Efficacy of high-intensity versus 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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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 analysing individual data from randomised and quasi-experimental trials by meta-analysis. The purpose is to (1) determine the treatment effectiveness of LTPP with low versus high intensity (up to 2 weekly sessions vs three or more), (2) compare their joint effectiveness to shorter therapies and treatments as usual, (3) identify predictors and moderators of treatment outcomes and (4) determine reciprocal relationships between different outcome domains (symptomatic and structural/personality change) over the courses of LTPP.

Methods and analysis We include studies from (randomised controlled trial, RCT) and quasi-experimental trials, where at least one condition was LTPP of high or low frequency. Long-term treatment is defined as ≥1 year or ≥50 sessions. To be eligible studies must include a standardised outcome measure of symptoms (global or disorder specific) with at least one proof of reliability. The primary outcome is symptom reduction (global or disorder specific) with at least one proof of reliability.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Individual participant data (IPD) meta-analysis has increased power to detect differences between treatment groups and to examine prognostic and prescriptive factors associated with outcome.
⇒ The inclusion of quasi-experimental trials and the examination of non-randomised 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, for example, non-response of the authors, difficulties with data sharing.

PROSPERO registration number CRD42022304982; Pre-results.

INTRODUCTION

Short-term psychodynamic psychotherapy (STPP) has demonstrated comparable efficacy to cognitive–behavioural therapy (CBT) and other bona fide psychotherapies.1–3 However, common mental disorders often take a chronic course4 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 characterised by rigidity or inflexibility, for example, personality disorders (PDs), chronic mental disorders (eg, chronic depression).7 They show high comorbidity with other mental and physical health conditions8 and are associated with considerable functional impairments.9 Regardless of a categorical diagnosis of PD, lower levels
of personality organisation are typically found in more severe mental disorders.\textsuperscript{10} Previous data on dose–effect relations have indicated that patients with such disorders need longer treatments.\textsuperscript{11,12} Nevertheless, most evidence for psychotherapy is based on short-term treatments and short-term outcomes, the latter usually assessed at treatment termination.\textsuperscript{13} Only a few trials report 1-year follow-up, and longer-term follow-ups of 2 and more years are scarce.\textsuperscript{2,14} To our best knowledge, long-term remission rates of bona fide short-term psychotherapies are often unsatisfactory\textsuperscript{14} and up to half of the study, patients have been found to seek auxiliary psychotherapy during follow-up.\textsuperscript{15} Naturalistic trials further indicate that many patients require and receive long-term treatments up to several years.\textsuperscript{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 organisation\textsuperscript{17–19} in addition to symptoms. Structural integration (ie, personality functioning) comprises different domains of psychological functioning, for example, identity, affect differentiation and tolerance, and self-other regulation which relate to core developmental tasks of attachment/relatedness and individuation/self-definition.\textsuperscript{20–22} Conceptualised by the term personality functioning, the alternative model of PDs has introduced a similar\textsuperscript{23,24} model to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).\textsuperscript{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 PDs. In the psychoanalytic literature, improvements in these domains have been described as structural change\textsuperscript{17–19} and have been related to treatments with higher frequency promoting greater capacity for self-analysis.\textsuperscript{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.\textsuperscript{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 conceptualise 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.\textsuperscript{15,28–32} In the long run, several studies indicated LTPP to be more effective than treatment as usual (TAU)\textsuperscript{29} or short-term treatments.\textsuperscript{15,33}

Huber et al.\textsuperscript{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,\textsuperscript{34,35} but stronger evidence for restructuring in psychoanalytic treatment groups.\textsuperscript{32,35} 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 1-year\textsuperscript{36} or 3-year follow-up.\textsuperscript{37} Town et al.\textsuperscript{38} 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 randomised controlled trials (RCTs) and quasi-experimental observational studies, Leichsenring and Rabung\textsuperscript{6,7,39} found LTPP to be more effective than short term psychotherapies 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.\textsuperscript{40} questioned the effectiveness of LTPP, as they found it more effective only in comparison to control conditions that were no specialised forms of therapy. Exploratory analyses indicated that a greater difference in treatment intensity between LTPP and the control group was related to the effect size. The seemingly conflicting findings between Leichsenring and Rabung\textsuperscript{6,7} and Smit et al.\textsuperscript{40} meta-analyses have been discussed elsewhere.\textsuperscript{39} More recently, Woll and Schönbrodt aimed to replicate and update Leichsenring et al.'s\textsuperscript{39} 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.\textsuperscript{12}

Beyond efficacy studies, psychotherapy research, in general, has identified numerous patient, psychotherapist and relational prognostic factors (predictors) for psychotherapy outcome, for example, racial or social minority status, high symptom load or high self-criticism.\textsuperscript{15} However, less is known about prescriptive variables (moderators) associated with different outcomes depending on the type of treatment, for example, maladaptive defenses or rigid relationship patterns for psychodynamic treatments.\textsuperscript{14,40} Identifying prescriptive variables that reliably predict differential treatment outcomes has become the main target of personalised treatment approaches.\textsuperscript{13,46} 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.\textsuperscript{12,40} 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. Several studies found greater changes, eg, in personality or reflective functioning associated with greater and sustained symptom reduction. However, the studies mostly focused on between-person (BP) 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 subgroups with differential outcome is prohibited. Additional problems include the utilisation of different designs (RCT vs quasi-experimental), varying definitions of LTPP (eg, 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 (eg, 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. A one-stage approach is favoured, especially when the original trials have small samples. It has increased statistical power to detect differences between treatment conditions and to examine prognostic and prescriptive variables associated with treatment efficacy. Compared with conventional meta-analyses that rely on the aggregated level data extracted from published reports, with IPD the same statistical methods can be applied across all studies involved. This allows for the application of newer statistical modelling techniques and similar handling of missing data, thus increasing comparability. 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.

In summary, the current project aims to:

1. Compare treatment effectiveness of LTPP of low versus 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-intensity 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-Analyses for IPD. Project planning and preliminary literature research have started in June 2022, and we expect the completion of the project within 3 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 1 weekly session, and high-intensity treatments are treatments with two or more weekly sessions. We will include randomised and quasi-experimental clinical trials on LTPP. We will include trials that directly compared high-intensity versus low-intensity LTPP, and trials that compared high-intensity and/or low-intensity LTPP to shorter treatments or TAU. In our main analysis, we will compare high-intensity versus low-intensity LTPP as defined above. A sensitivity analysis will be conducted to contrast 1 weekly session with three or more (instead of up to two). In a second analysis, we will compare high-intensity and low-intensity LTPP (combined) to shorter treatments and TAU (combined). We will conduct a sensitivity analysis excluding TAU. Due to randomisation difficulties for LTPP, especially psychoanalysis, we include quasi-experimental cohort studies along with prospective RCTs. Eligible studies must contain LTPP. LTPP is defined according to Leichsenring and Rabung’s criteria for LTPP by (1) studies of psycho-dynamic therapy; (2) working with transference and resistance and (3) duration of at least 50 sessions or at least 1 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 (eg, CBT) from various psychotherapeutic backgrounds, or TAU. Treatment must be individual therapy for common mental disorders (eg, depression, anxiety or PDs) 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 postdoc and one doctoral candidate) will apply the outlined selection criteria to the titles and abstracts of the references retrieved from the systematic literature.
Trials (via Wiley). We define five categories of search strings:

### Table 1: Selection criteria

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<thead>
<tr>
<th>Inclusion</th>
<th>Prospective RCT or quasi-experimental cohort study</th>
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<tr>
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<td>Baseline assessment and post/follow-up assessment that exceeds at least 1 year</td>
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<td></td>
<td>Outpatient individual treatment</td>
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<td>Participants (≥18–65 Jahre)</td>
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<td>One treatment is LTPP (psychodynamic or -analytic long-term psychotherapy, psychoanalysis)</td>
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<td>Long-term is defined as ≥1 year or ≥50 sessions</td>
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<td>Standardised outcome measure of symptoms (global or specific) with at least one empirical proof of reliability</td>
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<td></td>
<td>Data on frequency of sessions are available</td>
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<td>Treatment is carried out by licensed psychotherapists</td>
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<td>Exclusion</td>
<td>Focus on psychotic disorders</td>
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<td>Focus on organic disorders</td>
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<td></td>
<td>Single-case studies</td>
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<td>Serial case studies</td>
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<td>Qualitative studies</td>
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#### Table 2: Systematic literature search

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<th>Data banks</th>
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<td>PsycINFO</td>
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<td></td>
<td>Web of Science</td>
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<td></td>
<td>Cochrane Central Register of Controlled Trials</td>
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#### Search terms

**Category**

- **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 OR 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 diagnosis* OR anxiety* OR mood disorder* OR affective disorder* OR personality disorder* OR borderline personality* OR depression* OR post-traumatic stress disorder* OR post-traumatic neurosis* OR PTSD

LTPP, long-term psychoanalytic psychotherapy.

(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. Second, 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, third edition https://www.ipa.world/en/Psychoanalytic_Theory/Research/open_door.aspx; accessed on 10 July 2023. Third, we will handsearch published meta-analyses40–42 and the citations of the included trials to identify other possibly eligible trials. We will contact experts in the field through a list-serv of related societies (eg, Society for Psychotherapy Research, Psychoanalytic Research Society, International Psychoanalytic Society) to ask for yet unpublished trials or studies we have missed.

### Search strategy

To identify as many relevant studies as possible, different search strategies will be used. First, 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 and the citations of the included trials to identify other possibly eligible trials. We will contact experts in the field through a list-serv of related societies (eg, Society for Psychotherapy Research, Psychoanalytic Research Society, International Psychoanalytic Society) to ask for yet unpublished trials or studies we have missed.

### Data collection and management

Named corresponding authors will be contacted via email. They will be provided with all necessary information.
events defined according to the definition of the International Conference on Harmonisation of pharmaceuticals for the human use-Good Clinical Practice as a medical occurrence resulting in death, being life-threatening, requiring any form of hospitalisation or resulting in persistent or significant disability of the patient. As original trials may not have applied this definition, we will also evaluate their definition of adverse events. If possible, additional subgroup analyses will be performed for specific mental disorders (major depression, anxiety, PDs). To identify potential prognostic and prescriptive factors for treatment response, we include patient-specific characteristics at baseline: sociodemographic data (eg, 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 (eg, social occupational functioning, comorbid disorders, childhood adversity). Patient characteristics will be included when they are consistently reported among trials and can be standardised in a coherent way (eg, 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 (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 pretreatment 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 (eg, 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 standardised 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 different grouping variables (1 weekly session vs 3 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

**Measures**

The primary outcome is treatment effectiveness of low-intensity versus high-intensity LTPP as assessed by a global measure of symptomology, most commonly the Symptom Checklist-90, or disorder-specific measures at treatment termination and follow-up. Secondary outcomes are: (1) Remission, reliable change, no change and deterioration, calculated based on the primary outcome measure. (2) Changes in functional capacities, personality, personality functioning or relationship pathology, most commonly the Inventory of Interpersonal Problems, at treatment termination and long-term follow-up. (3) Serious adverse

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Cochrane assessments tools for quasi-experimental trial and RCTs 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. As the type of measures applied by individual studies will likely vary, individual scores will be standardised using z-transformation or a common metric approach for continuous measures. Centring 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 ITT 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 summarise 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 (missing data on variables for all participants) 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.

**Data analysis**

To address research questions 1 and 2, we will carry out a one-stage IPD meta-analysis. To analyse 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 generalised linear mixed model framework, as participants are clustered in trials and treatment groups. Following Riley et al recommendations for IPD-meta-analysis, we will use restricted maximum likelihood estimation and obtain 95% CIs 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 LTTP of low versus high intensity, and to compare joint LTTP 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 analysed for symptom outcome only using multilevel logistic regression. We intend to perform subgroup analysis by repeating analysis steps in subgroups with different mental disorders (A) depressive disorders, (B) anxiety disorders and (c) PDs. The primary diagnosis given in the original trial will define group membership. Next, we will analyse prognostic factors by adding available participant-level 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 analyse prescriptive variables by adding interaction terms between the predictor and treatment groups. The third research question will be addressed by a two-stage IPD meta-analysis approach. We will first, estimate multigroup random intercept cross-lagged panel models to examine the respective lagged and cross-lagged effects of personality functioning and symptoms on 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 WP centring of scores prior to analyses to derive standardised coefficients for lagged and cross-lagged effects. Next, findings will be meta-analysed using random effects meta-analytical structural equation modelling, a technique to meta-analyse path or structural equation models. Analyses will be carried out in R-lavaan and R-metaSEM. 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 research question 1 and 2 based on these studies without standardising 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 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 deidentified. 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.
DISCUSSION
This study protocol describes a systematic review with meta-analysis of IPD 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. Previous research found a potential benefit of LTPP over short-term treatments for complex mental disorders. Yet, little is known about the role of treatment intensity in LTPP, including psychoanalysis and psychoanalytic/psychodynamic long-term psychotherapy. Given unsatisfactory response rates, for example, about 41% for (short-term) psychotherapy 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 optimised treatment planning. The project serves to close this gap, by consolidating the evidence base for LTPP for the major common mental disorders (eg, depression, anxiety and PDs). 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. 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. Hence, changing underlying structural capacities should enable patients to gain further benefits in the follow-up phase.

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 analysed 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. We have specified secondary outcomes, however, our analyses will not be controlled for type I and type II errors.

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Contributors MEB, ML-B and EB conceived the original idea. LK wrote the first draft of the manuscript reviewed and edited by MEB, ML-B and EB. LK and PS developed the analysis plan. HL-S, JB, DH, GK, TJ, HR-S, 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. This work is part of the PhD of LK.

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