'gold
15
16
17 489 standard' of meta-analysis.[12]

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19 490 IPD meta-analyses also have a number of limitations. First, although IPD meta-
20
21 491 analyses are generally considered the most reliable approach to evidence
22
23 492 synthesis,[12] this does not mean that they are bias-free and selection bias, publication
24
25 493 bias, and data availability bias need to be considered.[39] We try to overcome this
26
27 494 limitation by performing a systematic literature search that also aims to identify grey
28
29 495 literature and unpublished work, and by testing for differences between studies for
30
31 496 which IPD was and was not obtained. Second, IPD meta-analyses rely on variables
32
33 497 previously assessed in individual studies and available across multiple trials. For this
34
35 498 reason, it is possible that not all variables of interest can be examined as potential
36
37 499 predictors or moderators. Third, and related, it is necessary to standardize
38
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41 500 predictor/moderator variables for the analyses, but doing so might involve recoding and
42
43 501 possibly omitting important information for some variables. Fourth, although combining
44
45 502 multiple trials reduces the possibility that predictors/moderators identified are chance
46
47 503 findings in single study samples, generalizability of the findings might still be limited to
48
49 504 patients who volunteer to participate in scientific outcome research. Fifth, the predictors
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53 505 and moderators identified in this study can either apply specifically to STPP or can be
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3 506 more general factors associated with depression treatment efficacy. We intend to
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5 507 address this distinction in this study's outcome reports in the context of the
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8 508 predictors/moderators identified.
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11 510 **Conclusion**

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14 511 We described the study protocol for a systematic review and meta-analysis of IPD
15
16 512 aimed at examining if certain subgroups of depressed patients can benefit specifically
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18 513 from STPP. We will collect the participant-level data of studies examining the efficacy of
19
20 514 STPP for depression identified by a thorough literature search. We will combine these
21
22 515 datasets and conduct IPD meta-analyses to identify predictors and moderators of STPP
23
24 516 efficacy. Knowledge of such predictors and moderators can have important implications
25
26 517 for clinical practice, as they can, respectively, inform expectations of treatment efficacy
27
28 518 for individual patients, and help patients and clinicians to make an informed choice
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31 519 concerning the best treatment option for a given patient.
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36 522 **AUTHORS' CONTRIBUTIONS**

37
38 523 ED, AAA, JPB, JJMD, MF, SDH, EPJ, SCMdM, JMT, JWRT, HLV, EW, and PC made
39
40 524 substantial contributions to the study design. ED, AAA, JPB, MBCG, JJMD, PF, SDH,
41
42 525 JMT, HLV, and PC made substantial contributions to the acquisition of individual
43
44 526 participant data. ED, EW, and PC drafted the manuscript. ED, AAA, JPB, MBCG, JJMD,
45
46 527 MF, PF, SDH, EPJ, SCMdM, JMT, JWRT, HLV, EW, and PC revised it critically for
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3 528 important intellectual content and approved the final version of this manuscript. ED is
4
5 529 the guarantor of the review.
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11
12 532 **FUNDING STATEMENT**
13

14 533 An American Psychoanalytic Association Research Fund supported this work. The
15
16 534 funder had no role in the development of this study protocol, nor was there editorial
17
18 535 direction or censorship from the sponsor in this manuscript.
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26 538 **COMPETING INTERESTS STATEMENT**
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28 539 AAA practices and provides training in methods of STPP and receives royalties from a
29
30 540 book he wrote on STPP. JPB has given talks on STPP at workshops and conferences
31
32 541 for which organizers often have not paid for travel and accommodations. JPB and JJMD
33
34 542 receive royalties from books on STPP they have co-authored. JMT has given talks on
35
36 543 STPP at workshops and conferences for which organizers have paid for travel and
37
38 544 accommodations. PF declares being Chief Executive of the Anna Freud Centre (UK).
39
40 545 He teaches mentalization-based treatment trainings and dynamic-interpersonal therapy
41
42 546 trainings in the UK and internationally. He is the Co-PI on The IMPACT Study – The
43
44 547 Effectiveness of Psychological Treatment for Depressed Adolescents, and Consultant to
45
46 548 the Child and Family Program at the Menninger Department of Psychiatry and
47
48 549 Behavioural Sciences at Baylor College of Medicine, Houston, TX, USA. PF also
49
50 550 receives royalties from books on interpersonal psychotherapy which he has co-authored
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3 551 with others. HLV and SCMdM are trainers and registered supervisors of short-term
4
5 552 psychodynamic supportive psychotherapy. They also receive royalties from books on
6
7 553 STPP they have co-authored. SDH reports no financial conflicts, but acknowledges an
8
9 554 intellectual passion for the cognitive and behavioral interventions for depression. ED,
10
11 555 MBCG, MF, JWRT, EW, and PC declare that they have no known conflicts of interest.
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For peer review only

556 **REFERENCES**

- 557 1 Kessler RC. The costs of depression. *Psychiatr Clin North Am* 2012;35:1-14.
- 558 2 World Health Organization. Depression and other common mental disorders. Global
559 health estimates. [http://apps.who.int/iris/bitstream/10665/254610/1/WHO-MSD-
560 MER-2017.2-eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/254610/1/WHO-MSD-
560 MER-2017.2-eng.pdf?ua=1) (accessed July 2017).
- 561 3 Marcus SC, Olfson M. National trends in the treatment of depression from 1998 to
562 2007. *Arch Gen Psychiatry* 2010;67:1265-73.
- 563 4 Driessen E, Hegelmaier LM, Abbass AA, et al. The efficacy of short-term
564 psychodynamic psychotherapy for depression: a meta-analysis update. *Clin
565 Psychol Rev* 2015;42:1-15.
- 566 5 Barber JP. Toward a working through of some core conflicts in psychotherapy
567 research. *Psychother Res* 2009;19:1-12.
- 568 6 Kraemer HC, Wilson GT, Fairburn CG, et al. Mediators and moderators of treatment
569 effects in randomized clinical trials. *Arch Gen Psychiatry* 2002;59:877-83.
- 570 7 Driessen E, Cuijpers P, Hollon SD, et al. Does pretreatment severity moderate the
571 efficacy of psychological treatment of adult outpatient depression? A meta-analysis.
572 *J Consult Clin Psychol* 2010 78;688-80.
- 573 8 Driessen E, Smits N, Dekker JJM, et al. Differential efficacy of cognitive behavioral
574 therapy and psychodynamic therapy for major depression: a study of prescriptive
575 factors. *Psychol Med* 2016;46:731-44.
- 576 9 Barber JP, Barrett MS, Gallop R, et al. Short-term dynamic therapy vs.
577 pharmacotherapy for major depressive disorder. *J Clin Psychiatry* 2012;73:66-73.

- 1
2
3 578 10 Fisher DJ, Carpenter JR, Morris TP, et al. Meta-analytical methods to identify who
4
5 579 benefits most from treatments: daft, deluded, or deft approach? *BMJ* 2017;356:j573.
6
7
8 580 11 Lambert PC, Sutton AJ, Abrams KR, et al. A comparison of summary patient-level
9
10 581 covariates in meta-regression with individual patient data meta-analysis. *J Clin*
11
12 582 *Epidemiol* 2002;55:86-94.
13
14
15 583 12 Stewart LA, Parmar MKB. Meta-analysis of the literature or of individual patient data:
16
17 584 is there a difference? *Lancet* 1993;341:418-22.
18
19
20 585 13 Driessen E, Cuijpers P, de Maat SCM, et al. The efficacy of short-term
21
22 586 psychodynamic psychotherapy for depression: a meta-analysis. *Clin Psychol Rev*
23
24 587 2010;30:25-36.
25
26
27 588 14 Cuijpers P, van Straten A, Warmerdam L, et al. Psychological treatment of
28
29 589 depression: A meta-analytic database of randomized studies. *BMC Psychiatry*
30
31 590 2008;8:36.
32
33
34 591 15 Cuijpers P, Weitz E, Twisk J, et al. Gender as predictor and moderator of outcome in
35
36 592 cognitive behavior therapy and pharmacotherapy for adult depression: an “individual
37
38 593 patient data” meta-analysis. *Depress Anxiety* 2014;31:941-51.
39
40
41 594 16 Weitz ES, Hollon SD, Twisk J, et al. Baseline depression severity as moderator of
42
43 595 depression outcomes between cognitive behavioral therapy vs pharmacotherapy:
44
45 596 an individual patient data meta-analysis. *JAMA Psychiatry* 2015;72:1102-09.
46
47
48 597 17 Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions
49
50 598 Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available at:
51
52 599 <http://www.cochrane-handbook.org>.

- 1
2
3 600 18 Driessen E, Van HL, Don FJ, et al. The efficacy of cognitive-behavioral therapy and
4
5 601 psychodynamic therapy in the outpatient treatment of major depression: a
6
7 602 randomized clinical trial. *Am J Psychiatry* 2013;170:1041-50.
8
9
10 603 19 Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*
11
12 604 1960;23:56–62.
13
14 605 20 Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression.
15
16 606 *Arch Gen Psychiatry* 1961;4:561–71.
17
18
19 607 21 Sterne JAC, White IA, Carlin JB, et al. Multiple imputation for missing data in
20
21 608 epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393.
22
23
24 609 22 Donders A, van der Heiden G, Stijnen T, et al. Review: a gentle introduction to
25
26 610 imputation of missing values. *J Clin Epidemiol* 2012;59:1087–91.
27
28
29 611 23 Jolani S, Debray TPA, Koffijberg H, et al. Imputation of systematically missing
30
31 612 predictors in an individual participant data meta-analysis: a generalized approach
32
33 613 using MICE. *Stat Med* 2015;34:1841-63.
34
35
36 614 24 Audigier V, White IR, Jolani S, et al. Multiple imputation for multilevel data with
37
38 615 continuous and binary variables. <https://arxiv.org/abs/1702.00971> (accessed July
39
40 616 2017).
41
42
43 617 25 Riley RD, Lambert PC, Staessen JA, et al. Meta-analysis of continuous outcomes
44
45 618 combining individual patient data and aggregate data. *Stat Med* 2008;27:1870-93.
46
47 619 26 Debray TPA, Moons KGM, van Valkenhoef G, et al. Get real in individual participant
48
49 620 data (IPD) meta-analysis: a review of the methodology. *Res Synth Methods* 2015;6:
50
51 621 293-309.
52
53
54
55
56
57
58
59
60

- 1
2
3 622 27 Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-
4
5 623 stage and two-stage approaches, and why they may differ. *Stat Med* 2017;36:855-
6
7 624 75.
- 8
9
10 625 28 Higgins JPT, Whitehead A, Turner RM, et al. Meta-analysis of continuous outcome
11
12 626 data from individual patients. *Stat Med* 2001;20:2219-41.
- 13
14 627 29 Kenward MG, Roger JH. Small sample inference for fixed effects from restricted
15
16 628 maximum likelihood. *Biometrics* 1997;53:983-97.
- 17
18
19 629 30 Cornell JE, Mulrow CD, Localio R, et al. Random-effects meta-analysis of
20
21 630 inconsistent effects: a time for change. *Ann Intern Med* 2014;160:267-70.
- 22
23
24 631 31 Higgins JPT, Thomspson SG, Spiegelhalter DJ. A re-evaluation of random-effects
25
26 632 meta-analysis. *J R Stat Soc* 2009;172:137-59.
- 27
28 633 32 Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and
29
30 634 interpreting funnel plot asymmetry in meta-analyses of randomized controlled trials.
31
32 635 *BMJ* 2011;343:d4002.
- 33
34
35 636 33 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating
36
37 637 quality of evidence and strength of recommendations. *BMJ* 2008;336:924.
- 38
39
40 638 34 Fokkema M, Smits N, Zeileis A, et al. Detecting treatment-subgroup interactions in
41
42 639 clustered data with generalized linear mixed-effects model trees. *Working Papers in*
43
44 640 *Economics and Statistics* No. 2015-10.
- 45
46
47 641 35 Friedman J, Hastie T, Tibshirani R. *The Elements of Statistical Learning* (2nd Ed.).
48
49 642 Berlin: Springer 2009.
- 50
51 643 36 Philipp M, Zeileis A, Strobl C. A toolkit for stability assessment of tree-based
52
53 644 learners. *Working Papers in Economics and Statistics* No. 2016-11.
- 54
55
56
57
58
59
60

- 1
2
3 645 37 Simmonds M, Stewart G, Stewart L. A decade of individual participant data meta-
4
5 646 analyses: A review of current practice. *Contemp Clin Trials* 2015;45:76-83.
6
7
8 647 38 Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data:
9
10 648 rationale, conduct, and reporting. *BMJ* 2010;340:c221.
11
12 649 39 Ahmed I, Sutton AJ, Riley R. Assessment of publication bias, selection bias, and
13
14 650 unavailable data in meta-analyses using individual participant data: a database
15
16
17 651 survey. *BMJ* 2011;344:d7762.
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
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