Motivational Interviewing for patients with acute psychosis.

Study Type:	Other Clinical Trial according to ClinO, Chapter 4
Risk Categorisation:	Risk category A according to ClinO, Art. 61
Study Registration:	"**Motivational Interviewing for patients with acute psychosis" (MIA)** Registration intended: SNCTP (CH-Register) und clinicaltrial.gov
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Investigated Intervention:	Psychotherapeutic intervention for patients with psychosis using the method of "Motivational Interviewing" on acute psychiatric wards.
Version and Date:	Version 2.0 (dated 10/02/2023)

PROTOCOL SIGNATURE FORM

Study Title	Motivational Interviewing for patients with acute psychosis
Study ID	MIA

The Sponsor-Investigator has approved the protocol version 2.0 (dated 10/02/2023) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements.

Sponsor-Investigator:

Name: Philipp Homan

Date: _____ Signature: _____

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GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
ASR	*Annual Safety Repot*
BARS	*Brief Adherence Rating Scale*
BASEC	*Business Administration System for Ethical Committees*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV)*
CRF	*Case Report Form*
CTCAE	*Common Terminology Criteria for Adverse Events*
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders, Version 4*
FADP	*Federal Act on Data Protection (in German: DSG)*
FOPH	*Federal Office of Public Health*
FPTM	*Fragebogen zur Erfassung der Psychotherapiemotivation (in English: Questionnaire to measure the motivation for psychotherapy)*
GCP	*Good Clinical Practice*
GSE	*General Self-Efficacy Scale*
*G*Power*	*G*Power Statistical Power Analyses*
HRA	*Human Research Act*
ICD-10	*International Classification of Diseases, Version 10*
ICH	*International Conference on Harmonisation*
MATRICS	*Measurement and Treatment Research to Improve Cognition in Schizophrenia (Consensus Cognitive Battery)*
MI	*Motivational Interviewing*
PANSS	*Positive and Negative Symptom Scale*
PUK	*Psychiatrische Universitätsklinik Zürich (in English: Psychiatric University Hospital Zurich)*
SAE	*Serious Adverse Event*
SNCTP	*Swiss National Clinical Trial Portal*
STAR	*Scale to Assess Therapeutic Relationship*
TAU	*Treatment as usual*

1 BACKGROUND AND RATIONALE

Psychosis includes perceptual and cognitive disturbances that are mediated, in most cases, by the dysregulation of dopamine and glutamate neurotransmission (Lieberman & First, 2018). The main symptoms of the disease have long been subdivided into positive and negative symptoms as well as cognitive deficits corresponding to clinical observations. Delusions, hallucinations, disorganized speech or behavior are described as the most common positive symptoms. Negative symptoms include a reduction or complete loss of motivation, interest, or expression (Stahl & Buckley, 2007).
Psychotic disorders are among the top ten causes of long-term disability (Murray & Lopez, 1996) and have a high chronicity potential and a high risk of invalidity (Kahn et al., 2015). Patients with psychosis are at risk for complications and derivative effects of psychosis, particularly suicide attempts, substance abuse, homelessness, victimization by others, and committing acts of violence (Lieberman & First, 2018). Especially schizophrenia, the most frequent form of psychotic disorders, is associated with a more severe course of illness and poorer outcomes compared to other psychotic and non-psychotic disorders (Jobe & Harrow, 2005). One-fifth of all patients with schizophrenia suffer from chronic symptoms and impairments (Owen et al., 2016), and the disease is associated with low long-term work performance(Rabinowitz et al., 2012), a high degree of all mental health care resources (Mueser & McGurk, 2004) and high socioeconomic costs (Kennedy et al., 2014). These findings demonstrate the importance of sufficient treatment for psychotic disorders and, most importantly, point to a need for research so that more effective treatments can be developed in the future.

Psychotherapeutic interventions for psychosis
In the recent decade, various psychotherapeutic programs with cognitive-behavioral background have been developed for patients with psychosis, and their efficacy has been investigated(Lincoln & Pedersen, 2019; Galderisi et al., 2021). Meta-analyses have shown superiority of cognitive-behavioral therapy for psychosis over standard treatment, both in combination with antipsychotic medication and without (Morrison et al., 2012, 2014). Many of the psychological approaches have focused primarily on treating the deficits associated with psychosis, as for example cognitive remediation or social skills training (Bark et al., 2003; Aghotor et al., 2010; Puig et al., 2014; Mehl & Lincoln, 2014). However, these methods are not feasible in the acute setting and there are only a few psychotherapeutic instruments that can be used within a short period of time for in-patient treatment.
The NICE-guidelines for the treatment of schizophrenia (National Institute for Health and Clinical Excellence, 2010) recommend a combination of antipsychotic medication and psychosis-specific cognitive behavioral therapy. This includes all stages of the illness, also in the acute phase (Kuipers et al., 2014). The Swiss Society for Psychiatry and Psychotherapy (SGPP) has stated in its treatment guidelines for schizophrenia that "our group recommends a structured psychotherapeutic approach even in the acute phase of the disease. The best evidence currently exists for cognitive-behavioral approaches, […]. In any case, the psychotherapeutic procedure must be adapted to the circumstances of the acute phase and there is an urgent need for research on how this can be arranged in the setting of an acute ward.” (Kaiser et al., 2016, p.10). Despite this explicit recommendation, to our knowledge there have been no studies that have systematically investigated this in the acute setting and results of which could therefore inform future treatment recommendations.

Rationale for planned project
While recent guidelines for the treatment of psychotic disorders recommend to offer psychotherapy right from the start of the inpatient treatment, it is well known that psychotherapeutic interventions tend to be offered to patients relatively late in the course of the hospitalization – if at all. On the other hand, it has been shown that a majority of symptoms that patients with a psychotic disorder report as disturbing can be treated with psychotherapy (Freeman et al., 2019). The challenge is that there is little evidence on which mechanisms of psychotherapy are most

effective and applicable in the acute phase. As proposed by the SGPP, we would like to systematically test and evaluate psychotherapeutic interventions in the setting of an acute care unit in an initial pilot trial.

Expected relevance
Therapeutic alliance during the acute phase of psychotic illness is one of the most pressing obstacles for successful long term recovery (e.g. Cavelti et al., 2016). In order for patients to accept much-needed medication and psychosocial therapy and not drop out prematurely, intrinsic motivation to adhere to therapy is crucial. Motivational Interviewing is a method, that has been developed and evaluated over the last three decades and that shows promising results, not only for patients with addiction but also for other patients who struggle with compliance and ambivalence towards treatment and change of behavior. For further information on the method see chapter *3.4. Study intervention.*
At the same time, it is well known from clinical experience that patients are offered psychotherapy only late during the course of hospitalizations and not when it is most needed – during the acute phase of their illness. Accordingly, there is a clear gap in the literature as to which interventions are particularly useful in this challenging yet crucial phase of the illness.
We believe that the current project and the psychotherapeutic interventions tested here, can provide valuable data on acceptance, feasibility and effectiveness of such interventions and which can then be used to supplement a large multicentre trial across Switzerland.

2 STUDY OBJECTIVES AND DESIGN

2.1 Hypothesis and Objectives

The **primary objective** of the study is to investigate the impact of a brief intervention with Motivational Interviewing in an acute psychiatric inpatient setting on factors that impact treatment outcome such as therapeutic alliance and adherence to treatment.

The **second objective** is to examine if the effect of Motivational Interviewing can be measured in changes in symptom severity.

The **third objective** is to examine secondary effects of Motivational Interviewing on motivation for further psychotherapeutic treatment and higher expectations of self-efficacy after discharge from the hospital.

Therefore, the study grounds on three **hypotheses**:

1. Four sessions of psychotherapeutic intervention with motivational interviewing for newly admitted acute patients improves the therapeutic alliance and the adherence for treatment compared to supportive counseling.
2. Four sessions of psychotherapeutic intervention with motivational interviewing for newly admitted acute patients decreases symptom severity compared to supportive counseling.
3. Patients show higher motivation to seek psychotherapeutic treatment and have a higher self-efficacy expectation after leaving the inpatient stay, when they received an intervention with motivational interviewing compared to supportive counseling.

2.2 Primary and secondary endpoints

Primary endpoints are the therapeutic alliance as assessed with the *Scale to Assess Therapeutic Relationship STAR* (McGuire-Snieckus et al., 2007) and adherence to treatment as measured with the *Brief Adherence Rating Scale BARS* (Byerly et al., 2008). These variables will be measured before and after the study intervention or control intervention.

Secondary endpoints include changes in symptom severity as assessed with the *Positive and*

Negative Symptom Scale PANSS (Kay et al., 1987), as well as the motivation for psychotherapy (measured with the German version of the *Questionnaire to measure the motivation for psychotherapy* by Schulz et al., 1995) and self-efficacy (measured with the *General Self-Efficacy Scale* by Schwarzer & Jerusalem, 1995). All secondary variables will be measured before and after the study intervention or control intervention.

As this study (risk category A) does not include drugs or other medical products and patients are hardly exposed to any more risks than in routine clinical care, no safety endpoints are defined.

2.3 Study design

This will be an interventional study with randomized control and open label trial. A parallel-group design with pre- and post-measurements (longitudinal design) will be employed, using subjective and objective measurements with questionnaires and structured interviews. It is a single center and national project.

The study consists of five phases:
1. Screening: Screening will be conducted by the applicant and master's students enrolled in the project who are bound to medical confidentiality, using electronic patient files at the hospital. The patients will be invited to the study by their treating physician or psychologist.
2. Pre-interventional measurement (1 session within the first week, max. 60minutes):
First, the psychopathological symptoms are to be assessed in order to decide about inclusion or exclusion (with PANSS; see also inclusion criteria). In addition, the therapeutic alliance and motivation for psychotherapy are measured. In order to record moderating effects or covariables, demographics (e.g. age, gender, education, years of illness) and two additional questionnaires will be added (attitude towards recovery and the individual motives).
3. Intervention (4 sessions within two weeks, 25- 40 minutes/session):
The patients receive either four sessions of motivational interviewing (intervention group) or four sessions of supportive counseling (control group). For Details see *2.4 "Study intervention"*
4. Post-interventional measurement (1 session, max. 60 minutes): At the end of the intervention the motives, the negative symptoms, the hope for recovery, well-being and the level of functioning will be measured again.

The risk of bias should be kept at a minimum. Various precautions are being taken to this end.
- The most important confounding variables are controlled to prevent a bias.
- In order to avoid selection bias, patients are randomly assigned either to the intervention group or to the control group. Randomization is carried out at a 1:1 ratio, using pre-defined random lists (using the online randomization generator: http://www.pubmed.de/tools/zufallsgenerator) and a block schema prepared by the principal investigator.
- Block randomization ensures that the patients are distributed in the desired proportion to the two treatment modalities. All patients are randomized only once during the entire examination period.
- For minimizing bias some patients will have to be excluded from the study (see exclusion criteria)
- The study will be conducted as single-blind, as it is possible that the expectation towards one of the methods could have an impact on the outcomes.
- Raters will be blinded to the intervention and will receive prior training in the application of the rating scales.

2.4. Study intervention

Motivational interviewing (MI) is an intervention that helps people identify problems as such, build and maintain a commitment to change specific behaviors, and actually do so (Miller & Rollnick, 2002). It combines elements of behavior analysis with the principles of client-centered therapy, in which the patient learns to talk about his or her problems in empathetic but strategic

conversations. The therapeutic alliance plays a central role in this process. Ambivalence is not seen as resistance, but is respected and explored as a natural phenomenon, in order to support the patient's individual decision regarding the pros and cons. MI includes several techniques to help to manage ambivalence and decision making. If necessary, the patient is made aware of the ambivalences he or she has toward a specific topic (Barkhof et al., 2006).
In psychosis patients, there are several risk behaviors for relapse described in the literature, with the biggest problem of non-adherence to antipsychotic medication (Kane et al., 2013) which is consistent with our experience in clinical practice. The goal here is to guide patients to identify and increase their own motivation to change their behavior, and ultimately to ensure that psychiatric treatment is and remains effective. Accordingly, the overall goal of the intervention is to enter into a therapeutic alliance with the patient so that the patient's inner motivation to participate in treatment can be increased and the process can begin from within rather than being imposed from without.
Clinician-delivered motivational interviewing has been identified as effective for enhancing adherence among patients with psychosis (Kemp et al., 1996; Chien et al., 2016). Nevertheless, the literature also points to a lack of evidence. Although previous studies have shown that MI can positively influence important aspects of disease-related impairments, such as medication adherence, frequency and severity of psychotic relapses, duration of hospitalization, functional level, insight into the disease, and cognitive rehabilitation, data are still insufficient in schizophrenic patients (Reimer et al., 2019).

In our **study intervention**, patients should receive four session of motivational interviewing within two weeks. Throughout the MI sessions, interviewers use common MI techniques including open-ended questions, affirmations, reflections, summaries, asking permission, expressing empathy, supporting self-efficacy, etc. Interviewers are clinical psychologists who received MI training immediately prior to the study.

In the **control intervention** patients should also be given four sessions, in which no MI techniques take place. They will be carried out in the sense of supportive conversations. Supportive conversations aim to promote stabilization of the patient's current state without pursuing a goal set by the therapist. Supportive therapy includes tasks such as assistance with everyday requirements, emotional relief in the event of problems, or the provision of a reliable relationship. The topics are preferably defined by the patient. The clarification and processing of conflicts and problems that underlie the psychopathology is not usually the subject of therapy (Weierstall & Schonauer, 2016).
Since we want to check whether the patients really benefit from the specific intervention and not from getting more speaking time, the patient in the control group will also be given four conversations. It is known that supportive conversations can have a certain effect on the well-being and recovery process of patients, as the therapeutic relationship, i.e. appreciation, attention and/or attention, is an important efficacy factor (e. g. Grawe, 1995).

3 STUDY POPULATION AND STUDY PROCEDURES

3.1 Inclusion and exclusion criteria, justification of study population

As the aim of the study is to improve psychotherapeutic treatment in the acute phase of psychosis, the inclusion of patients suffering from this disorder is necessary and cannot be studied in healthy people.
We will recruit newly admitted inpatients from the Psychiatric University Hospital with a diagnosis of a psychotic spectrum disorder (schizophrenia, schizoaffective disorder, acute psychotic

disorder, psychosis not otherwise specified, bipolar disorder with psychotic features, major depression with psychotic features). Patients are recruited within the first three days of hospitalization to test psychotherapeutic interventions in the acute phase of illness.

Patients fulfilling all of the following inclusion criteria may be enrolled in the study:
- Informed consent as documented by signature
- Male and female patients from PUK inpatient units between 18 and 65 years of age
- ICD-10 diagnosis of psychosis (F2) meeting DSM-IV criteria
- Fluent in German and able to understand the instructions

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:
- Organic schizophrenia-like disorder (ICD: F0.6)
- Cognitive impairments: strongly below average values in more than two cognitive tests (percentage rank < 5)
- Drug or alcohol abuse during treatment
- Previous enrolment in the current study
- Enrolment of the investigator, his/her family members, employees and other dependent persons.
- During study: Complete stop of taking antipsychotic medications without the consent of the attending physician.

3.2 Recruitment, screening and informed consent procedure

Recruitment of patients will take place at the Psychiatric University Hospital Zurich in the form of ongoing recruitment by the study coordinator in the clinical setting as well as by other physicians and psychologists at the hospital. The study is presented and reminded to them in regular intervals at internal clinic reports.

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he or she may withdraw from the study at any time and that withdrawal of consent will not affect his or her subsequent medical assistance and treatment.

The participant will be informed that his or her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. Enough time (one to five days) will be given to the participant to decide whether to participate or not.

The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure.

The consent form will be signed and dated by the investigator or his designee at the same time as the participant sign. A copy of the signed informed consent will be given to the study participant. The consent form will be retained as part of the study records. The informed consent process must be documented in the patient file and any discrepancy to the process described in the protocol must be explained.

In the case of incapacity to judge or if there is doubt about the capacity to judge, a separate procedure takes place:

The study information must be explained verbally to the interested patient in any case. Handing over the written study information alone is not sufficient. The patient should be able to describe in general terms what participation in the study entails and what the patient's rights are.

If there are doubts about the patient's ability to judge, either because he/she is unable to reproduce what is contained in the study information, or because of critical comments by the health

care personnel and/or trusted persons of the patient, an evaluation is carried out using the "U-Doc" (Hermann et al., 2020; Trachsel & Biller-Andorno, 2022). The information for this is collected on an interdisciplinary basis and discussed with the patient's legal representative and/or a close confidant. Any conflicts of interest in the evaluation can be critically reflected upon and transparently documented in U-Doc. Both the patient and his/her representative have the right to inspect this documentation at any time and can also refuse it.

If an incapacitated person explicitly wishes to participate in the study, we will conduct a detailed information session about the study, at which not only the patient but also the legal representative must be present. It is desirable to have a conversation on site, in exceptional cases the conversation can take place by telephone conference. If there is no legal representative, the law prescribes a cascade of possible representatives (spouse, partner, offspring, parents, siblings). The conversation is recorded (in the CRF). The documentation of the conversation is accessible to the patient and her representative at all times. It is important to note that incapacity is relevant in relation to the decision on medical measures.

Participants will receive financial compensation after completing the study (after post-measurement). A payment of 40 swiss francs per participant is calculated in the budget.

3.3 Study procedures

Time schedule

The study will last from October 2022 to September 2023.

- From October to December 2022, the study will be planned, and the ethics application will be written and submitted.
- From January, the concrete preparations will take place and
- from February 2023, the implementation will take place. The survey phase will last until August 2023.
- From August to October 2023, the study is to be evaluated, completed and the data analysed.

As can be seen in Table 2, the duration for each patient is between 13 and max. 16 days during their inpatient stay. The goal is to start with the study intervention as soon as possible after entering the psychiatric hospital.

Table 1: Study Flow Chart

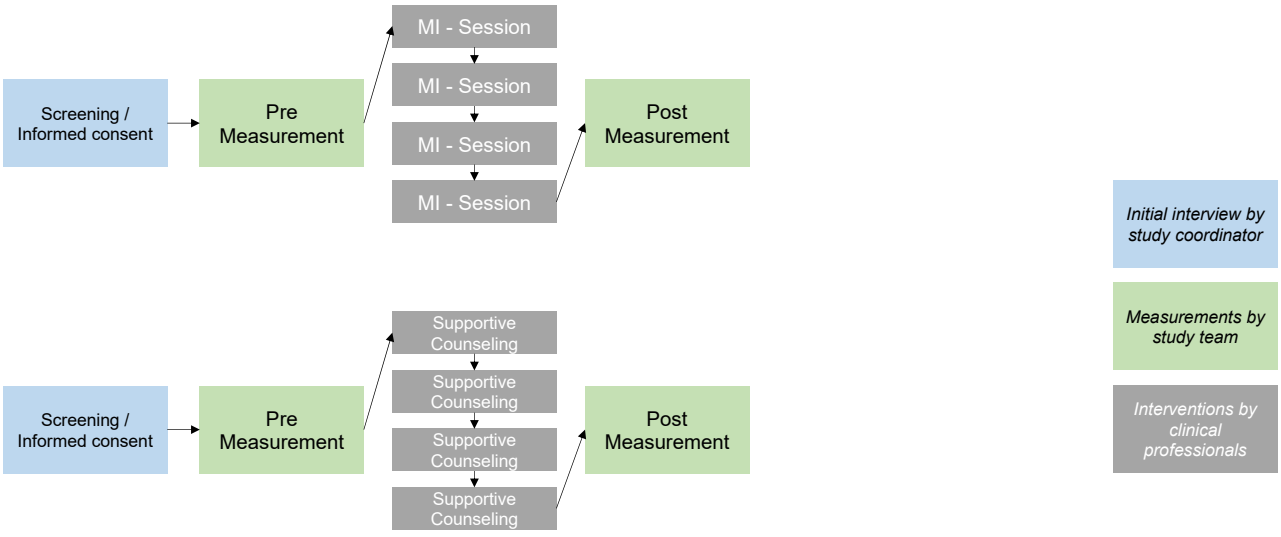

Table 2: Overview study procedure

* If questions / need for feedback occur after the last visit, an additional visit shall be provided

	Re-cruit-ment	Pre-Meas-ure-ment	Intervention phase				Post-Measure-ment	
Visits	**1** max. 30min.	**2** max. 60min.	**3** 25-40min.	**4** 25-40min.	**5** 25-40min.	**6** 25-40min.	**7** max. 60min.	**Follow up** max. 60min.
Time (days)	**-3 +/-2d**	**0**	**2 +/-1d**	**4 +/-1d**	**6 +/-1d**	**8 +/-1d**	**10 +/-1d**	**60 +/5d**
Check with treating physician or psychologist	x							
Patient Information and Informed Consent	x							
Randomization	x							
Demographics and information about current treatment	x							
Examination of symptoms with PANSS and MATRICS		x					x	x
Control of In- and Exclusion Criteria		x						
Measurements of secondary outcome variables		x					x	
MI-Intervention (intervention group) or supportive conversations (controls)			x	x	x	x		
Possibility for patients to ask questions and give a feedback							x*	

Detailed description of the planned intervention

Motivational Interviewing is a technique that aims in particular to promote intrinsic motivation and to make ambivalences visible and reduce them. It involves a therapeutic attitude based on the humanistic approach as well as on person-centred psychotherapy according to Carl Rogers. The original founders of MI defined five basic principles: 1. make clear, consensual agreements, 2. show empathy, 3. develop the will to change and clarify discrepancies, 4. redirect resistance, 5. promote self-confidence and responsibility. In addition, MI compliant skills such as active listening, supporting positive behaviours, asking open-ended questions, summarizing and reflecting, supporting self-motivating statements are applied. The concept of MI is that the conversation with the patient goes through different phases of decision making and motivation building. The therapist always addresses and emphasizes the patient's stated desires, reasons, or abilities to change. This is called "change talk." In the same way, however, doubts and counterarguments are also addressed ("sustain talk") and appreciated. The aim is to increase the patient's

discrepancy in a trustworthy and empathic way, so that he or she moves on to the phase of actual decision-making and finally to goal-directed behaviour on the basis of self-developed arguments.
Four interviews will be conducted using this method as part of the study intervention. The content of these will be about participation in treatment. In order to make the intervention measurable, the conversations will be recorded on an audio device and subsequently evaluated by two independent raters according to the number of MI principles and techniques applied.

Psychometric tests used in the study

Primary diagnosis at point of admittance and medical history are assessed by physicians and psychologists at PUK and documented electronically. The applicant and master's students enrolled in the project will use this available data and document them in specific study protocols. These assessments are part of standard assessments at the hospital by physicians and psychologists. For primary psychiatric diagnoses the International Classification of Diseases (ICD-10) is used.

- Psychotic symptoms are assessed with the *Positive and Negative Syndrome Scale* (PANSS). This is a structured interview, which consists of four scales measuring positive and negative syndromes of schizophrenia, their differential, and general severity of illness.
- Two cognitive tests: Letter-Number-Span (LNS), Symbol-Coding-Test (SCT) from MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia, Consensus Cognitive Battery; Nuechterlein et al., 2008)
- The *Brief Adherence Rating Scale* BARS (Byerly et al, 2008) is a brief, pencil-paper, clinician-administered adherence assessment instrument. It consists of 4 items: 3 questions and an overall visual analog rating scale to assess the proportion of doses taken by the patient in the past month (0%–100%).
- The therapeutic relationship will be evaluated with the *Scale to Assess Therapeutic Relationship* STAR (McGuire-Snieckus et al., 2007). The patient (STAR-P) and clinician scales (STAR-C) each have 12 items comprising three subscales: positive collaboration and positive clinician input in both versions, non-supportive clinician input in the patient version, and emotional difficulties in the clinician version.
- Motivation for psychotherapy will be measured with the *Fragebogen zur Erfassung der Psychotherapiemotivation* (FPTM; engl: "Questionnaire to measure the motivation for psychotherapy ") by Schulz, Nübling und Rüddel (1995), a 4-point Likert-scale with 39 items.
- Self-efficacy is measured with the German version of the *General Self-Efficacy Scale* (GSE) by Schwarzer & Jerusalem (1995), an instrument that has been proved with a sample of more than 19'000 persons in 25 countries and shows good psychometric properties.

Expected biases to the study

There are several risks for biases as already described in chapter 2.3 *Study design*. With regard to the method, it must be noted that the effect of psychotherapy is multifactorial and thus difficult to control whether any effects are only due to the difference of the specific method (MI) compared to supportive talks (as a control intervention). In order to control for other possible influencing factors, the level of training of the therapists will be included and controlled for. The degree of motivation for psychotherapy of the patients before the beginning of the intervention as well as the attitude towards recovery on the therapist's side can also influence the outcome of a psychotherapeutic intervention, independent of the method. These specific variables will also be included in our calculations. In addition, it is possible that expectation or attitude toward one of the two therapy methods may have an effect on the outcomes. We will therefore blind the study so that patients do not know which group they belong to ("single-blind").

3.4 Withdrawal and discontinuation

Participants have the right to abort the study at any point and without providing a reason. The principal investigator and the co-investigator have the right to withdraw participants if they knowingly provide incorrect information, withdraw consent, do not adhere to protocol requirements (i.e. missing appointments, ignoring instructions) or if the disease has progressed (see exclusion criteria).
If participants do not finish the experiment, the data will be stored properly and taken into analysis as far as possible and useful. Additional participants will be recruited to replace the withdrawn participants.
Since they are inpatients, there is a very low risk of missed appointments. If this is still the case, the appointments can be made up on the following day.
If participants are discharged before the end of the study, they may attend the remaining appointments as outpatients if the majority of the study has already taken place (at least 3 psychotherapy sessions must have taken place during inpatient treatment).

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan and sample size calculation

Hypothesis 1: Four sessions of motivational interviewing for newly admitted acute patients (within the first 7 days of hospitalization) improve the therapeutic alliance and the adherence for treatment compared to supportive counseling.

Statistical analysis for hypothesis 1: To apply the statistically most sensitive test, we will use an ANCOVA to analyze the treatment effect of motivational interviewing compared to supportive counseling, with baseline values used as covariates.

Hypothesis 2: Four sessions of motivational interviewing for newly admitted acute patients decreases symptom severity compared to supportive counseling.

Statistical analysis for hypothesis 2: We will use an ANCOVA to analyze the treatment effect of motivational interviewing compared to supportive counseling, with baseline values used as covariates.

Hypothesis 3: Patients show higher motivation to seek psychotherapeutic treatment and have a higher self-efficacy expectation after leaving the inpatient stay, when they received an intervention with motivational interviewing compared to supportive counseling.

Statistical analysis for hypothesis 3: We will use an ANCOVA to analyze the treatment effect of motivational interviewing compared to supportive counseling, with baseline values used as covariates.

Additional calculations: We also want to investigate how the number of hospitalization days and the severity of symptoms at the beginning of the intervention have an influence on the therapy outcome. We calculate this with a multiple regression with days of hospitalization and/or the PANSS total score as independent variables. The treatment outcome is defined as the delta between symptoms before and after the intervention and serves as dependent variable.

General statistical considerations: We will use routine procedures of data processing and use data transformation if necessary (in case of non-normal distribution). Standard statistical calculations will be computed. The level of significance will be set to $p < 0.05$ (two tailed). Effect sizes will be calculated for significant results. The IBM® SPSS Statistics® statistical software as well as the program R will be used.

Sample size justification: Comparable studies found effect sizes that were moderate (Cohen's *d* = 0.3 - 0.5). An effect sizes of f = 0.25 will require us to recruit at least 64 patients per group to achieve 80% power and to detect such an effect with reasonable certainty at an alpha level of 0.05. We therefore plan to include a minimum of N = 128 patients (calculated with G*Power 3.1).

Analysis population: There is only one analysis population for all hypothesis. For inclusion criteria see chapter 4.1.

Analysis of gender differences: Analyses of gender differences are not planned because there is no research evidence to suggest that gender may be a determining variable. However, it is planned to conduct a group comparison between patients who benefit strongly from MI and those who benefit little, and to investigate possible discriminatory factors as part of this.

4.2. Handling of missing data and drop-outs

All patients who completed the study will be taken into analysis. All collected data will be checked at each study assessment, and missing data will thus be avoided as much as possible. If missing data nevertheless does occur, data has to be excluded.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

5.2 (Serious) Adverse Events and notification of safety and protective measures

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation subject which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavourable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect

Both Investigator and Sponsor-Investigator make a causality assessment of the event to the trial intervention, (see table below based on the terms given in ICH E2A guidelines). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident

Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Both Investigator and Sponsor-Investigator make a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

Reporting of SAEs (see ClinO, Art. 63)**:** All SAEs are documented and reported immediately (within a maximum of 24 hours) to the Sponsor-Investigator of the study. If it cannot be excluded that the SAE occurring in Switzerland is attributable to the intervention under investigation, the Investigator reports it to the Ethics Committee via BASEC within 15 days.
Exceptions to expedited reporting are possible if the SAE is either a clear consequence of the underlying illness or known before onset: In this study, exacerbation of psychotic symptoms may occur, possibly accompanied by unwillingness to treat and leading to coercive measures. Similarly, suicidal behaviors may occur in the course of acute psychoatric treatment, which are usually an expression of a subjectively stressful situation and are not directly related to the study.

Follow up of (Serious) Adverse Events: Participants terminating the study (either regularly or prematurely) with reported ongoing SAE, or any ongoing AEs of laboratory values or of vital signs being beyond the alert limit will return for a follow-up investigation. This visit will take place up to 30 days after terminating the treatment period. Follow-up information on the outcome will be recorded on the respective SAE page in the CRF.
Follow-up investigations may also be necessary according to the investigator's medical judgment even if the participant has no SAE at the end of the study. However, information related to these investigations does not have to be documented in the CRF but must be noted in the source documents.

Notification of safety and protective measures (see ClinO, Art 62, b): If immediate safety and protective measures have to be taken during the conduct of the study, the investigator notifies the Ethics committee of these measures, and of the circumstances necessitating them, within 7 days.

5.3 (Periodic) safety reporting

An annual safety report (ASR) is submitted once a year to the local Ethics Committee by the Investigator (ClinO, Art. 43 Abs 1).

5.4 Radiation

Not applicable.

5.5 Pregnancy

This study (risk category A) does not include drugs or other medical products and is based exclusively on psychotherapeutic intervention. Pregnancy is therefore not an exclusion criterion and there are no risks for pregnant women to participate in the study, but it will be noted in the CRF.

5.6 Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study

documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.

Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of study site(s) or of study leader and sponsor (ClinO, Art. 29).

A list of all non-substantial amendments will be submitted once a year to the competent EC together with the ASR.

5.7 Notification and reporting upon completion, discontinuation or interruption of the study

Upon regular study completion, the Ethics Committee is notified via BASEC within 90 days (ClinO, Art. 38).

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, e.g.

- Ethical concerns,
- Insufficient participant recruitment,
- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive),
- Alterations in accepted clinical practice that make the continuation of the study unwise, or
- Early evidence of harm or benefit of the experimental intervention

Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38).

When the study is finished the datasheet with the patient-identification number will be printed and then deleted from the clinic server. The encoded datasheet and the printed form of the datasheet with the patient-identification number and the corresponding identification-number will be stored and secured.
A final report is submitted to the Ethics Committee via BASEC within a year after completion or discontinuation of the study, unless a longer period is specified in the protocol (ClinO, Art. 38).

5.8 Insurance

In the event of project-related damage or injuries, the liability of the University Hospital of Psychiatry Zurich provides compensation, except for claims that arise from misconduct or gross negligence.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

This study (risk category A) does not include drugs or other medical products and is based exclusively on a psychotherapeutic intervention. Patients are hardly exposed to any more risks than in routine clinical care, so no safety measures are required. The time commitment for participants is limited to six sessions of 25 to 60 minutes. Participants may benefit from additional discussions in both conditions: either MI sessions or supportive conversations, but both groups have more support than patients who do not participate in the study. In addition, participants will receive financial compensation for their participation.

6.2 Risk-benefit assessment

We have identified several risks to this project, including the risk of unauthorized data access or inadvertent identification of project participants. We have taken appropriate measures for both (see section 7.2 Data recording and source data)
This is a standard psychotherapy study, and participants generally tolerate this type of study very well, as they are exposed to almost no additional risks during the psychotherapy intervention itself. Although there will be no immediate benefit to the project participant, the results of the pilot project will form the basis for further and larger-scale psychotherapy studies, and these in turn should benefit future patients by providing more effective psychotherapeutic treatment for psychosis in the acute stage of the illness.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

The study coordinator is implementing and maintaining quality assurance and quality control systems including written working instructions to ensure that trials are conducted, and data are generated, documented, and reported in compliance with the protocol.
The study will strictly follow the protocol. If any changes become necessary, they must be laid down in an amendment to the protocol. For quality assurance the sponsor, the Ethics Committee or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions.
Study personnel will be trained in diagnostic skills by the study coordinator, including PANSS training. Clinical psychologists participating in the study and delivering the interventions with patients will receive an update (if they have previous experience with MI) or training (if they do not have experience) in MI.
The study coordinator will present interim data as well as organizational and feasibility findings to the Sponsor-Investigator at regular intervals.
We will take several measures for quality control regarding the data such as double data entry and independent data review.

7.2 Data recording and source data

All acquired data will be stored at the University Hospital of Psychiatry and will be treated strictly confidential. The data and the decoding list will be archived separately. Only researchers who are involved in the study will have access to the project plan, dataset, statistical code, etc. during and after the research project. The results of the study will be published in an anonymized manner.
For each participant a paper CRF is maintained. CRFs do not identify participants by their name or birth date but provide appropriate coded identification. CRF's are filled in manually and transferred to a SPSS file by the study staff and checked by another person. The file is stored in a folder on the clinic server, which is only accessible to study staff. CRFs must be kept current to reflect participant status at each phase during the course of study. An audit trail ensures that all changes to the original data are documented and apparent.

Source data must be available at the site to document the existence of the study participants and substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant. The following information will be included in the source documents:

- Demographic data (age, sex, education, work situation) and relevant information about disease (year of onset, number of psychotic episodes, medication, other diagnosis)
- Inclusion and Exclusion Criteria details
- Participation in study and signed and dated Informed Consent Forms
- Visit dates

- Key efficacy and safety data
- SAEs (related) and concomitant medication
- Results of relevant examinations (questionnaires, observations)
- Reason for premature discontinuation
- Randomization number

We will not collect any data during the daily practice (routinely collected).

7.3 Confidentiality and coding

Trial and participant data will be handled with uttermost discretion and is only accessible to authorized personnel (study team) who require the data to fulfil their duties within the scope of the study.

On the CRFs and other study specific documents, participants are only identified by a unique participant number. The participant identification list will be stored in a locked closet at the University Psychiatric Hospital. Only the Sponsor-Investigator and the study coordinator do have access. When a patient is enrolled in the study, they are assigned a number by the study coordinator. The patient is added to the participant identification list and the list is then locked again. There must be no name on any documents, only the participant number. It must be assured that any authorized person, who may perform data entries and changes in the CRF, can be identified. A list with signatures and initials of all authorized persons will be filed in the study site file and the trial master file, respectively.

Electronic data are stored on the University Psychiatric Hospital server, which is password protected and accessible only to the study team.

7.4 Retention and destruction of study data and biological material

All study data are archived for 10 years after study termination (planned for September 2023) or premature termination of the study. Location of storage is the Psychiatric University Hospital. Data could potentially be shared with other researchers to promote Open Science for a longer period than 10 years, i.e., for meta analyses or secondary analyses. However, we will only share deidentified data with other researchers.

8 MONITORING AND REGISTRATION

Monitoring visits at the investigator's site at the start and during the course of the study will help to follow up the progress of the clinical study, to assure utmost accuracy of the data and to detect possible errors at an early time point. The Sponsor-Investigator organizes professional independent monitoring for the study and will therefore collaborate with other research groups from the Psychiatric University Hospital.

All original data including all patient files, progress notes and copies of laboratory and medical test results will be available for monitoring. The monitor will review all or a part of the CRF and written informed consents. The accuracy of the data will be verified by reviewing the above referenced documents.
The monitoring plan for this study includes:

pre-study visit	-
Initiation / first visit	January 2023
Visits	One visit during the study intervention phase in April 2023
Review of key data	• Existence and consent in 100% of patients • 100% of the other key data (if available at the time of the visit) in at least 20% of the patients • One 100%-source data comparison is performed for one patient

	from the sample
Additional contacts	Additional contacts by phone and/or e-mail will be made as required.
Final visit	August 2023

The study will be registrated in the Swiss National Clinical Trial Portal (SNCTP via BASEC) and clinicaltrial.gov.

9. FUNDING / PUBLICATION / DECLARATION OF INTEREST

The Psychiatric University Hospital provides rooms, electronic equipment (computer, telephone, photocopier), test batteries and administrative material (paper, pens, folders, etc.). The master's students work free of charge as part of their academic training.
This study is funded by the «Stiftung zur Förderung von Psychiatrie und Psychotherapie» (Zurich, Switzerland). There is no conflict of interest.

Publication policy of the study: After the statistical analysis of this trial the sponsor will make every endeavor to publish the data in a scientific journal.
If gender effects are observed, they will be published in the final study report. If an analysis is performed but no gender effects are observed, this will also be published.

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