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Efficacy of psychoanalytically oriented long-term treatments and determinants of outcome -Individual Participant Data **Me**ta-Analysis of **L**ong-term **A**nalytic Treatment **S**tudies (**MeLAS)**

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ABSTRACT

Introduction: Long-term psychodynamic/ psychoanalytic psychotherapy (LTPT) is an important treatment option for complex mental disorders. Compared to short-term therapies only few trials are available, often lacking statistical power due to small samples. Their statistical synthesis will facilitate the investigation of important questions for research and praxis, such as the role of therapy dose in LTPT.

Methods and Analysis: We present a study protocol for a systematic review and individual participant data (IPD) meta-analysis aggregating and analyzing individual data from original trials by meta-analysis. The purpose is to 1a) determine treatment effectiveness of LTPT with low vs. high dose, 1b) compare their effectiveness to shorter therapies, 2) Identify moderators of treatment outcomes, and 3) determine reciprocal relationships between different outcome domains (symptomatic and structural/personality change) over the courses of LTPT. Primary outcome criteria are global and disorder specific measures of symptomology, secondary outcome criteria are functional capacities, personality, and interpersonal pathology. The study aims at closing the research gap between psychodynamic practice and research which to date has been mostly based on short-term trials with brief follow-up periods. It will contribute to the question of who benefits most from long-term treatments and how different outcome domains interact over time. **Ethics and dissemination:** Aggregation of data from primary trials collected based on ethics votes. Dissemination into clinical practice via open access publications of findings. The study is an IPD meta-analysis, registered on the International prospective register of systematic reviews (PROSPERO; 304982) before conducting the main search and soliciting data.

Keywords

psychodynamic, psychoanalytic, long-term therapy, long-term follow up, anxiety, depression, personality disorder, personalized psychotherapy

STRENGTH AND LIMITATION OF THIS STUDY

- The IPD meta-analysis systematically addresses the efficacy of high vs. low dose LTPT by combining data from rarely conducted long-term studies
- IPD meta-analysis has increased power to detect differences between treatment groups and to examine prognostic and prescriptive factors associated with outcome
- As we rely on variables assessed by previously conducted trials not all variables of interest can be examined
- In IPD meta-analysis bias may be introduced as not all relevant studies identified can be included, e.g., non-response of the authors, difficulties with data-sharing

INTRODUCTION

Short-term psychodynamic psychotherapy (STPP) has demonstrated comparable efficacy to cognitive behavioral therapy (CBT) and other bona fide psychotherapies,[1–3]. However, common mental disorders often take a chronic course,[e.g.; 4,5] and short-term treatments have been shown to be insufficient for patients with complex (e.g., personality, chronic, or multiple) mental disorders,[5,6]. This is consistent with data on dose-effect relations indicating that patients with such disorders need longer treatments,[7,8]. Nevertheless, evidence for psychotherapy is based mostly upon short-term treatments and short-term outcomes, the latter usually assessed at treatment termination,[9]. Only a few trials report one-year follow-up, and longer-term follow-ups of two and more years are scarce,[2,10]. To our best knowledge, long-term remission rates of bona fide STPP and CBT treatments are often unsatisfactory,[10], and up to half of the study, patients have been found to seek auxiliary psychotherapy during follow-up,[11]. Naturalistic trials further indicate that many patients require and receive long-term treatments up to several years,[12].

A basic claim of long-term psychoanalytic therapies (LTPT), comprising psychoanalysis and long-term psychoanalytic/psychodynamic psychotherapy (LTPP), has been to improve structural capacities related to the personality organization,[13–15] in addition to symptoms. Structural integration (i.e. personality functioning) comprises different domains of psychological functioning e.g., identity, affect differentiation and tolerance, and self-other regulation which relate to core developmental tasks of attachment/relatedness and individuation/self-definition,[e.g., 16–18]. Conceptualized by the term personality functioning, the alternative model of personality disorders has introduced a similar,[19,20] model to the DSM-5,[21,22]. Here, impairment in personality functioning is described along the dimensions of self (identity perception, self-regulation) and interpersonal (empathy, intimacy) functioning as shared characteristic of all personality disorders. In psychoanalytic literature,

improvements in these domains have been described as structural change,[13–15] and have been related to treatments with higher frequency promoting greater capacity for self-analysis,[23]. In line with the traditionally transdiagnostic scope of psychoanalysis, LTPT studies have focused on global or disorder-specific symptom improvement, and social and personality functioning with long-term outcomes up to 10 years,[e.g., 11]. However, the number of available trials on LTPT with long-term follow-up is comparably small, as they pose special methodological challenges of recruitment, study design, duration, and funding. For ethical reasons, placebo or waiting-list control conditions are not feasible over extended periods, and it would be difficult to conceptualize plausible interventions with similar frequency and duration of intervention. Studies that included long-term follow-ups have shown that LTPT indeed led to lasting changes at the level of symptoms and other domains of functioning,[11,24–28]. In the long run, several studies indicated LTPP to be more effective than treatment as usual (TAU),[25] or short-term treatments,[11,29].

Huber et al.,[26] found psychoanalytic treatment to be more effective than CBT at long-term follow-up, while others reported a comparable reduction of symptoms in psychoanalytic therapy and CBT at the three-year assessment,[30], but stronger evidence of personality change in psychoanalytic treatment groups,[28]. Other studies have focused on the comparison of psychodynamic psychotherapy with more intensive and longer psychoanalytic treatment and found the latter to be more effective at one-,[31] or three-year follow-up,[32]. Yet, in a meta-analysis on psychodynamic psychotherapy. Town et al.,[33] found that therapy effects were maintained and continued to improve following termination of psychodynamic therapies of different frequency and length. To our knowledge, only four conventional meta-analyses have focused on the effectiveness of LTPT specifically. Focusing on RCTs, Leichsenring & Rabung,[6,34,35] found LTPP to be more effective than STPT with medium to large effect sizes in terms of symptom reduction and social and personality functioning. Using different inclusion criteria, the meta-analysis of Smit et al.,[36] questioned the effectiveness of LTPP, as they found it more effective only in comparison to control conditions that were no specialized forms of therapy. Exploratory analyses indicated that a greater difference in treatment intensity between LTPP and the control group was related to effect size. The seemingly conflicting findings between Leichsenring and Rabung's,[6,34] and Smit et al's.,[36] meta-analyses have been discussed elsewhere,[e.g., 35,37]. More recently, Woll and Schönbrodt aimed to replicate and update Leichsenring et al.'s,[35] meta-analysis, but only found small additional gains for LTPP in comparison to other forms of psychotherapy, regarding symptoms and social functioning. No significant differences were found with respect to personality functioning. Restricting their meta-analysis to psychoanalysis proper, defined as the patient lying on the couch with at least two sessions, one research group found large within-group effect sizes regarding symptomatic

improvement and personality characteristics. Yet, most of the trials they examined were naturalistic and did not have control groups,[38].

Beyond efficacy studies, psychotherapy research, in general, has identified numerous patient, therapist, and relational prognostic factors (predictors) for psychotherapy outcome, e.g., racial or social minority status, high symptom load, or high self-criticism,[39]. However, less is known about prescriptive variables (moderators) associated with different outcomes depending on the type of treatment, e.g., maladaptive defenses or rigid relationship patterns for psychodynamic treatments,[1,40,41]. Identifying prescriptive variables that reliably predict differential treatment outcomes has become the main target of personalized treatment approaches,[39,42]. To our knowledge, no meta-analysis has examined prognostic or prescriptive variables in LTPT.

Given the evidence outlined above, we presume that LTPT facilitates changes in intrapsychic, structural processes underlying mental disorders in addition to improving symptoms. Yet, it remains unclear whether this is due to effects of psychoanalytic technique or its high treatment frequency and duration,[8,36]. Changes in structural functioning have been posited as a mechanism of change in psychotherapy, and psychoanalytic/psychodynamic psychotherapies specifically, with a stronger focus on insight and self-understanding,[43]. Several studies found greater changes e.g. in personality or reflective functioning associated with greater,[30,44] and sustained,[45,46] symptom reduction. However, the studies mostly focused on between-person effects and did not apply lagged analysis over multiple time points to investigate if changes in structural capacities were associated with a decrease in symptoms at subsequent assessment.

Due to the limitations of the individual trials, empirical evidence on the role of treatment intensity for the efficacy of LTPT and the identification of prescriptive variables has been limited. Small samples and unequal group sizes as well as decreasing case numbers throughout therapy and follow-up have led to methodological problems in data analysis of individual trials, including a lack of statistical power. Hence, small differences between different treatment approaches cannot be identified and testing for sub-groups with differential outcome is prohibited,[47]. Additional problems include the utilization of different designs (RCT vs. quasi-experimental), varying definitions of LTPT (e.g., ranging from 42 to over 300 sessions), varying frequency of measurements, definition and timing of follow-

ups, and the comparability of measures of relevant variables (e.g., sociodemographic, clinical characteristics) and different outcome measures.

The current study aims to conduct a systematic review and individual participant data (IPD) meta-analysis concerning the efficacy of LTPT treatments of different intensities and associated prognostic and prescriptive factors in common mental disorders. IPD meta-analysis is a technique to examine treatment effects by combining participant-level data of multiple trials collected from the original data and is currently considered the gold standard in evidence synthesis,[48,49]. A one-stage approach is favored, especially when the original trials have small samples,[50]. It has increased statistical power to detect differences between treatment conditions and to examine prognostic and prescriptive variables associated with treatment efficacy,[42]. Compared to conventional meta-analyses that rely on the aggregated level data extracted from published reports, with IDP the same statistical methods can be applied across all studies involved. This allows for the application of newer statistical modeling techniques and similar handling of missing data, thus increasing comparability,[51]. The use of the original data may further circumvent bias related to the publication of positive results or the removal of patients before analysis in published trials,[52].

In summary, the current project aims to:

1) Compare treatment effectiveness of LTPT of low vs. high dose (based on session frequency and duration)
    a. At treatment termination
    b. At long-term follow-up (stability of outcome)
    c. Compared to shorter therapies as included in the trials
2) Identify individual characteristics that reliably predict or moderate differential treatment outcomes
3) Examine the reciprocal relationship of symptoms and personality functioning over time

METHODS AND ANALYSIS

The study is an IPD meta-analysis, registered on the International prospective register of systematic reviews (PROSPERO; CRD42022304982)

before conducting the main search and soliciting any data. Amendments will be documented here. Eligible studies will be identified through systematic literature research. Study results will be reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Individual Participant Data (PRISMA-IPD; Stewart et al. 2015). The project is expected to start in June 2022 and be completed in about two years.

Selection of studies

Due to randomization difficulties for LTPT, especially psychoanalysis, we include quasi-experimental cohort studies along with prospective randomized controlled trials (RCT). Eligible studies must contain LTPT. LTPT is defined according to Leichsenring & Rabung 2011 criteria for LTPP by 1) Studies of psychodynamic therapy; 2) Working with transference and resistance and 3) Duration of at least 50 sessions or at least one year. Moreover, we will include psychoanalysis proper, meaning up to five sessions per week in a supine position. Control conditions are psychodynamic treatments of shorter duration (fewer than 50 sessions), other treatments (e.g., CBT) from various psychotherapeutic backgrounds, or TAU. Treatment must be individual therapy for common mental disorders (e.g., depression, anxiety, or personality disorders) in adults. The exact inclusion and exclusion criteria can be found in Table 1. We will apply a three-step selection process. During the first step, two independent raters (one post-doc and one doctoral candidate) will apply the outlined selection criteria to the titles and abstracts of the references retrieved from the systematic literature research. In case of disagreement, consensus will be reached through discussion. If a study is considered as potentially fulfilling inclusion criteria, we will request full texts. Next, full texts will be rated according to the selection criteria by two independent raters. Disagreements will be resolved through discussion or involvement of a third rater. Finally, selected studies will be rated by experts (full professor with analytic training) to confirm that the treatment investigated is LTPT.

Table 1. Selection criteria

Inclusion	Prospective RCT or quasi-experimental cohort study
	Baseline assessment and Post/Follow-Up assessment that exceeds at least one year
	Outpatient individual treatment
	Participants (≥18-65 Jahre)
	Treatment is LTPP (psychodynamic or -analytic long-term psychotherapy, psychoanalysis)
	Long-term is defined as ≥ 1 year or ≥ 50 sessions
	Standardized outcome measure with at least one empirical proof of reliability
	Data on frequency of sessions are available
	Treatment is carried out by licensed therapists
Exclusion	Focus on psychotic disorders
	Focus on organic disorders
	Single-case studies
	Serial case studies
	Qualitative studies
	Information on session frequency and therapy duration is not available
Outcomes	Primary:
	Standardized global symptom assessment
	Standardized disorder specific symptom assessment
	Secondary:
	Standardized assessment of personality/structure
	treatment adherence/ drop-out additional treatments (medication, psychotherapy)

Search Strategy

To identify as many relevant studies as possible, different search strategies will be used. Firstly, we will conduct a systematic literature review using the following databases: PubMed, PsycINFO (via EBSCO), Web of Science (via Elsevier), and theCochrane's Central Register of Controlled Trials (via Wiley). We define five categories of search strings (1) treatment, (2) long-term (3) study, (4) effectiveness and (5) common mental disorders, with synonyms that will be searched as index and free text terms. The Boolean combination of search strings is depicted in table 2. We will not apply language or date restrictions for the searches, yet the included studies must be written in English, French, or German for our team to conduct risk of bias (RoB) assessments. Secondly, we will search the controlled-trial register to identify ongoing and unpublished studies https://www.isrctn.com/search?q=&filters=conditionCategory%3AMental+and+Behavioural+Disorders and the Open Door Review of Clinical, Conceptual, Process and Outcome Studies in Psychoanalysis, 3rd edition https://www.ipa.world/en/Psychoanalytic_Theory/Research/open_door.aspx; accessed 11/21/21. Thirdly, we will hand-search published meta-analyses,[36–38] and the citations of the included trials to identify other possibly eligible trials. We will contact experts in the field through a listserv of related societies (e.g., Society for Psychotherapy Research, Psychoanalytic Research Society, International Psychoanalytic Society) to ask for yet unpublished trials or studies we have missed.

Table 2. Systematic literature search

Data banks	PubMed PsycInfo Web of Science Cochrane Central Register of Controlled Trials
Category:	**Search terms:**
Treatment	emotion focused OR mentalization OR mentalization OR self-psychology OR transference-focused OR insight-oriented OR interpretativ* OR psychodynamic* OR psychoanalys* OR psychoanalytic* OR "psychotherapy, psychodynamic" OR “psychoanalytic therapy"
	AND
Long-term	“follow-up studies” OR follow OR long-term OR longer-term OR open-ended
	AND
study	study OR studies OR trial*
	AND
Effectiveness	treatment outcome OR outcome OR effect* OR efficacy OR result* OR change*
	AND
Common mental disorder	mental disorder*OR psychiatric illness*OR psychiatric disease*OR mental illness*OR psychiatric disorder* OR behavior disorder*OR behaviour disorder* OR psychiatric diagnos* OR anxiet*OR mood disorder* OR affective disorder* OR

	personality disorder*OR borderline personalit* OR depress*OR post-traumatic stress disorder* OR post-traumatic neuros* OR PTSD

Data collection and management

Named corresponding authors will be contacted via e-mail. They will be provided with all necessary information (including a link to the project's PROSPERO registration and the protocol) and asked whether they would be willing to participate/collaborate. Contact information will be retrieved from the relevant publications or if unavailable or outdated through online searches. Authors will be offered co-authorship on the published paper in return for sharing the studies' de-identified individual participant data. Following Driessen et al.,[53], authors who do not respond will be contacted three times by mail. If we do not get a response, we will try to establish contact by phone, next send up to three letters by post. This procedure will be repeated first with the corresponding author, then the PI, and then sequentially with all other authors of the study. If we still do not get a response, we will contact colleagues or other persons who may help to establish contact. If we do not succeed in contacting the authors with the above-outlined efforts, or if authors respond that the individual participant data cannot be shared or has been deleted, study data is considered unavailable. If authors choose to share their data, data-sharing agreements between all parties will need to be drawn up. The procedures are country-dependent and will need to be taken into consideration. Once data-sharing agreements in line with GDPR ethical standards are arranged, authors will be asked to transfer de-identified individual-level data sets encrypted using a save cloud service, procedures will be provided by the University Medical Center Mainz. Authors will be asked to send item-based data sets if available and to provide a description of how the data was coded (codebook). Datasets will contain de-identified participant-level data comprising sociodemographic data, prognostic and prescriptive variables assessed at baseline, outcome variables assessed at baseline, during and after treatment, therapy duration and session frequency, additional treatment, and case status (ITT/ATP). Study-level data, e.g., requirements of therapists' professional experience (e.g., years of licensed practice), supervision, treatment integrity, and adherence, and interrater reliability for diagnostic assessment of primary outcome measures will be retrieved from the publication or requested, if unavailable. Example code for analyses, detailed RoB ratings, list of studies excluded at full-text stage including reasons for exclusion will be shared via the Open Science Framework (OSF).

Measures

The primary outcome is treatment effectiveness of low- vs. high dose LTPT as assessed by a global measure of symptomology, most commonly the Symptom Checklist-90 (SCL-90),[54] or disorder-specific measures at treatment termination and follow-up. Secondary outcomes are functional capacities, personality, or relationship pathology, most commonly the Inventory of Interpersonal Problems (IIP),[55] at treatment termination and long-term follow-up. Additional subgroup analyses will be performed for specific mental disorders (major depression, anxiety, personality disorders). To identify prognostic and prescriptive factors for treatment response we include patient-specific characteristics at baseline: Sociodemographic data (e.g., gender, education, employment, income, migration background), previous treatments including psychopharmacological treatments, and continuous measures of personality, relationships, functional capacities, and life events (e.g., social occupational functioning, comorbid disorders, childhood adversity).

Data Integrity and preparation

Received data sets will be thoroughly examined to identify out of range items or invalid scoring and will be compared with the original publication (sample size, missing data, gender, age, mean pre-treatment scores in the primary outcome as defined by the study, and mean post-treatment scores in the primary outcome as defined by the study). In case of deviations, we will contact the authors to resolve the issue (e.g., cases dropped from the analysis, imputation method used for computing mean scores of the questionnaires received). Next, all variables relevant for the IPD meta-analysis will be extracted from each study including all potential prognostic or prescriptive variables, treatment information received, and outcomes at baseline, intermediate, and follow-up assessment. The resulting variables will be copied into a new data set and study-level criteria (study type, treatment integrity, RoB assessment) and a participant ID containing numeric ID and an abbreviation of the study will be added. A copy of this file containing a study's raw data relevant to IPD will be standardized to the variable names and coding used in the IPD database. All studies will be integrated into the database structured by the created ID. RoB will be evaluated in line with Cochrane's assessments tools,[56,57]

As the type of measures applied by individual studies will likely vary, individual scores will be standardized (using z-transformation or a common metric approach,[58]). Centering will be applied within individual trials.

Missing Data

We intend to conduct intention to treat analysis. Missing data will be assessed in each study received, including the amount of missing data per participant and variable and possible reasons for missing. We will compare subsamples of participants without missing data to those with missing data per study and summarize distributions per variable. Missing Data will be handled using multilevel multiple imputation, an approach that handles sporadically (missing data on variables for some but not all participants) and systematically (variables that have not been assessed by a specific study) missing values and can adequately preserve between-study heterogeneity. As we expect some of the included studies to have small sample size and the overall number of studies to be rather small, we will use a full conditional specification approach (FCS; also Multiple imputation by chained equations; MICE),[59–62]. We will follow White's et al.,[63] rule of thumb and impute one data set per percent of participants with one or more missing variables. We will include all variables and interactions relevant to our analysis model and variables potentially predictive for missing data. Specifically, we will use the R-packages mice and its extension micemd,[60]

Data Analysis

To address research question 1 and 2, we will carry out a one-stage IPD meta-analysis. To analyze effectiveness, we will statistically predict symptom severity (global if available, otherwise specific) and remission (binary) controlling for baseline severity. To predict symptom severity over time we will use a generalized linear mixed model framework (GLMM), as participants are clustered in trials and treatment groups. Following Riley et al.'s [64] recommendations for IPD-meta-analysis, we will use restricted maximum likelihood estimation (REML) and obtain 95% confidence intervals for treatment effects using the Kenward-Roger approach. We will specify a random treatment effect to account for heterogeneity in study populations (intercept) and treatment effects (slope). To account for clustering within trials, we will fit a random intercept for each trial. Separate models will be estimated to compare LTPT of low vs. high dose, and to compare LTPT against control groups as provided by the trials. The estimation procedure will be repeated using our secondary outcome measures based on the trials providing these additional measures. Remission will be analyzed for symptom outcome only using multilevel logistic regression. To define remission, we will use the cut-offs of the given questionnaire. We intend to perform subgroup analysis by repeating analyses steps in subgroups with different mental disorders (a) Depressive Disorders, (b) Anxiety disorders, (c) Personality Disorders. The primary diagnosis given in the original trial will define group membership. Next, we will analyze prognostic factors by adding available participant- and study-level variables as predictors to the specified models. The selection of variables builds on the summarized evidence but will ultimately depend on the available data provided by the trials. If possible, continuous variables will be kept on a continuous scale to avoid loss of power. We will analyze prescriptive variables by adding interaction terms between the predictor and treatment groups. The third research question will be addressed by a two-stage individual participant data meta-analysis approach. We will first, estimate multi-group random intercept cross-lagged panel models (RI-CLPM,[65,66]) to examine the respective lagged and cross-lagged effects of personality functioning and symptoms on between person (BP) and within person (WP) level per study. We will consider every study providing data of personality functioning and symptoms for baseline, treatment termination and follow-up. We will use within person (WP) centering,[67,68] of scores prior to analyses to derive at standardized coefficients for lagged and cross-lagged effects. Next, findings will be meta-analyzed using random effects meta-analytic structural equation modelling (MASEM), a technique to meta-analyze path or structural equation models. Analyses will be carried out in R-lavaan [69] and R-metaSEM [70]. Sensitivity analysis for all research questions will be carried out based on complete cases. If enough studies have used the same instrument, we will rerun analysis for RQ1 and RQ2 based on these studies without standardizing the variables.

Patient and Public Involvement

No Patient and Public Involvement.

ETHICS AND DISSEMINATION

Given that all studies obtained ethical approval from the relevant ethics boards, further ethical approval is not necessary but requirements for data-sharing need to be met. A data-sharing agreement based according to principles of the General Data Protection Rules (GDPR) of the European Union will be signed between the University Medical Center Mainz and all parties involved (shared responsibility). All parties sharing their data are responsible to ensure that data sharing is in line with their institutional, local, and international requirements, which they confirm by signing the agreement on shared responsibility. All data transferred will be de-identified. The results of the study will be presented at international conferences for clinician scientists and practitioners. Scientific reports of the study results will be submitted for publication in international, preferably open access journals.

DISSCUSSION

This study protocol describes a systematic review with meta-analysis of individual participant data to determine the effectiveness of low vs. high dose LTPT at the end of treatment and long-term follow-up. Additionally, we aim to identify associated prognostic and prescriptive variables and the interaction of different outcome domains over time.

Clinical and scientific relevance

The evidence base of effectiveness for psychotherapy in general but also for psychodynamic treatments has been predominantly based on short-term therapies and short-term outcomes,[9]. Previous research found a potential benefit of LTPP over short-term treatments for complex mental disorders,[6,34,35,37]. Yet, little is known about the role of treatment dose in LTPT, including psychoanalysis, and psychoanalytic/ psychodynamic long-term psychotherapy. Given unsatisfactory response rates, e.g., about 41 % for (short-term) psychotherapy,[71], but high additional costs of extensive treatment, the effectiveness of LTPT at long-term follow-up represents a health outcome of public interest. Individual studies lack sufficient power to reliably examine prognostic and prescriptive variables, however, identifying

factors associated with benefits from (specific) treatments is an important step towards optimized treatment planning,[42]. The project serves to close this gap, by consolidating the evidence base for LTPT for the major common mental disorders (e.g., depression, anxiety, and personality disorders). As LTPT treatments strive to achieve structural and personality changes, outcomes will go beyond symptom change and cover relevant outcome domains, such as personality, interpersonal and social-occupational functioning. This is consistent with the recommendations for updating the criteria of evidence-based therapies,[72]. Of particular interest is the stability of therapeutic gains during long-term follow-up, as psychoanalytic theory posits that change does not necessarily cease at the end of treatment. Rather, insights gained during therapy are understood to promote further development during follow-up, when autonomy and greater capacity for self-analysis evolve,[73]. Hence, changing underlying structural capacities should enable patients to gain further benefit in the follow-up phase,[33,45,46].

Limitations

Limitations of data aggregation and analyses include different designs regarding the assessment of process and follow-up. Moreover, definitions of LTPT differ between studies regarding the frequency of sessions and setting. We cannot conduct a conventional meta-analysis to compare our results with trials not providing original data if some original studies will have analyzed low-and-high dose LTPT together. If enough trials provide separate analyses, we will conduct a conventional meta-analysis based on these trials. Not all trials included will be RCTs. An important limitation of IPD meta-analysis is that some trials may not be integrated due to non-response, problems with data-sharing, or the deletion of the original data. Thus, even if IPD meta-analyses are considered the gold standard in evidence synthesis, bias cannot be precluded, and information obtained by IPD should be used in addition to conventional meta-analyses and reviews. Identifying, collecting, and aggregating relevant data will require a certain time, and newly published trials cannot easily be incorporated. Even though IPD meta-analysis will likely have enough power to examine prognostic and prescriptive treatment variables, the choice of variables examined depends on the variables included in the original trials. Moreover, results may be restricted to individuals who choose to participate in treatment trials.

Conclusion

The present study will aggregate and analyze data of patients from LTPT over long follow-up periods. It will go beyond previous individual trials by targeting a large sample size and include different outcome domains, e.g., personality, structural and social-occupational functioning. It will contribute to the key question of personalized psychotherapy, that is differential indication.

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Authors Contributions

MEB, MLB and EB conceived the original idea. LK wrote the first draft of the manuscript reviewed and edited by MEB, MLB and EB. LK and PS developed the analysis plan. HLS, JB, GK, TJ, HRS, FR, SS, FL and ME revised the manuscript for important intellectual content. All authors have reviewed the final version of the manuscript, agree with its submission and are responsible for all aspects of the work.

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Competing interests

Manfred E. Beutel, Falk Leichsenring, Marianne Leuzinger-Bohleber, Henriette Löffler-Stastka, are state-licensed psychoanalysts, involved in the training of psychodynamic therapists/ psychoanalysts. Josef Brockmann, Dorothea Huber, Guenther Klug, Thorsten Jakobsen, Hemma Rössler-Schülein, Felicitas Rost and Simone Salzer are state-licensed psychoanalysts/ psychodynamic therapist. Mareike Ernst is training as psychodynamic therapist.

They have conceived and/or performed trials that will serve as a data source for the proposed study (*Frankfurt-Hamburg Study*, Josef Brockmann; *Göttingen Study*, Falk Leichsenring, *Heidelberg-Berlin Study*, Thorsten Jakobsen; *Munich Psychotherapy Study*, Dorothea Huber, Guenther Klug, *LAC Study*, Marianne Leuzinger-Bohleber, Manfred E. Beutel, Mareike Ernst; *Tavistock Depression Study,* Felicitas Rost; *Viennese Psychoanalytic Process and Outcome Study*, Henriette Löffler-Stastka, Hemma Rössler-Schülein)

Elmar Brähler, Peter Schmidt, and Lina Krakau declare no competing interests.

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Efficacy of high- vs. low-intensity psychoanalytically oriented long-term treatments and determinants of outcome -Individual Participant Data Meta-Analysis of Long-term Analytic Treatment Studies (MeLAS)

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Efficacy of high- vs. low-intensity psychoanalytically oriented long-term treatments and determinants of outcome -Individual Participant Data **Me**ta-Analysis of **L**ong-term **A**nalytic Treatment **S**tudies (**MeLAS)**

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ABSTRACT

Introduction: Long-term psychodynamic/ psychoanalytic psychotherapy (LTPP) is a prevalent treatment option for complex mental disorders. Yet, little is known about the role of treatment intensity in LTPP. We present a study protocol for a systematic review and individual participant data (IPD) meta-analysis aggregating and analyzing individual data from randomized and quasi-experimental trials by meta-analysis. The purpose is to 1a) determine the treatment effectiveness of LTPP with low vs. high intensity (up to two weekly sessions vs. three or more), 1b) compare their joint effectiveness to shorter therapies and TAU, 2) Identify predictors and moderators of treatment outcomes, and 3) determine reciprocal relationships between different outcome domains (symptomatic and structural/personality change) over the courses of LTPP. **Methods and Analysis:** We include studies from randomized (RCT) and quasi-experimental trials, where at least one condition was LTPP of high or low frequency. Long-term treatment is defined as ≥ one year or ≥ 50 sessions. To be eligible studies must include a standardized outcome measure of symptoms (global or disorder specific) with at least one proof of reliability. The primary outcome is symptom reduction (global or specific), secondary outcome criteria are reliable change, remission, functional capacities, personality, personality functioning, and interpersonal pathology. Relevant studies will mainly be identified by searching relevant databases: PubMed, PsycINFO (via EBSCO), Web of Science (via Elsevier), Chochrane's Central Register of Controlled Trials (via Wiley). Risk of bias will be evaluated in line with the Cochrane assessments tools for quasi-experimental trials and RCTs, respectively. **Ethics and dissemination:** Aggregation of data from primary trials collected based on ethics votes. Dissemination into clinical practice via open access publications of findings. The study is an IPD meta-analysis, registered on the International prospective register of systematic reviews (PROSPERO; 304982) before conducting the main search and soliciting data.

Keywords

psychodynamic, psychoanalytic, long-term therapy, long-term follow up, anxiety, depression, personality disorder

STRENGTH AND LIMITATION OF THIS STUDY

- IPD meta-analysis has increased power to detect differences between treatment groups and to examine prognostic and prescriptive factors associated with outcome.
- Combining individual participant data allows for comparisons that were not carried out in the original trials and can therefore not be examined in conventional meta-analysis (i.e., regrouping of patients according to treatment intensity).
- The inclusion of quasi-experimental trials and the examination of non-randomized conditions (high vs. low treatment intensity) lowers the quality of the evidence according to gold standard.
- In IPD meta-analysis bias may be introduced as not all relevant studies identified can be included, e.g., non-response of the authors, difficulties with data-sharing.

INTRODUCTION

Short-term psychodynamic psychotherapy (STPP) has demonstrated comparable efficacy to cognitive behavioral therapy (CBT) and other bona fide psychotherapies,[1–3]. However, common mental disorders often take a chronic course,[e.g.; 4,5] and short-term treatments might be insufficient for patients with complex mental disorders ,[5,6]. Complex mental disorders have been defined as mental disorders characterized by rigidity or inflexibility, e.g., personality disorders (PD), chronic mental disorders (e.g., chronic depression),[7]. They show high comorbidity with other mental and physical health conditions [8] and are associated with considerable functional impairments [9]. Regardless of a categorical diagnosis of PD, lower levels of personality organization are typically found in more severe mental disorders [10]. Previous data on dose-effect relations has indicated that patients with such disorders need longer treatments,[11,12]. Nevertheless, most evidence for psychotherapy is based upon short-term treatments and short-term outcomes, the latter usually assessed at treatment termination,[13]. Only a few trials report one-year follow-up, and longer-term follow-ups of two and more years are scarce,[2,14]. To our best knowledge, long-term remission rates of bona fide short-term psychotherapies are often unsatisfactory,[14], and up to half of the study, patients have been found to seek auxiliary psychotherapy during follow-up,[15]. Naturalistic trials further indicate that many patients require and receive long-term treatments up to several years,[16].

A basic claim of long-term psychoanalytic psychotherapies (LTPP), comprising psychoanalysis and long-term psychoanalytic/psychodynamic psychotherapy, has been to improve structural capacities related to the personality organization,[17–19] in addition to symptoms. Structural integration (i.e. personality functioning) comprises different domains of

psychological functioning e.g., identity, affect differentiation and tolerance, and self-other regulation which relate to core developmental tasks of attachment/relatedness and individuation/self-definition,[e.g., 20–22]. Conceptualized by the term personality functioning, the alternative model of personality disorders has introduced a similar,[23,24] model to the DSM-5,[25,26]. Here, impairment in personality functioning is described along the dimensions of self (identity perception, self-regulation) and interpersonal (empathy, intimacy) functioning as shared characteristic of all personality disorders. In the psychoanalytic literature, improvements in these domains have been described as structural change,[17–19] and have been related to treatments with higher frequency promoting greater capacity for self-analysis,[27]. In line with the traditionally transdiagnostic scope of psychoanalysis, LTPP studies have focused on global or disorder-specific symptom improvement, and social and personality functioning with long-term outcomes up to 10 years,[e.g., 15]. However, the number of available trials on LTPP with long-term follow-up is comparably small, as they pose special methodological challenges of recruitment, study design, duration, and funding. For ethical reasons, placebo or waiting-list control conditions are not feasible over extended periods, and it would be difficult to conceptualize plausible interventions with similar frequency and duration of intervention. Studies that included long-term follow-ups have shown that LTPP indeed led to lasting changes at the level of symptoms and other domains of functioning,[15,28–32]. In the long run, several studies indicated LTPP to be more effective than treatment as usual (TAU),[29] or short-term treatments,[15,33].

Huber et al.,[30] found psychoanalytic treatment to be more effective than CBT at long-term follow-up, while others reported a comparable reduction of symptoms in psychoanalytic therapy and CBT at the three-year assessment,[34], but stronger evidence of personality change in psychoanalytic treatment groups,[32]. Other studies have focused on the comparison of psychodynamic psychotherapy with more intensive and longer psychoanalytic treatment and found the latter to be more effective at one-,[35] or three-year follow-up,[36]. Yet, in a meta-analysis on psychodynamic psychotherapy. Town et al.,[37] found that therapy effects were maintained and continued to improve following termination of psychodynamic therapies of different frequencies and lengths. To our knowledge, only four conventional meta-analyses have focused on the effectiveness of LTPP specifically. Focusing on RCTs, Leichsenring & Rabung,[6,7,38] found LTPP to be more effective than STPT with medium to large effect sizes in terms of symptom reduction and social and personality functioning. Using different inclusion criteria, the meta-analysis of Smit et al.,[39] questioned the effectiveness of LTPP, as they found it more effective only in comparison to control conditions that were no specialized forms of therapy. Exploratory analyses indicated that a greater difference in treatment intensity between LTPP and the control group was related to effect size. The seemingly conflicting findings between Leichsenring and Rabung's,[6,7] and

Smit et al's.,[39] meta-analyses have been discussed elsewhere,[e.g., 38,40]. More recently, Woll and Schönbrodt aimed to replicate and update Leichsenring et al.'s,[38] meta-analysis, but only found small additional gains for LTPP in comparison to other forms of psychotherapy, regarding symptoms and social functioning. No significant differences were found with respect to personality functioning. Restricting their meta-analysis to psychoanalysis proper, defined as the patient lying on the couch with at least two sessions, one research group found large within-group effect sizes regarding symptomatic improvement and personality characteristics. Yet, most of the trials they examined were naturalistic and did not have control groups,[41].

Beyond efficacy studies, psychotherapy research, in general, has identified numerous patient, psychotherapist, and relational prognostic factors (predictors) for psychotherapy outcome, e.g., racial or social minority status, high symptom load, or high self-criticism,[42]. However, less is known about prescriptive variables (moderators) associated with different outcomes depending on the type of treatment, e.g., maladaptive defenses or rigid relationship patterns for psychodynamic treatments,[1,43,44]. Identifying prescriptive variables that reliably predict differential treatment outcomes has become the main target of personalized treatment approaches,[42,45]. To our knowledge, no meta-analysis has examined prognostic or prescriptive variables in LTPP.

Given the evidence outlined above, we presume that LTPP facilitates changes in intrapsychic, structural processes underlying mental disorders in addition to improving symptoms. Yet, it remains unclear whether this is due to the effects of psychoanalytic technique or its treatment frequency and duration,[12,39]. Changes in structural functioning have been posited as a mechanism of change in psychotherapy, and LTPP specifically, with a stronger focus on insight and self-understanding,[46]. Several studies found greater changes e.g. in personality or reflective functioning associated with greater,[34,47] and sustained,[48,49] symptom reduction. However, the studies mostly focused on between-person effects and did not apply lagged analysis over multiple time points to investigate if changes in structural capacities were associated with a decrease in symptoms at subsequent assessment.

Due to the limitations of the individual trials, empirical evidence on the role of treatment intensity for the efficacy of LTPP and the identification of prescriptive variables has been limited. Small samples and unequal group sizes as well as decreasing case numbers throughout therapy and follow-up have led to

methodological problems in data analysis of individual trials, including a lack of statistical power. Hence, small differences between different treatment approaches cannot be identified and testing for sub-groups with differential outcome is prohibited,[50]. Additional problems include the utilization of different designs (RCT vs. quasi-experimental), varying definitions of LTPP (e.g., ranging from 42 to over 300 sessions), varying frequency of measurements, definition and timing of follow-ups, and the comparability of measures of relevant variables (e.g., sociodemographic and clinical characteristics) and different outcome measures.

The current study aims to conduct a systematic review and individual participant data (IPD) meta-analysis concerning the efficacy of LTPP treatments of different intensities and associated prognostic and prescriptive factors in common mental disorders. IPD meta-analysis is a technique to examine treatment effects by combining participant-level data of multiple trials collected from the original data and is currently considered the gold standard in evidence synthesis,[51,52]. A one-stage approach is favored, especially when the original trials have small samples,[53]. It has increased statistical power to detect differences between treatment conditions and to examine prognostic and prescriptive variables associated with treatment efficacy,[45]. Compared to conventional meta-analyses that rely on the aggregated level data extracted from published reports, with IDP the same statistical methods can be applied across all studies involved. This allows for the application of newer statistical modeling techniques and similar handling of missing data, thus increasing comparability,[54]. The use of the original data may further circumvent bias related to the publication of positive results or the removal of patients before analysis in published trials,[55].

In summary, the current project aims to:

1) Compare treatment effectiveness of LTPP of low vs. high intensity (based on average weekly sessions)
    a. At treatment termination
    b. At long-term follow-up (stability of outcome)
    c. Compare their joint efficacy to shorter therapies and TAU as included as control groups in the trials
2) Identify individual characteristics that reliably predict or moderate differential treatment outcomes of low- and high-intensity LTPP

3) Examine the reciprocal relationship of symptoms and personality functioning over time

METHODS AND ANALYSIS

The study is an IPD meta-analysis, registered on the International prospective register of systematic reviews (PROSPERO; CRD42022304982) before conducting the main search and soliciting any data. Amendments will be documented here. Eligible studies will be identified through systematic literature research. Study results will be reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Individual Participant Data (PRISMA-IPD; Stewart et al. 2015). Project planning and preliminary literature research have started in June 2022, and we expect the completion of the project within three years.

Selection of studies

The aim of the study is the examination of the efficacy of LTPP with different intensity in adult outpatient populations with common mental disorders. Low-intensity treatments are defined as treatments with up to two weekly sessions, and high-intensity treatments are treatments with three or more weekly sessions. We will include randomized and quasi-experimental clinical trials on LTPP. We will include trials that directly compared high- vs. low-intensity LTPP, and trials that compared high- and/or low-intensity LTPP to shorter treatments or treatments as usual /TAU). In our main analysis, we will compare high- vs. low-intensity LTPP. A sensitivity analysis will be conducted to contrast one weekly session (instead of up to two) with three or more. In a second analysis, we will compare high- and-low intensity LTPP (combined) to shorter treatments and TAU (combined). We will conduct a sensitivity analysis excluding TAU. Due to randomization difficulties for LTPP, especially psychoanalysis, we include quasi-experimental cohort studies along with prospective randomized controlled trials (RCT). Eligible studies must contain LTPP. LTPP is defined according to Leichsenring & Rabung 2011 criteria for LTPP by 1) Studies of psychodynamic therapy; 2) Working with transference and resistance and 3) Duration of at least 50 sessions or at least one year. Moreover, we will include psychoanalysis proper, meaning up to five sessions per week in a supine position. Control conditions are psychodynamic treatments of shorter duration (fewer than 50 sessions), other treatments (e.g., CBT) from various psychotherapeutic backgrounds, or TAU. Treatment must be individual therapy for common mental disorders (e.g., depression,

anxiety, or personality disorders) in adults. The exact inclusion and exclusion criteria can be found in Table 1. We will apply a three-step selection process. During the first step, two independent raters (one post-doc and one doctoral candidate) will apply the outlined selection criteria to the titles and abstracts of the references retrieved from the systematic literature research. In case of disagreement, consensus will be reached through discussion. If a study is considered as potentially fulfilling inclusion criteria, we will request full texts. Next, full texts will be rated according to the selection criteria by two independent raters. Disagreements will be resolved through discussion or the involvement of a third rater. Finally, selected studies will be rated by experts (full professors with analytic training) to confirm that the treatment investigated is LTPP.

Table 1. Selection criteria

Inclusion	Prospective RCT or quasi-experimental cohort study
	Baseline assessment and Post/Follow-Up assessment that exceeds at least one year
	Outpatient individual treatment
	Participants (≥18-65 Jahre)
	One treatment is LTPP (psychodynamic or -analytic long-term psychotherapy, psychoanalysis)
	Long-term is defined as ≥ 1 year or ≥ 50 sessions
	Standardized outcome measure of symptoms (global or specific) with at least one empirical proof of reliability
	Data on frequency of sessions are available
	Treatment is carried out by licensed psychotherapists
Exclusion	Focus on psychotic disorders
	Focus on organic disorders
	Single-case studies
	Serial case studies
	Qualitative studies
	Information on session frequency and therapy duration is not available
Outcomes	Primary:
	Standardized symptom assessment (global symptom level or disorder-specific)
	Secondary:
	Reliable change, no change and deterioration, calculated based on the primary outcome measure; Standardized assessments of personality/personality functioning, functional capacities, or relationship pathology

Search Strategy

To identify as many relevant studies as possible, different search strategies will be used. Firstly, we will conduct a systematic literature review using the following databases: PubMed, PsycINFO (via EBSCO), Web of Science (via Elsevier), and the Cochrane's Central Register of Controlled Trials (via Wiley). We define five categories of search strings (1) treatment, (2) long-term (3) study, (4) effectiveness and (5) common mental disorders, with synonyms that will be searched as index and free text terms. The Boolean combination of search strings is depicted in Table 2. We will not apply language or date restrictions for the searches, however, the included studies must be published in English, French, or German for our team to conduct risk of bias (RoB) assessments. Secondly, we will search the controlled-trial register to identify ongoing and unpublished studies https://www.isrctn.com/search?q=&filters=conditionCategory%3AMental+and+Behavioural+Disorders and the Open Door Review of Clinical, Conceptual, Process and Outcome Studies in Psychoanalysis, 3rd edition https://www.ipa.world/en/Psychoanalytic_Theory/Research/open_door.aspx; accessed 11/21/21. Thirdly, we will hand-search published meta-analyses,[39–41] and the citations of the included trials to identify other possibly eligible trials. We will contact experts in the field through a listserv of related societies (e.g., Society for Psychotherapy Research, Psychoanalytic Research Society, International Psychoanalytic Society) to ask for yet unpublished trials or studies we have missed.

Table 2. Systematic literature search

Data banks	PubMed PsycInfo Web of Science Cochrane Central Register of Controlled Trials
Category:	**Search terms:**
Treatment	emotion focused OR mentalization OR mentalization OR self-psychology OR transference-focused OR insight-oriented OR interpretativ* OR psychodynamic* OR psychoanalys* OR psychoanalytic* OR "psychotherapy, psychodynamic" OR “psychoanalytic therapy"
	AND
Long-term	“follow-up studies” OR follow OR long-term OR longer-term OR open-ended
	AND
study	study OR studies OR trial*
	AND
Effectiveness	treatment outcome OR outcome OR effect* OR efficacy OR result* OR change*
	AND
Common mental disorder	mental disorder*OR psychiatric illness*OR psychiatric disease*OR mental illness*OR psychiatric disorder* OR behavior disorder*OR behaviour disorder* OR psychiatric diagnos* OR anxiet*OR mood disorder* OR affective disorder* OR

	personality disorder*OR borderline personalit* OR depress*OR post-traumatic stress disorder* OR post-traumatic neuros* OR PTSD

Data collection and management

Named corresponding authors will be contacted via e-mail. They will be provided with all necessary information (including a link to the project's PROSPERO registration and the protocol) and asked whether they would be willing to participate/collaborate. Contact information will be retrieved from the relevant publications or if unavailable or outdated through online searches. Authors will be offered co-authorship on the published paper in return for sharing the studies' de-identified individual participant data. Following Driessen et al.,[56], authors who do not respond will be contacted three times by mail. If we do not get a response, we will try to establish contact by phone, next send up to three letters by post. This procedure will be repeated first with the corresponding author, then the PI, and then sequentially with all other authors of the study. If we still do not get a response, we will contact colleagues or other persons who may help to establish contact. If we do not succeed in contacting the authors with the above-outlined efforts, or if authors respond that the individual participant data cannot be shared or has been deleted, study data is considered unavailable. If authors choose to share their data, data-sharing agreements between all parties will need to be drawn up. The procedures are country-dependent and will need to be taken into consideration. Once data-sharing agreements in line with GDPR ethical standards are arranged, authors will be asked to transfer de-identified individual-level data sets encrypted using a save cloud service, procedures will be provided by the University Medical Center Mainz. Authors will be asked to send item-based data sets if available and to provide a description of how the data was coded (codebook). Datasets will contain de-identified participant-level data comprising sociodemographic data, prognostic and prescriptive variables assessed at baseline, outcome variables assessed at baseline, during and after treatment, therapy duration and session frequency, additional treatment, and case status (ITT/ATP). Study-level data, e.g., requirements of therapists' professional experience (e.g., years of licensed practice), supervision, treatment integrity, and adherence, and interrater reliability for diagnostic assessment of primary outcome measures will be retrieved from the publication or requested, if unavailable. Example code for analyses, detailed RoB ratings, list of studies excluded at full-text stage including reasons for exclusion will be shared via the Open Science Framework (OSF).

Measures

The primary outcome is treatment effectiveness of low- vs. high-intensity LTPP as assessed by a global measure of symptomology, most commonly the Symptom Checklist-90 (SCL-90),[57] or disorder-specific measures at treatment termination and follow-up. Secondary outcomes are functional capacities, personality, personality functioning, or relationship pathology, most commonly the Inventory of Interpersonal Problems (IIP),[58] at treatment termination and long-term follow-up. Additional subgroup analyses will be performed for specific mental disorders (major depression, anxiety, personality disorders). For the primary outcome, we will also assess reliable change criteria [59] including no change, and deterioration, to account for the fact that psychotherapy has not always been found to be beneficial. Moreover, we will assess the occurrence of adverse events (0 = no adverse event, 1 = adverse event) during trial participation. If enough data is available this will be added as a secondary outcome. To identify potential prognostic and prescriptive factors for treatment response we include patient-specific characteristics at baseline: Sociodemographic data (e.g., gender, education, employment, income, migration background, clinical characteristics, (diagnosis given by the trial, previous treatments including psychopharmacological treatments) and continuous measures of symptom severity, personality and personality functioning, relationships, functional capacities, and life events (e.g., social occupational functioning, comorbid disorders, childhood adversity). Patient characteristics will be included when they are consistently reported among trials and can be standardized in a coherent way (e.g., by collapsing categories). We will include a variable referring to the original trial design (predetermined length vs. Open ended treatment) and a variable indicating whether cases were treated according to protocol (ATP vs. Drop-out).

Data Integrity and preparation

Received data sets will be thoroughly examined to identify out-of-range items or invalid scoring and will be compared with the original publication (sample size, missing data, gender, age, mean pre-treatment scores in the primary outcome as defined by the study, and mean post-treatment scores in the primary outcome as defined by the study). In case of deviations, we will contact the authors to resolve the issue (e.g., cases dropped from the analysis, imputation method used for computing mean scores of the questionnaires received). Next, all variables relevant for the IPD meta-analysis will be extracted from each study including prognostic and prescriptive

variables, treatment information received, the diagnoses given within the original trial, and primary and secondary outcomes at baseline, intermediate, and follow-up assessment. The resulting variables will be copied into a new data set and study-level criteria (study type, treatment integrity, RoB assessment) and a participant ID containing numeric ID and an abbreviation of the study will be added. A copy of this file containing a study's raw data relevant to IPD will be standardized to the variable names and coding used in the IPD database. A variable will be created indicating the participants' group membership (high intensity LTPP, low intensity LTPP, Shorter Treatment/TAU). For the planned sensitivity analyses, we will create a second grouping variable (one weekly session vs. three or more and separating shorter treatment from TAU). All studies will be integrated into the database structured by the created ID. RoB will be evaluated in line with the Cochrane assessments tools for quasi-experimental trials,[60] and RCTs, [61], respectively. The results of the RoB ratings will be presented in tables listing each original study. They will be used for an overall appraisal for the quality of evidence of the IPD-MA, which is carried out following Tierney et al. [62]. As the type of measures applied by individual studies will likely vary, individual scores will be standardized (using z-transformation or a common metric approach,[63]) for continuous measures. Centering will be applied within individual trials. Data screening, data extraction and risk of bias assessment will be performed independently by two researchers (one postdoctoral researcher and one doctoral candidate).

Missing Data

We intend to conduct an intention-to-treat analysis. Missing data will be assessed in each study received, including the amount of missing data per participant and variable and possible reasons for missingness. We will compare subsamples of participants without missing data to those with missing data per study and summarize distributions per variable. Missing Data will be handled using multilevel multiple imputation, an approach that handles sporadically (missing data on variables for some but not all participants) and systematically (variables that have not been assessed by a specific study) missing values and can adequately preserve between-study heterogeneity. As we expect some of the included studies to have a small sample size and the overall number of studies to be rather low, we will use a full conditional specification approach (FCS; also Multiple imputation by chained

equations; MICE),[64–67]. We will follow White's et al.,[68] rule of thumb and impute one data set per percent of participants with one or more missing variables. We will include all variables and interactions relevant to our analysis model and variables potentially predictive for missing data. Specifically, we will use the R-packages mice and its extension micemd,[65].

Data Analysis

To address research questions 1(RQ1) and 2(RQ2), we will carry out a one-stage IPD meta-analysis. To analyze effectiveness, we will statistically predict symptom severity (global if available, otherwise specific) and remission (binary) controlling for baseline severity. To predict symptom severity over time we will use a generalized linear mixed model framework (GLMM), as participants are clustered in trials and treatment groups. Following Riley et al.'s [69] recommendations for IPD-meta-analysis, we will use restricted maximum likelihood estimation (REML) and obtain 95% confidence intervals for treatment effects using the Kenward-Roger approach. We will specify a random treatment effect to account for heterogeneity in study populations (intercept) and treatment effects (slope). To account for clustering within trials, we will fit a random intercept for each trial. Separate models will be estimated to compare LTPP of low vs. high intensity, and to compare joint LTPP against control groups as provided by the trials. The estimation procedure will be repeated using our secondary outcome measures based on the trials providing these additional measures. Reliable response, no change and deterioration will be analyzed for symptom outcome only using multilevel logistic regression. Response type will be calculated based on the reliable change index [59] of the symptom assessment within a given trial. We intend to perform subgroup analysis by repeating analysis steps in subgroups with different mental disorders (a) Depressive Disorders, (b) Anxiety disorders, (c) Personality Disorders. The primary diagnosis given in the original trial will define group membership. Next, we will analyze prognostic factors by adding available participant- and study-level variables as predictors to the specified models. If possible, continuous variables will be kept on a continuous scale to avoid loss of power. We will analyze prescriptive variables by adding interaction terms between the predictor and treatment groups. The third research question will be addressed by a two-stage individual participant data meta-analysis approach. We will first, estimate multi-group random intercept cross-lagged panel models (RI-CLPM,[70,71]) to examine the respective lagged and cross-lagged effects of personality functioning and symptoms on between-person (BP) and within-person (WP) level per study. We will consider every study providing data on personality functioning and symptoms for baseline, treatment termination and follow-up. We will use within-person (WP) centering,[72,73] of scores prior to analyses to derive standardized coefficients for lagged and cross-lagged effects. Next, findings will be meta-analyzed using random effects meta-analytic structural equation modelling (MASEM), a technique to meta-analyze path or structural equation models. Analyses will be carried out in R-lavaan [74] and R-metaSEM [75]. Sensitivity analyses for all research questions will be carried out based on complete cases. If enough studies have used the same instrument, we will rerun analysis for RQ1 and RQ2 based on these studies without standardizing the variables.

Patient and Public Involvement

No Patient and Public Involvement.

ETHICS AND DISSEMINATION

Given that all studies obtained ethical approval from the relevant ethics boards, further ethical approval is not necessary but requirements for data-sharing need to be met. A data-sharing agreement based according to principles of the General Data Protection Rules (GDPR) of the European Union will be signed between the University Medical Center Mainz and all parties involved (shared responsibility). All parties sharing their data are responsible to ensure that data sharing is in line with their institutional, local, and international requirements, which they confirm by signing the agreement on shared responsibility. All data transferred will be de-identified. The results of the study will be presented at international conferences for clinician scientists and practitioners. Scientific reports of the study results will be submitted for publication in international, preferably open-access journals.

DISSCUSSION

This study protocol describes a systematic review with meta-analysis of individual participant data to determine the effectiveness of low vs. high intensity LTPP at the end of treatment and long-term follow-up. Additionally, we aim to identify associated prognostic and prescriptive variables and the interaction of different outcome domains over time.

Clinical and scientific relevance

The evidence base of effectiveness for psychotherapy in general but also for psychodynamic treatments has been predominantly based on short-term therapies and short-term outcomes,[13]. Previous research found a potential benefit of LTPP over short-term treatments for complex mental disorders,[6,7,38,40]. Yet, little is known about the role of treatment intensity in LTPP, including psychoanalysis, and psychoanalytic/ psychodynamic long-term psychotherapy. Given unsatisfactory response rates, e.g., about 41 % for (short-term) psychotherapy,[76], but high additional costs of extensive treatment, the effectiveness of LTPP at long-term follow-up represents a health outcome of public interest. Individual studies lack sufficient power to reliably examine prognostic and prescriptive variables, however, identifying

factors associated with benefits from (specific) treatments is an important step towards optimized treatment planning,[45]. The project serves to close this gap, by consolidating the evidence base for LTPP for the major common mental disorders (e.g., depression, anxiety, and personality disorders). As LTPP treatments strive to achieve structural and personality changes, outcomes will go beyond symptom change and cover relevant outcome domains, such as personality, interpersonal and social-occupational functioning. This is consistent with the recommendations for updating the criteria of evidence-based therapies,[77]. The stability of therapeutic gains during long-term follow-up is of particular interest, as psychoanalytic theory posits that change does not necessarily cease at the end of treatment. Rather, insights gained during therapy are understood to promote further development during follow-up, when autonomy and greater capacity for self-analysis evolve,[78]. Hence, changing underlying structural capacities should enable patients to gain further benefits in the follow-up phase,[37,48,49].

Limitations

Limitations of data aggregation and analyses include different designs regarding the assessment of process and follow-up. Moreover, definitions of LTPP differ between studies regarding the frequency of sessions and setting. We cannot conduct a conventional meta-analysis to compare our results with trials not providing original data as some original studies will have analyzed low-and-high intensity LTPP together. If enough trials provide separate analyses, we will conduct a conventional meta-analysis based on these trials. The study includes RCTs and quasi-experimental cohort studies, lowering the quality of evidence according to gold-standards. Yet, the inclusion of quasi-experimental trials in diverse settings, where patients self-select their treatment, enhances the external validity of the results as treatment length and techniques in practice are individually adapted. An important limitation of IPD meta-analysis is that some trials may not be integrated due to non-response, problems with data-sharing, or the deletion of the original data. Thus, even if IPD meta-analyses are considered the gold standard in evidence synthesis, bias cannot be precluded, and information obtained by IPD should be used in addition to conventional meta-analyses and reviews. Identifying, collecting, and aggregating relevant data will require a certain time, and newly published trials cannot easily be incorporated. Even though IPD meta-analysis will likely have enough power to examine prognostic and prescriptive treatment variables, the choice of variables

examined depends on the variables included in the original trials. Moreover, results may be restricted to individuals who choose to participate in treatment trials. We have specified secondary outcomes, however, our analyses will not be controlled for type I and type II errors. To our knowledge, studies conducted in the field have not incorporated explicit measures on harmful effects, such as negative experiences during psychotherapy. Our analyses will therefore fall short of an equal focus on efficacy and harmful effects of LTPP. We try to counterbalance this with modeling no reliable change, deterioration, and adverse events.

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Authors Contributions

MEB, MLB and EB conceived the original idea. LK wrote the first draft of the manuscript reviewed and edited by MEB, MLB and EB. LK and PS developed the analysis plan. HLS, JB, DH, GK, TJ, HRS, FR, SS, FL and ME revised the manuscript for important intellectual content. All authors have reviewed the final version of the manuscript, agree with its submission and are responsible for all aspects of the work.

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Competing interests

Manfred E. Beutel, Falk Leichsenring, Marianne Leuzinger-Bohleber, Henriette Löffler-Stastka, are state-licensed psychoanalysts, involved in the training of psychodynamic therapists/psychoanalysts. Josef Brockmann, Dorothea Huber, Guenther Klug, Thorsten Jakobsen, Hemma Rössler-Schülein, Felicitas Rost and Simone Salzer are state-licensed psychoanalysts/psychodynamic psychotherapists. Mareike Ernst is training as a psychodynamic psychotherapist.

They have conceived and/or performed trials that will serve as a data source for the proposed study (*Frankfurt-Hamburg Study*, Josef Brockmann; *Göttingen Study*, Falk Leichsenring, *Heidelberg-Berlin Study*, Thorsten Jakobsen; *Munich Psychotherapy Study*, Dorothea Huber, Guenther Klug, *LAC Study*, Marianne Leuzinger-Bohleber, Manfred E. Beutel, Mareike Ernst; *Tavistock Adult Depression Study,* Felicitas Rost; *Viennese Psychoanalytic Process and Outcome Study*, Henriette Löffler-Stastka, Hemma Rössler-Schülein)

Elmar Brähler, Peter Schmidt, and Lina Krakau declare no competing interests.

PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD)

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	2
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation; noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-6
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	6-7
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	2
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	7-8
Identifying studies -	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers	10

information sources		and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	11-12
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	nA
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	13
		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of harmonising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	14-15
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	14-15
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	15
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	14;17
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable).	17

Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	17
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	15
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	27
Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	nA
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	nA
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	nA
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	nA
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	nA
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	nA
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	

Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	nA
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	nA
Discussion			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	nA
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	19-20
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	nA
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	18-19
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	21

A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA statement to suit the way that systematic review IPD meta-analyses are reported.

BMJ Open

Efficacy of high- vs. low-intensity psychoanalytically oriented long-term treatments and determinants of outcome -Individual Participant Data Meta-Analysis of Long-term Analytic Treatment Studies (MeLAS)

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Efficacy of high- vs. low-intensity psychoanalytically oriented long-term treatments and determinants of outcome -Individual Participant Data **Me**ta-Analysis of **L**ong-term **A**nalytic Treatment **S**tudies (**MeLAS)**

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ABSTRACT

Introduction: Long-term psychodynamic/ psychoanalytic psychotherapy (LTPP) is a prevalent treatment option for complex mental disorders. Yet, little is known about the role of treatment intensity in LTPP. We present a study protocol for a systematic review and individual participant data (IPD) meta-analysis aggregating and analyzing individual data from randomized and quasi-experimental trials by meta-analysis. The purpose is to 1a) determine the treatment effectiveness of LTPP with low vs. high intensity (up to two weekly sessions vs. three or more), 1b) compare their joint effectiveness to shorter therapies and TAU, 2) Identify predictors and moderators of treatment outcomes, and 3) determine reciprocal relationships between different outcome domains (symptomatic and structural/personality change) over the courses of LTPP. **Methods and Analysis:** We include studies from randomized (RCT) and quasi-experimental trials, where at least one condition was LTPP of high or low frequency. Long-term treatment is defined as ≥ one year or ≥ 50 sessions. To be eligible studies must include a standardized outcome measure of symptoms (global or disorder specific) with at least one proof of reliability. The primary outcome is symptom reduction (global or specific), secondary outcome criteria are reliable change, remission, functional capacities, personality, personality functioning, and interpersonal pathology. Relevant studies will mainly be identified by searching relevant databases: PubMed, PsycINFO (via EBSCO), Web of Science (via Elsevier), Chochrane's Central Register of Controlled Trials (via Wiley). Risk of bias will be evaluated in line with the Cochrane assessments tools for quasi-experimental trials and RCTs, respectively. **Ethics and dissemination:** Aggregation of data from primary trials collected based on ethics votes. Dissemination into clinical practice via open access publications of findings. The study is an IPD meta-analysis, registered on the International prospective register of systematic reviews (PROSPERO; 304982) before conducting the main search and soliciting data.

Keywords

psychodynamic, psychoanalytic, long-term therapy, long-term follow up, anxiety, depression, personality disorder

STRENGTH AND LIMITATION OF THIS STUDY

- IPD meta-analysis has increased power to detect differences between treatment groups and to examine prognostic and prescriptive factors associated with outcome.
- Combining individual participant data allows for comparisons that were not carried out in the original trials and can therefore not be examined in conventional meta-analysis (i.e., regrouping of patients according to treatment intensity).
- The inclusion of quasi-experimental trials and the examination of non-randomized conditions (high vs. low treatment intensity) lowers the quality of the evidence according to gold standard.
- In IPD meta-analysis bias may be introduced as not all relevant studies identified can be included, e.g., non-response of the authors, difficulties with data-sharing.

INTRODUCTION

Short-term psychodynamic psychotherapy (STPP) has demonstrated comparable efficacy to cognitive behavioral therapy (CBT) and other bona fide psychotherapies,[1–3]. However, common mental disorders often take a chronic course,[e.g.; 4,5] and short-term treatments might be insufficient for patients with complex mental disorders ,[5,6]. Complex mental disorders have been defined as mental disorders characterized by rigidity or inflexibility, e.g., personality disorders (PD), chronic mental disorders (e.g., chronic depression),[7]. They show high comorbidity with other mental and physical health conditions [8] and are associated with considerable functional impairments [9]. Regardless of a categorical diagnosis of PD, lower levels of personality organization are typically found in more severe mental disorders [10]. Previous data on dose-effect relations has indicated that patients with such disorders need longer treatments,[11,12]. Nevertheless, most evidence for psychotherapy is based upon short-term treatments and short-term outcomes, the latter usually assessed at treatment termination,[13]. Only a few trials report one-year follow-up, and longer-term follow-ups of two and more years are scarce,[2,14]. To our best knowledge, long-term remission rates of bona fide short-term psychotherapies are often unsatisfactory,[14], and up to half of the study, patients have been found to seek auxiliary psychotherapy during follow-up,[15]. Naturalistic trials further indicate that many patients require and receive long-term treatments up to several years,[16].

A basic claim of long-term psychoanalytic psychotherapies (LTPP), comprising psychoanalysis and long-term psychoanalytic/psychodynamic psychotherapy, has been to improve structural capacities related to the personality organization,[17–19] in addition to symptoms. Structural integration (i.e. personality functioning) comprises different domains of

psychological functioning e.g., identity, affect differentiation and tolerance, and self-other regulation which relate to core developmental tasks of attachment/relatedness and individuation/self-definition,[e.g., 20–22]. Conceptualized by the term personality functioning, the alternative model of personality disorders has introduced a similar,[23,24] model to the DSM-5,[25,26]. Here, impairment in personality functioning is described along the dimensions of self (identity perception, self-regulation) and interpersonal (empathy, intimacy) functioning as shared characteristic of all personality disorders. In the psychoanalytic literature, improvements in these domains have been described as structural change,[17–19] and have been related to treatments with higher frequency promoting greater capacity for self-analysis,[27]. In line with the traditionally transdiagnostic scope of psychoanalysis, LTPP studies have focused on global or disorder-specific symptom improvement, and social and personality functioning with long-term outcomes up to 10 years,[e.g., 15]. However, the number of available trials on LTPP with long-term follow-up is comparably small, as they pose special methodological challenges of recruitment, study design, duration, and funding. For ethical reasons, placebo or waiting-list control conditions are not feasible over extended periods, and it would be difficult to conceptualize plausible interventions with similar frequency and duration of intervention. Studies that included long-term follow-ups have shown that LTPP indeed led to lasting changes at the level of symptoms and other domains of functioning,[15,28–32]. In the long run, several studies indicated LTPP to be more effective than treatment as usual (TAU),[29] or short-term treatments,[15,33].

Huber et al.,[30] found psychoanalytic treatment to be more effective than CBT at long-term follow-up, while others reported a comparable reduction of symptoms in psychoanalytic therapy and CBT at the three-year assessment,[34], but stronger evidence of personality change in psychoanalytic treatment groups,[32]. Other studies have focused on the comparison of psychodynamic psychotherapy with more intensive and longer psychoanalytic treatment and found the latter to be more effective at one-,[35] or three-year follow-up,[36]. Yet, in a meta-analysis on psychodynamic psychotherapy. Town et al.,[37] found that therapy effects were maintained and continued to improve following termination of psychodynamic therapies of different frequencies and lengths. To our knowledge, only four conventional meta-analyses have focused on the effectiveness of LTPP specifically. Focusing on RCTs, Leichsenring & Rabung,[6,7,38] found LTPP to be more effective than STPT with medium to large effect sizes in terms of symptom reduction and social and personality functioning. Using different inclusion criteria, the meta-analysis of Smit et al.,[39] questioned the effectiveness of LTPP, as they found it more effective only in comparison to control conditions that were no specialized forms of therapy. Exploratory analyses indicated that a greater difference in treatment intensity between LTPP and the control group was related to effect size. The seemingly conflicting findings between Leichsenring and Rabung's,[6,7] and

Smit et al's.,[39] meta-analyses have been discussed elsewhere,[e.g., 38,40]. More recently, Woll and Schönbrodt aimed to replicate and update Leichsenring et al.'s,[38] meta-analysis, but only found small additional gains for LTPP in comparison to other forms of psychotherapy, regarding symptoms and social functioning. No significant differences were found with respect to personality functioning. Restricting their meta-analysis to psychoanalysis proper, defined as the patient lying on the couch with at least two sessions, one research group found large within-group effect sizes regarding symptomatic improvement and personality characteristics. Yet, most of the trials they examined were naturalistic and did not have control groups,[41].

Beyond efficacy studies, psychotherapy research, in general, has identified numerous patient, psychotherapist, and relational prognostic factors (predictors) for psychotherapy outcome, e.g., racial or social minority status, high symptom load, or high self-criticism,[42]. However, less is known about prescriptive variables (moderators) associated with different outcomes depending on the type of treatment, e.g., maladaptive defenses or rigid relationship patterns for psychodynamic treatments,[1,43,44]. Identifying prescriptive variables that reliably predict differential treatment outcomes has become the main target of personalized treatment approaches,[42,45]. To our knowledge, no meta-analysis has examined prognostic or prescriptive variables in LTPP.

Given the evidence outlined above, we presume that LTPP facilitates changes in intrapsychic, structural processes underlying mental disorders in addition to improving symptoms. Yet, it remains unclear whether this is due to the effects of psychoanalytic technique or its treatment frequency and duration,[12,39]. Changes in structural functioning have been posited as a mechanism of change in psychotherapy, and LTPP specifically, with a stronger focus on insight and self-understanding,[46]. Several studies found greater changes e.g. in personality or reflective functioning associated with greater,[34,47] and sustained,[48,49] symptom reduction. However, the studies mostly focused on between-person effects and did not apply lagged analysis over multiple time points to investigate if changes in structural capacities were associated with a decrease in symptoms at subsequent assessment.

Due to the limitations of the individual trials, empirical evidence on the role of treatment intensity for the efficacy of LTPP and the identification of prescriptive variables has been limited. Small samples and unequal group sizes as well as decreasing case numbers throughout therapy and follow-up have led to

methodological problems in data analysis of individual trials, including a lack of statistical power. Hence, small differences between different treatment approaches cannot be identified and testing for sub-groups with differential outcome is prohibited,[50]. Additional problems include the utilization of different designs (RCT vs. quasi-experimental), varying definitions of LTPP (e.g., ranging from 42 to over 300 sessions), varying frequency of measurements, definition and timing of follow-ups, and the comparability of measures of relevant variables (e.g., sociodemographic and clinical characteristics) and different outcome measures.

The current study aims to conduct a systematic review and individual participant data (IPD) meta-analysis concerning the efficacy of LTPP treatments of different intensities and associated prognostic and prescriptive factors in common mental disorders. IPD meta-analysis is a technique to examine treatment effects by combining participant-level data of multiple trials collected from the original data and is currently considered the gold standard in evidence synthesis,[51,52]. A one-stage approach is favored, especially when the original trials have small samples,[53]. It has increased statistical power to detect differences between treatment conditions and to examine prognostic and prescriptive variables associated with treatment efficacy,[45]. Compared to conventional meta-analyses that rely on the aggregated level data extracted from published reports, with IDP the same statistical methods can be applied across all studies involved. This allows for the application of newer statistical modeling techniques and similar handling of missing data, thus increasing comparability,[54]. The use of the original data may further circumvent bias related to the publication of positive results or the removal of patients before analysis in published trials,[55].

In summary, the current project aims to:

1) Compare treatment effectiveness of LTPP of low vs. high intensity (based on average weekly sessions)
    a. At treatment termination
    b. At long-term follow-up (stability of outcome)
    c. Compare their joint efficacy to shorter therapies and TAU as included as control groups in the trials
2) Identify individual characteristics that reliably predict or moderate differential treatment outcomes of low- and high-intensity LTPP

3) Examine the reciprocal relationship of symptoms and personality functioning over time

METHODS AND ANALYSIS

The study is an IPD meta-analysis, registered on the International prospective register of systematic reviews (PROSPERO; CRD42022304982) before conducting the main search and soliciting any data. Amendments will be documented here. Eligible studies will be identified through systematic literature research. Study results will be reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Individual Participant Data (PRISMA-IPD; Stewart et al. 2015). Project planning and preliminary literature research have started in June 2022, and we expect the completion of the project within three years.

Selection of studies

The aim of the study is the examination of the efficacy of LTPP with different intensity in adult outpatient populations with common mental disorders. Low-intensity treatments are defined as treatments with on average one weekly session, and high-intensity treatments are treatments with two or more weekly sessions. We will include randomized and quasi-experimental clinical trials on LTPP. We will include trials that directly compared high- vs. low-intensity LTPP, and trials that compared high- and/or low-intensity LTPP to shorter treatments or treatments as usual /TAU). In our main analysis, we will compare high- vs. low-intensity LTPP as defined above. A sensitivity analysis will be conducted to contrast one weekly session with three or more (instead of up to two). In a second analysis, we will compare high- and-low intensity LTPP (combined) to shorter treatments and TAU (combined). We will conduct a sensitivity analysis excluding TAU. Due to randomization difficulties for LTPP, especially psychoanalysis, we include quasi-experimental cohort studies along with prospective randomized controlled trials (RCT). Eligible studies must contain LTPP. LTPP is defined according to Leichsenring & Rabung 2011 criteria for LTPP by 1) Studies of psychodynamic therapy; 2) Working with transference and resistance and 3) Duration of at least 50 sessions or at least one year. Moreover, we will include psychoanalysis proper, meaning up to five sessions per week in a supine position. Control conditions are psychodynamic treatments of shorter duration (fewer than 50 sessions), other treatments (e.g., CBT) from various psychotherapeutic backgrounds, or TAU. Treatment must be individual therapy for common mental disorders (e.g., depression,

anxiety, or personality disorders) in adults. The exact inclusion and exclusion criteria can be found in Table 1. We will apply a three-step selection process. During the first step, two independent raters (one post-doc and one doctoral candidate) will apply the outlined selection criteria to the titles and abstracts of the references retrieved from the systematic literature research. In case of disagreement, consensus will be reached through discussion. If a study is considered as potentially fulfilling inclusion criteria, we will request full texts. Next, full texts will be rated according to the selection criteria by two independent raters. Disagreements will be resolved through discussion or the involvement of a third rater. Finally, selected studies will be rated by experts (full professors with analytic training) to confirm that the treatment investigated is LTPP.

Table 1. Selection criteria

Inclusion	Prospective RCT or quasi-experimental cohort study
	Baseline assessment and Post/Follow-Up assessment that exceeds at least one year
	Outpatient individual treatment
	Participants (≥18-65 Jahre)
	One treatment is LTPP (psychodynamic or -analytic long-term psychotherapy, psychoanalysis)
	Long-term is defined as ≥ 1 year or ≥ 50 sessions
	Standardized outcome measure of symptoms (global or specific) with at least one empirical proof of reliability
	Data on frequency of sessions are available
	Treatment is carried out by licensed psychotherapists
Exclusion	Focus on psychotic disorders
	Focus on organic disorders
	Single-case studies
	Serial case studies
	Qualitative studies
	Information on session frequency and therapy duration is not available
Outcomes	Primary:
	Standardized symptom assessment (global symptom level or disorder-specific)
	Secondary:
	Reliable change, no change and deterioration, calculated based on the primary outcome measure; Serious Adverse Events, Standardized assessments of personality/personality functioning, functional capacities, or relationship pathology

Search Strategy

To identify as many relevant studies as possible, different search strategies will be used. Firstly, we will conduct a systematic literature review using the following databases: PubMed, PsycINFO (via EBSCO), Web of Science (via Elsevier), and the Cochrane's Central Register of Controlled Trials (via Wiley). We define five categories of search strings (1) treatment, (2) long-term (3) study, (4) effectiveness and (5) common mental disorders, with synonyms that will be searched as index and free text terms. The Boolean combination of search strings is depicted in Table 2. We will not apply language or date restrictions for the searches, however, the included studies must be published in English, French, or German for our team to conduct risk of bias (RoB) assessments. Secondly, we will search the controlled-trial register to identify ongoing and unpublished studies https://www.isrctn.com/search?q=&filters=conditionCategory%3AMental+and+Behavioural+Disorders and the Open Door Review of Clinical, Conceptual, Process and Outcome Studies in Psychoanalysis, 3rd edition https://www.ipa.world/en/Psychoanalytic_Theory/Research/open_door.aspx; accessed 11/21/21. Thirdly, we will hand-search published meta-analyses,[39–41] and the citations of the included trials to identify other possibly eligible trials. We will contact experts in the field through a listserv of related societies (e.g., Society for Psychotherapy Research, Psychoanalytic Research Society, International Psychoanalytic Society) to ask for yet unpublished trials or studies we have missed.

Table 2. Systematic literature search

Data banks	PubMed PsycInfo Web of Science Cochrane Central Register of Controlled Trials
Category:	**Search terms:**
Treatment	emotion focused OR mentalization OR mentalization OR self-psychology OR transference-focused OR insight-oriented OR interpretativ* OR psychodynamic* OR psychoanalys* OR psychoanalytic* OR "psychotherapy, psychodynamic" OR “psychoanalytic therapy"
	AND
Long-term	“follow-up studies” OR follow OR long-term OR longer-term OR open-ended
	AND
study	study OR studies OR trial*
	AND
Effectiveness	treatment outcome OR outcome OR effect* OR efficacy OR result* OR change*
	AND
Common mental disorder	mental disorder*OR psychiatric illness*OR psychiatric disease*OR mental illness*OR psychiatric disorder* OR behavior disorder*OR behaviour disorder* OR psychiatric diagnos* OR anxiet*OR mood disorder* OR affective disorder* OR

	personality disorder*OR borderline personalit* OR depress*OR post-traumatic stress disorder* OR post-traumatic neuros* OR PTSD

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Data collection and management

Named corresponding authors will be contacted via e-mail. They will be provided with all necessary information (including a link to the project's PROSPERO registration and the protocol) and asked whether they would be willing to participate/collaborate. Contact information will be retrieved from the relevant publications or if unavailable or outdated through online searches. Authors will be offered co-authorship on the published paper in return for sharing the studies' de-identified individual participant data. Following Driessen et al.,[56], authors who do not respond will be contacted three times by mail. If we do not get a response, we will try to establish contact by phone, next send up to three letters by post. This procedure will be repeated first with the corresponding author, then the PI, and then sequentially with all other authors of the study. If we still do not get a response, we will contact colleagues or other persons who may help to establish contact. If we do not succeed in contacting the authors with the above-outlined efforts, or if authors respond that the individual participant data cannot be shared or has been deleted, study data is considered unavailable. If authors choose to share their data, data-sharing agreements between all parties will need to be drawn up. The procedures are country-dependent and will need to be taken into consideration. Once data-sharing agreements in line with GDPR ethical standards are arranged, authors will be asked to transfer de-identified individual-level data sets encrypted using a save cloud service, procedures will be provided by the University Medical Center Mainz. Authors will be asked to send item-based data sets if available and to provide a description of how the data was coded (codebook). Datasets will contain de-identified participant-level data comprising sociodemographic data, prognostic and prescriptive variables assessed at baseline, outcome variables assessed at baseline, during and after treatment, therapy duration and session frequency, additional treatment, and case status (ITT/ATP). Study-level data, e.g., requirements of therapists' professional experience (e.g., years of licensed practice), supervision, treatment integrity, and adherence, and interrater reliability for diagnostic assessment of primary outcome measures will be retrieved from the publication or requested, if unavailable. Example code for analyses, detailed RoB ratings, list of studies excluded at full-text stage including reasons for exclusion will be shared via the Open Science Framework (OSF).

Measures

The primary outcome is treatment effectiveness of low- vs. high-intensity LTPP as assessed by a global measure of symptomology, most commonly the Symptom Checklist-90 (SCL-90),[57] or disorder-specific measures at treatment termination and follow-up. Secondary outcomes are: (1) Reliable change, no change and deterioration, calculated based on the primary outcome measure. (2) Serious Adverse Events are defined according to the definition of the International Conference on Harmonization of pharmaceuticals for the human use – Good Clinical Practice (ICH-GCP) as a medical occurrence resulting in death, being life-threatening, requiring any form of hospitalization or resulting in persistent or significant disability of the patient, [58]. As original trials may not have applied this definition, we will also evaluate their definition of adverse events. (3) Changes in functional capacities, personality, personality functioning, or relationship pathology, most commonly the Inventory of Interpersonal Problems (IIP),[59] at treatment termination and long-term follow-up. Additional subgroup analyses will be performed for specific mental disorders (major depression, anxiety, personality disorders). For the primary outcome, we will also assess reliable change criteria [60] including no change, and deterioration, to account for the fact that psychotherapy has not always been found to be beneficial. Moreover, we will assess the occurrence of adverse events (0 = no adverse event, 1 = adverse event) during trial participation. If enough data is available this will be added as a secondary outcome. To identify potential prognostic and prescriptive factors for treatment response we include patient-specific characteristics at baseline: Sociodemographic data (e.g., gender, education, employment, income, migration background, clinical characteristics, (diagnosis given by the trial, previous treatments including psychopharmacological treatments) and continuous measures of symptom severity, personality and personality functioning, relationships, functional capacities, and life events (e.g., social occupational functioning, comorbid disorders, childhood adversity). Patient characteristics will be included when they are consistently reported among trials and can be standardized in a coherent way (e.g., by collapsing categories). We will include a variable referring to the original trial design (predetermined length vs. Open ended treatment) and a variable indicating whether cases were treated according to protocol (ATP vs. Drop-out).

Data Integrity and preparation

Received data sets will be thoroughly examined to identify out-of-range items or invalid scoring and will be compared with the original publication (sample size, missing data, gender, age, mean pre-treatment scores in the primary outcome as defined by the study, and mean post-treatment scores in the primary outcome as defined by the study). In case of deviations, we will contact the authors to resolve the issue (e.g., cases dropped from the analysis, imputation method used for computing mean scores of the questionnaires received). Next, all variables relevant for the IPD meta-analysis will be extracted from each study including prognostic and prescriptive variables, treatment information received, the diagnoses given within the original trial, and primary and secondary outcomes at baseline, intermediate, and follow-up assessment. The resulting variables will be copied into a new data set and study-level criteria (study type, treatment integrity, RoB assessment) and a participant ID containing numeric ID and an abbreviation of the study will be added. A copy of this file containing a study's raw data relevant to IPD will be standardized to the variable names and coding used in the IPD database. A variable will be created indicating the participants' group membership (high intensity LTPP, low intensity LTPP, Shorter Treatment/TAU). For the planned sensitivity analyses, we will create a second grouping variable (one weekly session vs. three or more and separating shorter treatment from TAU). All studies will be integrated into the database structured by the created ID. RoB will be evaluated in line with the Cochrane assessments tools for quasi-experimental trials,[61] and RCTs, [62], respectively. The results of the RoB ratings will be presented in tables listing each original study. They will be used for an overall appraisal for the quality of evidence of the IPD-MA, which is carried out following Tierney et al. [63]. As the type of measures applied by individual studies will likely vary, individual scores will be standardized (using z-transformation or a common metric approach,[64]) for continuous measures. Centering will be applied within individual trials. Data screening, data extraction and risk of bias assessment will be performed independently by two researchers (one postdoctoral researcher and one doctoral candidate).

Missing Data

We intend to conduct an intention-to-treat analysis. Missing data will be assessed in each study received, including the amount of missing data per participant and

variable and possible reasons for missingness. We will compare subsamples of participants without missing data to those with missing data per study and summarize distributions per variable. Missing Data will be handled using multilevel multiple imputation, an approach that handles sporadically (missing data on variables for some but not all participants) and systematically (variables that have not been assessed by a specific study) missing values and can adequately preserve between-study heterogeneity. As we expect some of the included studies to have a small sample size and the overall number of studies to be rather low, we will use a full conditional specification approach (FCS; also Multiple imputation by chained equations; MICE),[65–68]. We will follow White's et al.,[69] rule of thumb and impute one data set per percent of participants with one or more missing variables. We will include all variables and interactions relevant to our analysis model and variables potentially predictive for missing data. Specifically, we will use the R-packages mice and its extension micemd,[66].

Data Analysis

To address research questions 1(RQ1) and 2(RQ2), we will carry out a one-stage IPD meta-analysis. To analyze effectiveness, we will statistically predict symptom severity (global if available, otherwise specific) and remission (binary) controlling for baseline severity. To predict symptom severity over time we will use a generalized linear mixed model framework (GLMM), as participants are clustered in trials and treatment groups. Following Riley et al.'s [70] recommendations for IPD-meta-analysis, we will use restricted maximum likelihood estimation (REML) and obtain 95% confidence intervals for treatment effects using the Kenward-Roger approach. We will specify a random treatment effect to account for heterogeneity in study populations (intercept) and treatment effects (slope). To account for clustering within trials, we will fit a random intercept for each trial. Separate models will be estimated to compare LTPP of low vs. high intensity, and to compare joint LTPP against control groups as provided by the trials. The estimation procedure will be repeated using our secondary outcome measures based on the trials providing these additional measures. Reliable response, no change and deterioration will be analyzed for symptom outcome only using multilevel logistic regression. Response type will be calculated based on the reliable change index [60] of the symptom assessment within a given trial. We intend to perform subgroup analysis by repeating analysis steps in subgroups with different mental disorders (a) Depressive Disorders, (b) Anxiety disorders, (c) Personality Disorders. The primary diagnosis given in the original trial will define group membership. Next, we will analyze prognostic factors by adding available participant- and study-level variables as predictors to the specified models. If possible, continuous variables will be kept on a continuous scale to avoid loss of power. We will analyze prescriptive variables by adding interaction terms between the predictor and treatment groups. The third research question will be addressed by a two-stage individual participant data meta-analysis approach. We will first, estimate multi-group random intercept cross-lagged panel models (RI-CLPM,[71,72]) to examine the respective lagged and cross-lagged effects of personality functioning and symptoms on between-person (BP) and within-person (WP) level per study. We will consider every study providing data on personality functioning and symptoms for baseline, treatment termination and follow-up. We will use within-person (WP) centering,[73,74] of scores prior to analyses to derive standardized coefficients for lagged and cross-lagged effects. Next, findings will be meta-analyzed using random effects meta-analytic structural equation modelling (MASEM), a technique to meta-analyze path or structural equation models. Analyses will be carried out in R-lavaan [75] and R-metaSEM [76]. Sensitivity analyses for all research questions will be carried out based on complete cases. If enough studies have used the same instrument, we will rerun analysis for RQ1 and RQ2 based on these studies without standardizing the variables.

Patient and Public Involvement

No Patient and Public Involvement.

ETHICS AND DISSEMINATION

Given that all studies obtained ethical approval from the relevant ethics boards, further ethical approval is not necessary but requirements for data-sharing need to be met. A data-sharing agreement based according to principles of the General Data Protection Rules (GDPR) of the European Union will be signed between the University Medical Center Mainz and all parties involved (shared responsibility). All parties sharing their data are responsible to ensure that data sharing is in line with their institutional, local, and international requirements, which they confirm by signing the agreement on shared responsibility. All data transferred will be de-identified. The results of the study will be presented at international conferences for clinician scientists and practitioners. Scientific reports of the study results will be submitted for publication in international, preferably open-access journals.

DISSCUSSION

This study protocol describes a systematic review with meta-analysis of individual participant data to determine the effectiveness of low vs. high intensity LTPP at the end of treatment and long-term follow-up. Additionally, we aim to identify associated prognostic and prescriptive variables and the interaction of different outcome domains over time.

Clinical and scientific relevance

The evidence base of effectiveness for psychotherapy in general but also for psychodynamic treatments has been predominantly based on short-term therapies and short-term outcomes,[13]. Previous research found a potential benefit of LTPP over short-term treatments for complex mental disorders,[6,7,38,40]. Yet, little is known about the role of treatment intensity in LTPP, including psychoanalysis, and psychoanalytic/ psychodynamic long-term psychotherapy. Given unsatisfactory response rates, e.g., about 41 % for (short-term) psychotherapy,[77], but high additional costs of extensive treatment, the effectiveness of LTPP at long-term follow-up represents a health outcome of public interest. Individual studies lack sufficient power to reliably examine prognostic and prescriptive variables, however, identifying

factors associated with benefits from (specific) treatments is an important step towards optimized treatment planning,[45]. The project serves to close this gap, by consolidating the evidence base for LTPP for the major common mental disorders (e.g., depression, anxiety, and personality disorders). As LTPP treatments strive to achieve structural and personality changes, outcomes will go beyond symptom change and cover relevant outcome domains, such as personality, interpersonal and social-occupational functioning. This is consistent with the recommendations for updating the criteria of evidence-based therapies,[78]. The stability of therapeutic gains during long-term follow-up is of particular interest, as psychoanalytic theory posits that change does not necessarily cease at the end of treatment. Rather, insights gained during therapy are understood to promote further development during follow-up, when autonomy and greater capacity for self-analysis evolve,[79]. Hence, changing underlying structural capacities should enable patients to gain further benefits in the follow-up phase,[37,48,49].

Limitations

Limitations of data aggregation and analyses include different designs regarding the assessment of process and follow-up. Moreover, definitions of LTPP differ between studies regarding the frequency of sessions and setting. We cannot conduct a conventional meta-analysis to compare our results with trials not providing original data as some original studies will have analyzed low-and-high intensity LTPP together. If enough trials provide separate analyses, we will conduct a conventional meta-analysis based on these trials. The study includes RCTs and quasi-experimental cohort studies, lowering the quality of evidence according to gold-standards. Yet, the inclusion of quasi-experimental trials in diverse settings, where patients self-select their treatment, enhances the external validity of the results as treatment length and techniques in practice are individually adapted. An important limitation of IPD meta-analysis is that some trials may not be integrated due to non-response, problems with data-sharing, or the deletion of the original data. Thus, even if IPD meta-analyses are considered the gold standard in evidence synthesis, bias cannot be precluded, and information obtained by IPD should be used in addition to conventional meta-analyses and reviews. Identifying, collecting, and aggregating relevant data will require a certain time, and newly published trials cannot easily be incorporated. Even though IPD meta-analysis will likely have enough power to examine prognostic and prescriptive treatment variables, the choice of variables

examined depends on the variables included in the original trials. Moreover, results may be restricted to individuals who choose to participate in treatment trials. Akin to previous work including high frequent LTPP, we excluded trials on schizophrenia,[41]. We have specified secondary outcomes, however, our analyses will not be controlled for type I and type II errors. To our knowledge, studies conducted in the field have not incorporated explicit measures on harmful effects, such as negative experiences during psychotherapy. Our analyses will therefore fall short of an equal focus on efficacy and harmful effects of LTPP. We try to counterbalance this with modeling no reliable change, deterioration, and adverse events.

Authors Contributions

MEB, MLB and EB conceived the original idea. LK wrote the first draft of the manuscript reviewed and edited by MEB, MLB and EB. LK and PS developed the analysis plan. HLS, JB, DH, GK, TJ, HRS, FR, SS, FL and ME revised the manuscript for important intellectual content. All authors have reviewed the final version of the manuscript, agree with its submission and are responsible for all aspects of the work.

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Competing interests

Manfred E. Beutel, Falk Leichsenring, Marianne Leuzinger-Bohleber, Henriette Löffler-Stastka, are state-licensed psychoanalysts, involved in the training of psychodynamic therapists/psychoanalysts. Josef Brockmann, Dorothea Huber, Guenther Klug, Thorsten Jakobsen, Hemma Rössler-Schülein, Felicitas Rost and Simone Salzer are state-licensed psychoanalysts/psychodynamic psychotherapists. Mareike Ernst and Lina Krakau are training as a psychodynamic/ psychoanalytic psychotherapists.

They have conceived and/or performed trials that will serve as a data source for the proposed study (*Frankfurt-Hamburg Study*, Josef Brockmann; *Göttingen Study*, Falk Leichsenring, *Heidelberg-Berlin Study*, Thorsten Jakobsen; *Munich Psychotherapy Study*, Dorothea Huber, Guenther Klug, *LAC Study*, Marianne Leuzinger-Bohleber, Manfred E. Beutel, Mareike Ernst; *Tavistock Adult Depression Study,* Felicitas Rost; *Viennese Psychoanalytic Process and Outcome Study*, Henriette Löffler-Stastka, Hemma Rössler-Schülein)

Elmar Brähler and Peter Schmidt declare no competing interests.

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PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD)

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	2
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-6
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	6-7
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	2
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	7-8
Identifying studies -	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers	10

information sources		and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	11-12
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	nA
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	13
		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of harmonising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	14-15
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	14-15
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	15
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	14;17
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable).	17

Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	17
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	15
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	27
Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	nA
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	nA
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	nA
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	nA
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	nA
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	nA
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	

Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	nA
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	nA
Discussion			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	nA
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	19-20
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	nA
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	18-19
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	21

A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA statement to suit the way that systematic review IPD meta-analyses are reported.