Arts and culture on prescription. The impact of cultural prescription on the health of the elderly population living in the Lugano municipality – A pilot project.

Study Type:	Other Clinical Trial according to ClinO, Chapter 4
Risk Categorisation:	Risk category A according to ClinO, Art. 61
Study Registration:	1. The study will be registered on the International Clinical Trials Registry Platform (ICTRP) before it starts 2. The study will be registered on the FOPH portal SNCTP (Swiss National Clinical Trial Portal) before it starts
Sponsor:	Sponsor-Investigator
Principal Investigator:	Prof. Dr. med. Luca Gabutti
Investigated Intervention:	Attendance of an artistic or cultural activity (e.g., drawing, painting, photography) upon prescription by a family physician
Protocol ID:	Arts and culture on prescription
Version and Date:	Version 1 (dated 2.06.2025)

PROTOCOL SIGNATURE FORM

Study Title	Arts and culture on prescription. The impact of cultural prescription on the health of the elderly population living in the Lugano municipality – A pilot project.
Study ID	Arts and culture on prescription

The Sponsor has approved the protocol version 1 (dated 2/06/2025) 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.

Principal Investigator:

Name: *Prof. Dr. med. Luca Gabutti*

Date: 2 giugno 2025 Signature: 

TABLE OF CONTENTS

GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
BASEC	*Business Administration System for Ethical Committees*
CRF	*Case Report Form*
CTCAE	*Common Terminology Criteria for Adverse Events*
FADP	*Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)*
eCRF	*electronic Case Report Form*
FOPH	*Federal Office of Public Health*
GCP	*Good Clinical Practice*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
ICH	*International Conference on Harmonisation*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
SAE	*Serious Adverse Event*

1 STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Sponsor-Investigator
Study Title	Arts and culture on prescription. The impact of cultural prescription on the health of the elderly population living in the Lugano municipality – A pilot project.
Short Title / Study ID	Arts and culture on prescription.
Protocol Version and Date	Version 1 (dated 2/06/2025)
Study Registration	The study will be registered on the International Clinical Trials Registry Platform (ICTRP) and on the FOPH portal SNCTP (Swiss National Clinical Trial Portal) before it starts.
Study Category and Rationale	This study qualifies as Risk Category A under ClinO, Article 61, which covers clinical trials with minimal risk. According to ClinO, Article 2, minimal risks refer to interventions that do not exceed those of routine medical procedures, such as non-invasive examinations and standard psychological tests. The study involves cultural and artistic activities (e.g., painting, drawing, dance) as part of the LAC program, which are non-invasive and carry minimal risk. Additionally, it includes blood draws, medical examinations, monitoring through a smartwatch, and questionnaires. While the blood draw and medical examination involve low risk (e.g., discomfort at the injection site), they are common practices, and the smartwatch monitoring is non-invasive.
Background and Rationale	Cultural prescribing, an innovative approach that integrates arts and culture into healthcare, has shown promise in enhancing well-being across various health conditions. However, little is known about its acceptability among elderly individuals, particularly those managing lifestyle-related pathological conditions. This pilot project aims to explore how older adults (≥65 years) living in the Lugano municipality perceive and engage with cultural prescriptions—recommendations to participate in art workshops, cultural activities, and experiential programs—as part of their healthcare. Sex and gender are important factors in this study. It is crucial to consider both dimensions not only to ensure equitable engagement with the cultural prescriptions but also to tailor interventions that are more inclusive and effective for different groups. To achieve this, we will aim for a balanced sample with a 50:50 gender distribution. Gender will be integrated into the analysis to identify any differences in engagement or outcomes, ensuring that the interventions are appropriately adapted for all participants.
Risk / Benefit Assessment	The study's minimal risks are outweighed by the potential benefits of enhanced mental health and well-being, social connection, and improved health outcomes through engagement in artistic and cultural prescriptions.
Objective(s)	Primary objective: Explore programme feasibility and acceptability by assessing programme uptake, attendance rates, reasons for non-attendance, and barriers to engagement. Secondary objectives: Test whether there is any indication of an improvement in health orientation; compare health orientation and health outcomes of those participating in the programme versus the control group.
Endpoint(s)	Primary endpoints: Uptake and feasibility of recruitment and research procedures. Secondary endpoints: Health Orientation, Mental health and well-being, physiological measures, consultations and hospitalizations/emergency department accesses.
Study Design	Double-arm feasibility study with a control group, incorporating baseline and post-intervention assessments.
Inclusion- / Exclusion Criteria	The study population will consist of male and female patients identified by general practitioners who meet the following inclusion criteria: • Aged 65 or older • Resident in the Lugano municipality • Having access to a GP • Diagnosed > six months with one or more of the following pathological conditions: Obesity (BMI ≥30); Obstructive sleep apnea syndrome; Type 2 Diabetes Mellitus; Chronic Obstructive Pulmonary Disease (COPD) (GOLD 2 or higher); Uncontrolled hypertension; Uncontrolled gouty arthritis; Metabolic dysfunction and alcohol-related liver disease (MetALD). We will exclude:

	• Individuals who are still in employment (as the study focuses on retirees). Those who undertake occasional freelance work or small consultancies (e.g., fewer than 8 hours per week) may still be eligible, provided their professional activities do not interfere with participation in the study. • Individuals diagnosed with moderate to severe dementia or cognitive impairment that affects their ability to provide informed consent. • Individuals with significant mobility restrictions that would prevent engagement in artistic and cultural activities (unless safe accommodations can be arranged).
Number of Participants with Rationale	The study will recruit 100 participants, with 80 assigned to the experimental group for an artistic or cultural course, and 20 matched participants in the control group who will not participate in these activities but will receive a free ticket for a museum, concert, or show. This design is in line with pilot studies aiming to measure feasibility and assess preliminary differences between the experimental and control groups in preparation for a future RCT.
Study Intervention	A link worker from the Città di Lugano will contact participants to provide detailed information about the available cultural offerings and the research procedure. The link worker will work closely with participants to understand their personal preferences and interests, ensuring that the selected cultural activities align with their tastes and needs. By tailoring the experience to each participant, the link worker will help identify the most appropriate events or activities that can enhance their engagement and overall well-being, while also supporting the goals of the study. Participants will receive up to six sessions with their link worker, which is a pragmatic allocation based on trial feasibility, though in real-world practice, individuals may receive additional support if needed. Each session will last up to one hour and will be conducted in person, over the phone, or via video call, depending on participant preference and accessibility. All cultural activities will be fully funded, ensuring that financial barriers do not limit participation. The available activities are part of a curated set designed specifically for this program, including drawing, painting, music, photography, museotherapy, dance, and theater. Link workers will not have complete autonomy over referrals but will guide participants toward these pre-selected activities that align with the research framework. Every activity includes up to 25 sessions lasting 1-2 hours each per week. The sessions take place at LAC.
Control Intervention	The control group will be offered a free ticket for a museum, concert o show.
Study procedures	The study will consist of the following procedures: 1. Baseline assessment: Conducted after obtaining informed consent, this includes a blood draw, urine test, completion of questionnaires, and the wearing of a monitoring device. 2. Artistic or cultural prescription assignment: About 3-4 weeks after the baseline assessment, participants will be contacted by a link worker who will identify and match them with a suitable art or cultural program. 3. Program participation: Participants will begin attending the assigned cultural or artistic course, which is scheduled to take place once per week for 1-2 hours over a 6-month period. 4. Second assessment (6-month follow-up): Six months after initiating the intervention, participants will undergo a second assessment, which will include a blood draw, urine test, questionnaires, and device wearing. This is also when we will start conducting the first set of qualitative interviews. 5. Third assessment (12-month follow-up): Six months after the second assessment, participants will complete a long-term follow-up assessment, which will again involve a blood draw, urine test, questionnaires, and device wearing. This is when we will start conducting the second set of qualitative interviews. Participants will be required to attend all assessments at the Family Medicine Service of the Ospedale Italiano in Lugano. Questionnaires will be completed using a tablet. Nurses and physicians holding a GCP certificate will be responsible for conducting blood draws, reviewing medications, and overseeing the proper use of wearable devices.
Study Duration and Schedule	Estimated duration for the main investigational plan: 18 months. Planned 06/2025 of First-Participant-In Planned 12/2026 of Last-Participant-Out
Investigator(s)	Prof. Dr. med. Luca Gabutti Istituto di Medicina di Famiglia

	Università della Svizzera italiana Ente Ospedaliero Cantonale Via Buffi 13, 6900 Lugano luca.gabutti@eoc.ch
Study Center(s)	Istituto di Medicina di Famiglia Università della Svizzera italiana Ente Ospedaliero Cantonale Via Buffi 13, 6900 Lugano
Statistical Considerations:	Participant characteristics will be summarized at baseline, and statistical significance will be set at $p<0.05$, with results interpreted using p-values and 95% confidence intervals. Acceptability will be measured through participant retention and session attendance, and reasons for non-completion will be summarized. Feasibility will be evaluated by analyzing recruitment time, follow-up completion, and missing data. Primary and secondary outcomes will be assessed using paired t-tests, linear mixed-effects models, or repeated-measures ANOVA to account for individual variability. Gender will be analyzed as part of all statistical evaluations. All quantitative analyses will be performed using Stata or R.
Data privacy	To ensure privacy, each participant will be assigned a unique code. A list linking these codes to participants' names will be stored on a password-protected server (Switchdrive), accessible only by the research team. All data from questionnaires, medical visits, smartwatch monitoring, or blood tests will be stored anonymously, with no participant names, but linked to the unique code. Blood and urine samples will be labeled with the unique anonymous code assigned to each participant. This system guarantees confidentiality and protects the privacy of participants while handling both data and any applicable biological material.
Ethical consideration	The scientific value of this study lies in its exploration of the impact of cultural prescribing on the well-being of older adults, particularly those managing lifestyle-related conditions. This approach is innovative in integrating arts and cultural activities into healthcare, an area with limited research in elderly populations. By assessing how older adults engage with cultural prescriptions, the study could provide valuable insights into improving healthcare interventions for this group, potentially informing future practices. The methodology is carefully designed to assess the feasibility and acceptability of cultural prescribing through a controlled study, with a control group receiving a cultural activity alternative (museum, concert, or show) to allow for comparison. By assigning participants to two groups and monitoring health outcomes using statistical methods, the study ensures a rigorous and scientifically sound approach that will provide preliminary insights into the effectiveness of cultural prescribing. Regarding risks and benefits, the study presents minimal risks, primarily associated with the blood draw, medical examination, and monitoring through the smartwatch, which are common procedures in clinical research. These risks will be mitigated through appropriate medical supervision and participant monitoring. The benefits include potential improvements in mental and physical well-being, reduced loneliness, and increased social support through engagement in cultural activities. Older adults are considered a vulnerable population due to the high prevalence of chronic conditions, poverty, and social isolation. We are fully committed to ensuring their protection throughout the study. We will take all necessary precautions to ensure their safety, understanding, and comfort during participation. Furthermore, we will provide appropriate resources and referrals to healthcare professionals if any issues arise during the study, whether related to physical or mental health concerns.
GCP Statement	This study will be 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.

2 BACKGROUND AND RATIONALE

Social prescribing is a strategy applied in primary care that involves connecting patients to non-clinical services to improve their health and well-being by addressing social determinants of health[1]. It encompasses various interventions, such as arts-on-referral (i.e., non-medical complementary interventions based on arts), exercise programs (e.g., cycling, dancing, swimming), educational opportunities (e.g., formal learning activities), green gyms (i.e., physical activities in natural environments), and cultural activities (e.g., playing music, painting, drawings), which have been studied for their positive impact on mental wellbeing and positive mood, self-esteem and confidence, quality of life, and their reduction in anxiety, depression and negative mood[2].

However, there is still a paucity of robust evidence on the effectiveness of the different interventions, especially the mechanisms explaining their effects on health[3]. Moreover, most research has focused primarily on arts-related interventions[2], and the most reported reasons for referral to a social prescription were anxiety, isolation, and depression[3]. Furthermore, there is little evidence concerning evaluating proactive and "formal" social prescribing, in which primary healthcare teams coordinate and build a network with the social or cultural intervention teams[4,5]. Moreover, research underlined the importance of the facilitator, also called the "link worker", in mediating between healthcare providers and community services, ensuring patient adherence to the social prescription and engagement[3].

Despite this growing body of evidence, arts and culture, as forms of social prescription, remain underexplored in many countries, including Switzerland. The promising impact of such programs in other regions highlights the potential for similar outcomes in Swiss communities, where the rich cultural heritage and vibrant arts scene provide an ideal setting for this approach. By launching Switzerland's first cultural prescribing pilot project in Lugano, we aim to build on international evidence and create a tailored program to set a precedent for integrating culture into healthcare across the country.

Due to its cultural landscape, the Lugano municipality presents an ideal setting for a project on cultural prescription. It offers a wide array of activities and a robust network of family physicians who are not only well-integrated into the local healthcare system but also open to testing innovative interventions aimed at improving patient well-being. This collaborative medical community will facilitate recruitment and implementation of the intervention.

Lifestyle-related conditions—such as obesity, insulin resistance, hypertension, and chronic obstructive pulmonary disease —pose a substantial public health burden, contributing to increased morbidity, reduced quality of life, and rising healthcare costs[6,7]. These conditions are often interconnected, elevating the risk of developing cardiovascular diseases, type 2 diabetes, and other chronic illnesses. Despite their largely preventable nature, they remain prevalent due to complex interactions between genetic predisposition, environmental factors, and behavioural patterns[8]. Addressing these conditions requires a multifaceted approach that includes medical interventions, lifestyle modifications, and supportive social and healthcare policies aimed at promoting sustainable health behaviours. While lifestyle changes and pharmacological treatments remain the cornerstone of management, effectively tackling the psychosocial and behavioural factors that contribute to these conditions is crucial for long-term success[9]. Social determinants of health, including mental well-being, social isolation, and access to supportive environments, play a significant role in the progression and management of these conditions.

Physical activity is a reliable lifestyle indicator and can be monitored to evaluate the impact of lifestyle interventions[10]. Heart Rate Variability (HRV) is a general indicator of cardiovascular health. In particular, HRV is a physiological marker of the autonomic nervous system (ANS) function. Improved HRV generally indicates better autonomic flexibility, good relaxation, and better cardiovascular health. It has been proved that improving awareness of HRV after myocardial infarction through biofeedback exercises may favourably impact HRV regulation and, therefore, cardiovascular health[11]. HRV biofeedback may be a valid instrument for raising awareness on CVD risk. Lifestyle significantly impacts sleep quality, which in turn contributes to cardiovascular risk and plays a central role in exacerbating its consequences[12–14]. Blood pressure

increase, as well as the other pathological lifestyle repercussions, directly contributes to increased cardiovascular risk[15].

The impact of illness awareness on disease self-management and health behaviour is well-supported by research, particularly in the context of chronic illnesses[16–18]. Illness awareness – a patient's understanding of their disease, including its causes, symptoms, treatment options, and the necessary lifestyle modifications – plays a key role in promoting more effective self-management and healthier behaviours. A study by Burton and colleagues[19] found that structured drama and visualization exercises, along with shared storytelling, helped participants shift from denial and frustration to acceptance of their illness, fostering a sense of community, reducing loneliness, increasing perceived social support, and enhancing confidence in sharing their experiences, particularly in in-person settings. Numerous studies suggest that greater acceptance of illness positively influences patients' quality of life and enhances their motivation to engage in behaviours that promote their well-being[20–25]. Recently, the health orientation construct has been developed as a comprehensive framework to capture individuals' attitudes, beliefs, and proactive engagement with their health[26]. This construct integrates multiple dimensions, including health awareness, motivation for self-care, and behavioural tendencies related to disease prevention and management. It provides a broader perspective on how individuals conceptualize and respond to their health conditions, further highlighting the role of illness awareness in shaping self-management behaviours and overall well-being.

Cultural prescribing, an emerging form of social prescription, offers a promising intervention by integrating non-clinical arts activities into primary care. Engaging patients in arts programs and cultural prescription activities has been shown to enhance their mental well-being, build social connections, and potentially improve their self-management of chronic conditions. Despite its growing use internationally, there is limited evidence of the effectiveness of cultural prescribing in managing chronic illnesses like metabolic syndrome, and the mechanisms underlying its health benefits remain to be fully understood.

The present project proposes a mixed-method study to test the feasibility and acceptability of cultural prescription for patients with lifestyle-related pathological conditions. Additionally, it aims to explore whether there is any indication of improvement in health orientation and health outcomes as a result of the intervention.

According to ClinO, Art. 61, this study falls under Risk Category A (minimal risk). The rationale for this categorization stems from the fact that the study involves procedures that are well-established in research (blood draw, urine test, medical examination, smartwatch monitoring, and completing questionnaires), which are common and have minimal risks. These risks are primarily associated with the physical examination and the blood draw, which are generally safe procedures, and the potential for discomfort or mild anxiety. Additionally, the cultural prescribing intervention (art workshops, cultural activities) poses no more than minimal psychological or physical risk, given the nature of the activities involved.

Regarding the relevance of "sex and gender" dimensions, these factors are indeed pertinent to the study. Sex and gender influence health outcomes and can affect how individuals experience and engage with health interventions. Biological differences (e.g., hormone levels, genetics) and social constructs (e.g., gender roles, expectations) may impact participants' responses to cultural prescribing activities, particularly in the context of older adults with lifestyle-related conditions. Therefore, gender dimensions will be taken into account to ensure that interventions are equitable and tailored to the needs of different participants. This will include analyzing any potential differences in engagement with and outcomes from the cultural prescribing intervention based on gender.

3 STUDY OBJECTIVES AND DESIGN

3.1 Hypothesis and primary objective

Primary objective:

1. Explore programme feasibility and acceptability by assessing programme uptake, attendance

rates, reasons for non-attendance, and barriers to engagement.

Secondary objectives:

2. Test whether there is any indication of an improvement in health orientation.

3. Compare health orientation and health outcomes of those participating in the programme versus the control group.

The study hypothesizes that cultural prescribing (artistic and cultural activities as part of healthcare) will be feasible and acceptable to older adults, and that participation in the program will lead to improvements in health orientation and health outcomes compared to a control group.

3.2 Primary and secondary outcomes

Primary outcome

Uptake and feasibility of recruitment and research procedures

Uptake will be assessed both quantitatively and qualitatively. The quantitative assessment will include the **range and average number of sessions attended by participants**, as reported by cultural facilitators, while the qualitative assessment will explore reasons for non-attendance and barriers to engagement among participants. To enhance practicality, attendance will be measured based on sessions attended with the link worker, alongside standardized measures of the types of cultural activities recommended and attended, and self-reported participation in these activities. Feasibility of recruitment procedures will be evaluated by measuring the **time required to recruit 100 participants, the number of individuals screened, and the number of eligible individuals who chose not to participate, as reported by GPs**. Feasibility of research procedures will be assessed through the proportion of participants who complete follow-up assessments at each timepoint and the extent of missing data at both baseline and follow-ups. These measures will provide insights into the practicality of implementing the intervention and conducting research within this population. A measure of uptake will also be applied to the control group to evaluate if they did independently engage in cultural activities.

Secondary outcomes

Health Orientation

To assess participants' **health orientation, the Health Orientation Scale (HOS)**[27], a validated scale, will be administered at **baseline and follow-ups**. The **HOS** is designed to measure **individual differences in health-related attitudes, beliefs, and behaviours**. It assesses various psychological and behavioural aspects of how people perceive, manage, and respond to their health. Higher scores on the **HOS** generally indicate a **stronger focus on health-related thoughts, emotions, and behaviours**. However, the interpretation depends on the specific dimension being measured. The **HOS** is a comprehensive measure because it assesses multiple psychological and behavioural dimensions of health, including awareness, anxiety, motivation, control beliefs, social perceptions, and future expectations, providing a holistic understanding of an individual's health-related attitudes and behaviours.

Mental health and well-being

Mental health and well-being will be assessed using validated questionnaires designed for similar adult populations. All measures are expected to demonstrate good internal consistency at all time points.

- **Generalized anxiety symptoms** will be measured using the Generalized Anxiety Disorder Assessment-7 (GAD-7)[28], with higher scores indicating greater anxiety symptoms.
- **Depressive symptoms** will be assessed using the Patient Health Questionnaire-9 (PHQ-9)[29], where higher scores will reflect more severe depressive symptoms.

- **Mental well-being** will be evaluated using the Warwick-Edinburgh Mental Wellbeing Scale[30], with higher scores representing greater positive mental well-being.
- **Self-compassion** will be assessed using the Self-Compassion Scale Short Form (SCS-SF)[31], where higher scores indicate greater self-compassion and reduced self-criticism.
- **Overall well-being** will be measured using the WHO-5 Well-Being Index[32], with higher scores reflecting better psychological well-being.
- **Quality of life** will be evaluated using the EQ-5D[33], a standardized instrument assessing five dimensions of health-related quality of life, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
- **Loneliness** will be assessed using the three-item UCLA Loneliness Scale[34], with higher scores indicating greater loneliness.
- **Social support** will be measured through the Medical Outcomes Study Social Support Survey[35], where higher scores will denote greater perceived social support.
- **Sleep quality** will be evaluated using the Bernese Sleep Health Questionnaire (BSHQ)[36] for the rapid assessment of sleep health and screening of sleep–wake circadian disorders.

Physiological measures
The physiological measures in this study will be collected using a combination of **clinical assessment, wearable technology and laboratory tests**.

Clinical assessment
Anthropometric parameters, blood pressure and bioimpedance will be registered during in-person assessments. Additionally, cognitive function will be evaluated using the Mini-Mental State Examination and the Clock Test.

Wearable measures
Participants will be asked to wear a **Garmin vívoactive® 5 smartwatch**, which is equipped with advanced sensors to track:

- **Heart rate variability (HRV):** The smartwatch uses an **optical heart rate sensor** to measure small variations in the time intervals between consecutive heartbeats. HRV is a key marker of **autonomic nervous system function** and cardiovascular health.

- **Sleep quality:** The smartwatch tracks sleep duration and stages (light, deep, and REM sleep) using accelerometer data and heart rate variability patterns. It provides insights into sleep efficiency and restfulness.

- **Physical activity and stress monitoring:** The device continuously records heart rate, oxygen saturation (SpO2), and stress levels, using HRV-based algorithms to assess daily stress exposure and recovery patterns.

Participants will wear the smartwatch for one week at three time points: baseline, first follow-up, and second follow-up. After each monitoring period, they will return the device either in person at the hospital or via a prepaid, self-addressed envelope provided by the research team.

Laboratory tests
Blood and urine tests to assess various **biochemical markers** will be performed.

- **Blood tests:**
    - **Glycated hemoglobin (HbA1c)** – an indicator of long-term blood sugar control.

- **Gamma-glutamyl transferase (GGT)** – a marker of liver function, bile duct abnormalities and enzymatic activity induction.
- **Uric acid** – a marker of metabolic health and inflammation.
- **Alanine aminotransferase (ALAT)** – a marker of liver function.
- **Creatinine** – a marker of kidney health.

- **Urine tests:**
  - **Sodium and potassium** – electrolytes relevant for cardiovascular prognosis.
  - **Albumin** – a marker of kidney health.
  - **Creatinine** – to normalize sodium, potassium and albumin excretion.

However, if these tests have already been conducted by the GP within the **previous month**, the basal blood draw and urine tests will not be performed.

Consultations and hospitalisations/emergency department accesses
We will administer a short questionnaire to the participant's general practitioner (GP) to collect additional data on the participant following the last follow-up (see the document "Questionario medici"). The questionnaire will include questions regarding the frequency of consultations with the GP in the year prior to the study and since its initiation, as well as the numer of hospitalizations or emergency department accesses before and after intervention. The GP will complete the questionnaire and return it to us by email or using a pre-stamped, self-addressed envelope.

Link workers' engagement with participants
To assess the quality of the link workers' engagement with participants, link workers will be asked to document each consultation by taking structured notes after each meeting (see the document "Questionario operatori"). These notes will capture:

- Key discussion points during the session
- Participant preferences and concerns related to cultural activities
- Recommendations made and the rationale for their selection
- Participant engagement levels and expressed motivation
- Barriers or facilitators to participation identified during the interaction

These notes will be systematically analysed to identify salient themes related to feasibility, acceptability, and participant engagement. This qualitative assessment will provide valuable insights into the effectiveness of the link worker's role, informing potential improvements in training, communication strategies, and support mechanisms to optimize the intervention.

Socio-demographic and condition-related variables
At baseline and after 6 and 12 months, data will be collected on participant demographics, socioeconomic status, and condition-related information, including:

- Demographic variables: Age, gender, marital status, educational level, and occupation status (e.g., volunteering activities). Age and gender will only be asked at baseline.
- Socioeconomic status: Household income level, housing situation, and access to healthcare services.
- Condition-related information: Medical diagnosis, duration of illness, and self-reported symptoms.

- Medication use: A comprehensive list of current medications taken by participants, including dosage and frequency.

3.3 Study design

The study will follow a mixed-method approach. It will be designed as a **double-arm feasibility study with a control group, incorporating baseline and post-intervention assessments**. A total of 100 participants will be recruited and screened by general practitioners (GPs) collaborating with the Institute of Family Medicine at USI to ensure they meet the inclusion criteria. Of these, 80 participants will be assigned to the experimental group and invited to enrol in an artistic or cultural course, selected from a curated selection based on recommendations from a link worker. The remaining 20 participants, matched to the experimental group in terms of gender, age, and medical condition, will serve as the control group and will not participate in these activities, but will be offered a free ticket for a museum, concert o show. Including a small control group in this feasibility study would allow testing of the randomisation procedure and understanding of how the control group would work. All participants will be monitored over time to evaluate the feasibility of the intervention and to assess its potential short-term and long-term effects, particularly in relation to health orientation and other secondary outcomes.

A **qualitative sub-study** will be nested within the main study to explore the feasibility, acceptability, and experiences of participants, link workers, and general practitioners. A total of 28 voluntary participants will be interviewed, including family physicians (n=10), link workers (n=3), and study participants (n=15). The qualitative study aims to capture subjective experiences of the artistic and cultural prescription intervention and its perceived impact on health and the patient-physician relationship. Participation will be voluntary, and data collection will continue until thematic saturation is reached[37]. Participants will be contacted by the Institute of Family Medicine and invited to take part to an optional interview. Interviews will be offered at both the first and second follow-up, with second follow-up interviews available only to those who did not participate in the first round. Efforts will be made to include individuals from diverse demographic backgrounds, health conditions, genders, and age groups. Separate semi-structured topic guides will be developed for each stakeholder group (see the document “Griglia intervista” for an overview of the topics that will be addressed with study participants). Physicians will be asked about recruitment processes and their experiences with the intervention, while link workers will provide insights into barriers and facilitators of engagement. Participants will discuss their experiences, including any barriers to participation, whether they found the programme enjoyable and beneficial for their symptoms, and if so, why. Interviews will be audio-recorded with participants’ consent. Thematic analysis will be performed on the transcriptions of the interviews following Braun and Clarke’s approach[38].

Successful **participant blinding** in experimental studies strengthens the credibility of the results, because knowledge of the assignment and perception of the treatment may affect outcomes[39]. In this study, participants may perceive that they are receiving superior or inferior care depending on the group they are assigned to, and may consequently report more positive or negative experiences and varying outcomes. This may potentially damage the quality of the data, but also be a source of harm for patients themselves. Hence, we decided to only inform participants of the purpose and procedures of the study in general terms (i.e., evaluation of their outcomes and their experience with an activity), so as to not reveal our specific objectives and the assigned group.

To ensure transparency and respect for participants, there will be a debriefing session after the study’s completion. This debriefing will take place through a phone call, where the researcher will provide verbal information explaining the specific objectives and rationale behind the group assignment. Following the call, participants will receive written information at home to ensure they have a clear understanding of the context of their involvement and the results of the study. This written document will serve as a reference to reinforce the spoken explanation and offer an

opportunity for participants to review the details at their convenience (see the document “Debriefing partecipanti”).

3.4. Study intervention

A **link worker from the Città di Lugano** will contact participants to provide detailed information about the available cultural offerings and the research procedure. The link worker will work closely with participants to understand their personal preferences and interests, ensuring that the selected cultural activities align with their tastes and needs. By tailoring the experience to each participant, the link worker will help identify the most appropriate events or activities that can enhance their engagement and overall well-being, while also supporting the goals of the research study.

Participants will receive up to six sessions with their link worker, which is a pragmatic allocation based on trial feasibility, though in real-world practice, individuals may receive additional support if needed. Each session will last up to one hour and will be conducted in person, over the phone, or via video call, depending on participant preference and accessibility.

All cultural activities will be **fully funded**, ensuring that financial barriers do not limit participation. The available activities are part of a curated set designed specifically for this program, including drawing, painting, music, photography, museotherapy, dance, and theater. Link workers will not have complete autonomy over referrals but will guide participants toward these pre-selected activities that align with the research framework. Each type of activity will include up to 25 weekly sessions, lasting 1-2 hours each and taking place at LAC. All activities will be facilitated by a cultural facilitator.

We propose participatory artistic activities, as opposed to more passive cultural experiences (such as being a spectator at events). This choice is grounded in the belief that active participation in the creative process fosters deeper emotional engagement, enhances personal expression, and can have therapeutic benefits for mental and physical well-being. By engaging participants in hands-on artistic creation, we aim to encourage a sense of accomplishment and connection to the cultural experience, as well as promote social interaction and personal growth.

Although link workers will not have prior clinical experience, they are trained social workers with expertise in community engagement and participant support. Before beginning their role, they will receive specialized training tailored to the study's objectives, covering aspects such as effective communication, cultural engagement strategies, goal-setting exercises, and data recording procedures.

To enhance participant engagement, link workers will use structured resources, including goal-setting exercises, to help individuals articulate their motivations, expectations, and desired outcomes from the cultural activities. Compliance with attendance at the prescribed cultural events will be closely monitored throughout the study to ensure adherence to the intervention and to assess engagement levels. Furthermore, the communication between the link worker and the GP will be standardized to ensure that the sense and purpose of the prescription are consistently maintained and aligned, avoiding any potential loss of focus regarding the intervention’s goals. In this regards, we will adopt best practice such as those suggested in the toolkit on how to implement social prescribing[40].

Cultural facilitators conducting the activities will also receive specific training on the project. They will be required to possess both expertise in the subject matter of their activities and skills in cultural and social mediation. Their role will include fostering an inclusive and engaging environment while adapting activities to participants’ needs. Cultural facilitators will work in close collaboration with link workers, who will, in turn, liaise with general practitioners as needed to ensure a coordinated approach.

4 STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

The study population will consist of male or female patients identified by GPs who meet the following **inclusion criteria**:

- Aged 65 or older
- Resident in the Lugano municipality
- Having access to a GP
- Diagnosed for at least six months with one or more of the following lifestyle-related pathological conditions:
    - Obesity (BMI ≥30)
    - Obstructive sleep apnea syndrome
    - Type 2 Diabetes Mellitus
    - Chronic Obstructive Pulmonary Disease (COPD) (GOLD 2 or higher)
    - Uncontrolled hypertension
    - Uncontrolled gouty arthritis
    - Metabolic dysfunction and alcohol-related liver disease (MetALD)

To ensure consistency in participant selection, individuals must have a confirmed diagnosis that meets these criteria. No specific treatment regimen or symptom severity threshold is required (except for COPD, since GOLD1 is asymptomatic).

The **GP will assess the appropriateness of participation based on the individual's clinical profile**.

We also envisioned a number of **exclusion criteria** to ensure the appropriateness of participant selection and the feasibility of the intervention. We will exclude:

- Individuals who are still in employment (as the study focuses on retirees). Those who undertake occasional freelance work or small consultancies (e.g., fewer than 8 hours per week) may still be eligible, provided their professional activities do not interfere with participation in the study.
- Individuals with diagnosed moderate to severe dementia or cognitive impairment that affects their ability to provide informed consent
- Individuals with significant mobility restrictions that would prevent engagement in artistic and cultural activities (unless safe accommodations can be arranged)

These criteria ensure that the study includes individuals who can actively participate in cultural prescribing interventions while considering medical appropriateness and potential barriers to engagement.

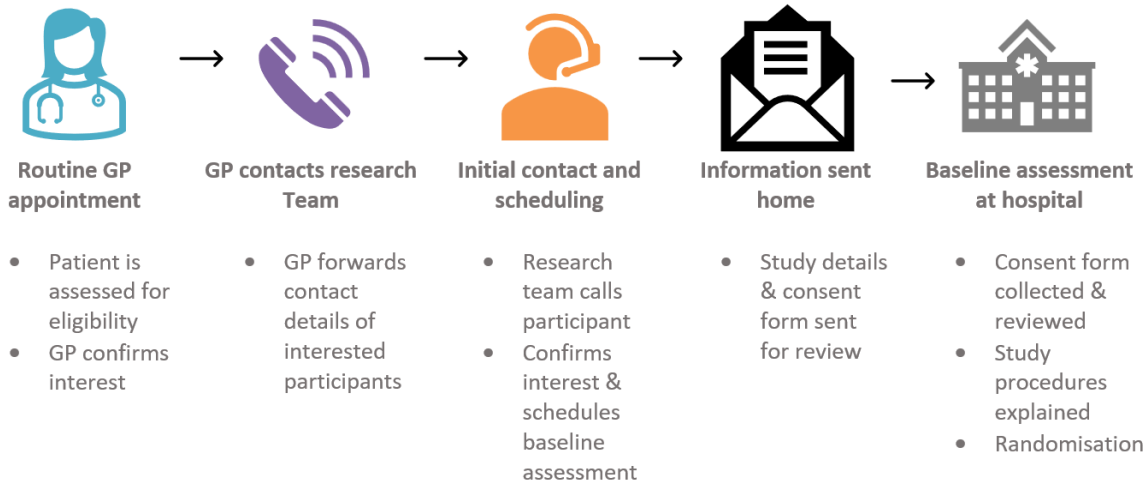
4.2 Recruitment, screening and informed consent procedure

The recruitment process will follow a number of steps (see Figure 1). Patients will be screened by their general practitioners (GPs) during routine appointments to confirm eligibility. Access to a GP is a prerequisite for inclusion in the study. To facilitate this process, the research team will provide GPs with a **structured screening form** (see the document “Formulario reclutamento”) to assess whether patients meet the inclusion criteria. Along with the screening form, GPs will receive a **standardized gridline** (see the document “Griglia introduzione studio”) to help introduce the study to the patient in a consistent and clear manner. If a patient is deemed eligible and expresses interest in participating, the GP will forward their contact details to the **research team at the Institute of Family Medicine** using the structured screening form.

Once referred, potential participants will be contacted over the phone to **confirm interest and schedule the baseline assessment**. Within three days from this phone call, potential participants will receive a written confirmation of their appointment (date, time, and address) and an **information sheet at home**, including a study description and a copy of the consent form (see document *ICF*), allowing them to review the materials before their baseline assessment.

GPs will **not** be responsible for handling consent forms but will collect and document key recruitment data, including the total number of individuals screened and those invited to participate, through a structured form provided by the research team (see the document "Rapporto screening"). This information will help estimate eligibility rates, assess recruitment efficiency, and inform planning for a larger-scale randomized controlled trial (RCT).

Figure 1. Recruitment process



The **research team at the Institute of Family Medicine at the Ospedale Italiano in Lugano** will manage the collection of consent forms during the baseline assessment, ensuring that participants fully understand the study before signing and before any study-related procedures. Participants will be asked if they have any questions before signing the document. 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 (at least one week). 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 first study participant will be included in the trial within two months following the issuance of the authorization by the Ethics Committee. The investigator or the sponsor notifies the Ethics Committee of the first study participant, in accordance with art 62 lit. c ClinO, resp. art 38 ClinO.

4.3 Study procedures

The study will consist of the following procedures:

1. **Baseline assessment:** Conducted after obtaining informed consent, this includes a **blood draw, urine test, completion of questionnaires, and the wearing of a monitoring device (smartwatch)**.

2. **Assignment to the experimental or control group:** Participants will be matched based on key factors such as gender, age, and chronic conditions. Using these criteria, participants will be assigned to either the experimental group, where they will engage in an artistic or cultural activity, or the control group, where they will receive a free ticket to visit a museum, show, or concert. This matching ensures balanced comparison between the two groups.

3. **Artistic or cultural prescription assignment:** About 3-4 weeks after the baseline assessment, participants will be contacted by a **link worker** who will identify and match them with a suitable **art or cultural activity**. Participants in the control group will receive the free ticket at home.

4. **Programme participation:** Participants will begin attending the assigned **cultural or artistic activity**, which is scheduled to take place over upt to 25 sessions, **once per week for 1-2 hours,** over a 6 month period.

5. **Second assessment (6-month follow-up):** Six months after initiating the intervention, participants will undergo a **second assessment (first follow-up)**, which will include a **blood draw, urine test, questionnaires, and device wearing**. This is also when we will start conducting the qualitative interviews.

6. **Third assessment (12-month follow-up):** Six months after the second assessment, participants will complete a third assessment (**long-term follow-up or second follow-up)**, which will again involve a **blood draw, urine test, questionnaires, and device wearing**.

7. **Debriefing:** Debriefing will involve providing participants with a thorough explanation of the study's purpose, procedures, and findings both during a phone call and in written form once their involvement is complete. This will include answering any questions they may have, clarifying the use of their data, and offering additional information on the results or conclusions of the study. Participants will also be reminded of their rights, including their right to withdraw any personal data if desired, and they will be given the opportunity to provide feedback on their experience.

Participants will be required to attend all assessments at the Family Medicine Service of the **Ospedale Italiano in Lugano**. Questionnaires will be completed using a tablet. **Nurses and physicians** holding a GCP certificate will be responsible for conducting blood draws, reviewing medications, and overseeing the proper use of wearable devices.

Approximately 3 months will be allocated for recruiting participants, during which general practitioners (GPs) will screen potential candidates for eligibility.

Each participant will be involved in the study for 13 months, which includes:
- 1 month for baseline assessment and assignment to a cultural or artistic activity.
- 6 months for participation in the cultural or artistic activity.
- 6 months of follow-up assessments and optional interviews.

Blood will be collected at baseline, at the 6-month follow-up, and at the 12-month follow-up. The blood samples will be used to measure relevant health markers as part of the study's secondary objectives. Blood samples will be stored securely at the Ospedale Italiano and anonymized with unique participant codes.

Efforts to recruit a diverse sample through multiple GP practices in the Lugano municipality will help mitigate selection bias. To address attrition, participants will be encouraged to attend all study assessments through clear communication and regular follow-up by the research team. Additionally, dropout reasons will be monitored and recorded to help assess and adjust for this bias in the analysis. Standardized protocols for data collection and use of validated tools (questionnaires, devices) will minimize measurement bias. Regular calibration and monitoring of devices will ensure accuracy. Key factors such as sex, gender, age, and pre-existing health conditions will be controlled for in the analysis by matching participants for these variables in the experimental and control groups. Additionally, the study will take into account potential confounding factors by adjusting for them in the statistical analysis models.

4.4 Withdrawal and discontinuation

Participants may be withdrawn from the study under the following circumstances:

1. **Withdrawal of informed consent**: If a participant decides to withdraw their consent at any point during the study, they will be removed from the study immediately.
2. **Disease progression or onset**: If a participant experiences significant disease progression or develops a new health condition that impacts their ability to participate in the study or could pose a safety risk, they may be withdrawn.

In the event of withdrawal, no further procedures will be conducted. Data collected up until that point will be anonymized by replacing any personally identifiable information with the unique participant code. If the participant requests, their name will be deleted, and only the unique code will remain associated with the data. This ensures that the participant's request is respected while preserving the integrity of the study data for future analysis.

5 STATISTICS AND METHODOLOGY

5.1. Statistical analysis plan and sample size calculation

Quantitative analysis

Participant characteristics **will be summarized** at **baseline** to provide an overview of the sample. For all analyses, statistical significance will be set at **p<0.05**, but results will be interpreted based on the strength of the evidence, with **continuous p-values and 95% confidence intervals (CIs) reported**. **Acceptability of the programme** will be assessed through **participant take-up and retention**. The range and **average number of sessions attended** will be reported, along with a summary of reasons for not completing the intervention. **Feasibility of recruitment and research procedures** will be evaluated by assessing the **time required to recruit 100 participants** and analyzing the **proportion of participants completing follow-up measures** along with the **amount of missing data at baseline and follow-up**. Primary and secondary outcome measures will be summarized at **baseline and follow-ups** to assess changes over time. To evaluate the **impact of the intervention**, statistical methods such as **paired t-tests** will be used to compare **pre- and post-intervention scores on health outcomes**. Additional statistical approaches, including **linear mixed-effects models or repeated-measures ANOVA**, may be applied to account for individual variability over time. Gender will be analyzed as part of all statistical evaluations. All **quantitative analyses will be performed using Stata or R**. The

sample size of 100 participants is in line with similar feasibility studies in the field[19]. Given that feasibility studies typically aim to assess the viability and practicality of an intervention rather than definitive outcomes, a sample size of 100 is appropriate for evaluating the key aspects of program implementation and data collection methods while providing insights for future larger-scale trials.

Qualitative analysis

Interview transcripts **will be checked** for accuracy against the **audio recordings** by a designated researcher, **deidentified** (with the removal of specific names and locations to maintain participant confidentiality), and **imported into NVivo V.12** for **data management**. An **inductive thematic analysis**[38] will be conducted to identify **potential mechanisms of action** of the program, describe experiences, and explore **barriers to engagement**. Two researchers will **independently review and familiarize themselves with** an initial set of transcripts, identifying meaningful fragments of text and generating **preliminary codes** that align with the study's research aims. These **initial codes** will be entered into NVivo, where the remaining transcripts will be coded systematically. As the analysis progresses, new codes will be developed based on emerging data, while existing codes will be applied to relevant text fragments. Codes will then be **organized into groups** reflecting similar topics, with a focus on elucidating **potential mechanisms of action** of the program and **barriers to engagement**. These topic groups will serve as the foundation for the development of **preliminary and final themes**. Ongoing discussions among the research team will ensure **rigor and coherence** in theme development, with continuous **peer review and validation** to refine and finalize the thematic framework.

5.2. Handling of missing data and drop-outs

After assessing the type and quantity of missing values, a sensitive analysis will be also performed using different approaches to eliminate possible biases due to these values.
In the event of drop-outs, participants who withdraw from the study before starting the artistic or cultural activity will be replaced by recruiting new participants to maintain an adequate sample size. This ensures that the study continues to have enough participants to evaluate the feasibility and outcomes effectively.

6 REGULATORY ASPECTS AND SAFETY

6.1 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 (ClinO Art. 5, Abs 2), the HRA as well as other locally relevant legal and regulatory requirements.

6.2 (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 participant 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 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 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 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.

Follow up of (Serious) Adverse Events

Participants who terminate the study with ongoing (Serious) Adverse Events (SAEs) will be asked to participate in a final assessment.

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.

6.3 Periodic reporting of safety and general progress of the clinical trial.

Once a year, the investigator submits to the Ethics Committee a list of the safety events including the severity of the events, their causality to the intervention and the safety of the study participants. The investigator also informs the Ethics Committee about the general progress of the clinical trial (ClinO, Art. 43).

6.4 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 participants may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible. A list of all non-substantial amendments will be submitted once a year to the competent EC together with the safety report / general study progress report.

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

Upon regular study completion, the Ethics Committee is notified via BASEC within 30 days (ClinO, Art. 38). The last follow-up visit of the last study participant is defined as the end of the trial. The Sponsor 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),
- 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 (Article 38 ClinO).

All biological materials and health-related data are anonymised upon end of data analysis.

A final report is submitted to the Ethics Committee via BASEC within a year after completion or discontinuation of the study (ClinO, Art. 38).

6.6 Insurance

In the event of study-related damage or injuries, the liability of the Ente Ospedaliero Cantonale provides compensation, except for claims that arise from misconduct or gross negligence.

7 FURTHER ASPECTS

7.1 Overall ethical considerations

The study will be conducted in accordance with **ethical guidelines**, with approval sought from the Ethics Committee of the Canton of Ticino. Participants' confidentiality and rights will be protected throughout the study.

Data will be systematically uploaded for analysis to **SwitchDrive**, a secure data storage system. Participants will each be assigned a unique identifier, and quantitative data from the questionnaires will be entered into an **Excel spreadsheet** by a designated researcher and subsequently checked for accuracy by a second researcher.

Informed consent will be obtained in writing before participation, ensuring that participants understand their right to withdraw from the study at any time without any consequences to their medical care. To minimize potential biases and preserve the integrity of the data, participants will not be informed in advance whether they are assigned to the experimental or control group. Instead, they will be provided with a general explanation of the study's objectives and the existence of two groups with different activities, without specifying the nature of each group's participation. At the conclusion of the second follow-up, participants will be fully debriefed about the study design and group allocation. This approach is in line with Article 18 of the Federal Act on Research involving Human Beings. Participants will receive an appropriate debriefing both

orally and in written form, and will be asked to provide written informed consent to the use of their data.

The **well-being of participants** will be the primary concern throughout the study. Any adverse effects or unintended consequences arising from participation in the event will be monitored and addressed promptly. Participants will be provided with support resources if needed, especially if their involvement leads to unexpected emotional or psychological responses.

To ensure a **safe and supportive environment**, link workers and staff involved in the study will be adequately trained to recognize and respond to participants' needs, including managing any emotional or psychological challenges that may arise during the activities. This training will equip them to provide appropriate guidance and support, ensuring that participants feel comfortable and secure throughout their involvement in the project. If a participant requires immediate attention, link workers will promptly get in contact with the participant's GP to ensure that appropriate medical or psychological support is provided.

The recruitment process will ensure that all eligible individuals have an **equal opportunity** to participate, without discrimination based on race, gender, socioeconomic status, or other factors. Efforts will be made to accommodate participants with diverse needs, ensuring that the cultural prescriptions are accessible and inclusive.

7.2 Risk-benefit assessment

The study carries minimal risks, including discomfort from blood draws, monitoring device wear, or participation in cultural activities. However, we expect immediate benefits from the artistic or cultural activities, which may enhance participants' well-being and health outcomes. Risks of unauthorized data access are mitigated by using anonymized data, secure storage with password protection, and limited access to research team members. While the primary goal is to assess the feasibility and preliminary impact of cultural interventions, the study also offers participants the opportunity to engage in activities that may improve their health and quality of life, with results contributing to future healthcare practices.

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

To ensure quality assurance and control, several measures will be implemented throughout the study. Data entry will be regularly reviewed by a second person to ensure accuracy and consistency. All study personnel will undergo training on key aspects of the study, including ethical considerations, participant management, and proper handling of data and biological material. Additionally, regular team meetings will be held to address any issues and ensure ongoing quality management. 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. All involved parties keep the participant data strictly confidential.

8.2 Data recording and source data

Study data will be recorded using an electronic Case Report Form (eCRF) in secuTrial®, ensuring secure and standardized data collection. An **audit trail** will be maintained to track all data entries and modifications. Each participant will have an individual **eCRF**, which will not contain identifiable information such as names or birth dates but will instead use a **unique coded identifier**. This coding system ensures participant confidentiality while allowing data linkage for analysis. Access

to the eCRF will be restricted to authorized study personnel only, with role-based permissions to prevent unauthorized modifications or access.

The study will collect source data through study-specific questionnaires (administered on a tablet), laboratory test results from blood draws conducted specifically for the study, medical examinations performed as part of study assessments, and data from a wearable device. Additionally, routinely collected data, including baseline laboratory test results from the past three months and relevant pre-existing medical history or medication records, will be imported into the electronic Case Report Form (eCRF).

8.3 Confidentiality and coding

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.
The investigator has appropriate knowledge and skills in the areas of data security and data protection or is able to ensure compliance by calling in appropriate expertise (Art. 6, ClinO).
Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited.
Trial and participant data will be handled with the utmost discretion and is only accessible to authorised personnel 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 securely stored by the research team at the University on SwitchDrive, a secure cloud storage service. Access to the list will be strictly limited to authorized research personnel, protected by password authentication and two-factor verification. To prevent unauthorized or accidental disclosure, alteration, deletion, copying, or theft, data will be regularly backed up on encrypted storage media. An audit trail, in accordance with ClinO, Art. 18, will ensure traceability by maintaining a record of all data modifications and access logs.

Biological material in this study is not identified by participant name but by a unique participant number. Biological material is appropriately stored in a restricted area only accessible to the authorised personnel. Traceability is ensured through a digital tracking system that records sample collection, storage, and any subsequent handling. The biological material is preserved in temperature-controlled freezers with continuous monitoring and alarm systems to detect temperature fluctuations. Regular maintenance and calibration of cooling equipment are conducted to ensure optimal storage conditions, preventing sample degradation and maintaining the integrity of the biological material.

8.4 Retention and destruction of study data and biological material

The investigator retains all documents necessary for the identification and follow-up of the trial participants and all other original data for at least twenty years after completion or discontinuation of the clinical trial. Health-related data collected during the research project will be securely stored for a period of 10 years following the publication of the study results. This duration ensures that data are available for potential further analysis, replication studies, or verification of findings. Data storage will comply with institutional policies and regulatory requirements to protect participant confidentiality and privacy. Biological materials collected as part of the research project will be securely destroyed upon analysis. Documentation of biological material destruction will include details such as the type and quantity of materials destroyed, the method of destruction (e.g., incineration, chemical treatment), and the date of destruction. This documentation will be maintained as part of the study records and made available for audit or regulatory inspection as required.

9 MONITORING AND REGISTRATION

The Clinical Trial Unit of Ente Ospedaliero Cantonale (CTU EOC) is responsible for fulfilling the monitoring duties of this study. Regular monitoring visits will take place at the investigator's site both prior to study initiation and throughout its duration to ensure compliance with the study protocol, Good Clinical Practice (GCP), and regulatory requirements. Monitoring will include verification of informed consent documentation, adherence to inclusion and exclusion criteria, data accuracy in case report forms (CRFs), and proper handling and storage of biological samples. The extent and nature of monitoring activities will be further detailed in a study-specific monitoring plan. All source data and study documents will be accessible to monitors, and study personnel will be available to address any queries during monitoring visits.
The study will be registered in the Swiss National Clinical trial Portal (SNCTP) via BASEC in the national language of Switzerland in which recruitment is intended (Italian).

In addition, the study will be registered in a primary registry recognized by the WHO (International Clinical Trials Registry Platform: https://www.who.int/clinical-trials-registry-platform).

10. FUNDING / PUBLICATION / DECLARATION OF INTEREST

IBSA Foundation will financially contribute to the study. The study follows a transparent publication policy, ensuring timely and open access dissemination of results in accordance with ethical and regulatory standards. Authorship will be determined based on substantial contributions to study design, data collection, analysis, and manuscript preparation, following recognized guidelines. Raw data access will be limited to authorized research team members, with data sharing considered upon reasonable request and in compliance with data protection regulations.

Sex and gender analyses will be reported in the final study publication. If no effects are observed, this will also be explicitly stated. The sponsor will enter and publish a summary of the trial results in a public register as per ClinO Art. 65a within one year of study completion or discontinuation. If an interruption exceeds two years, the trial will be considered discontinued. Additionally, a lay summary of the results will be made available in BASEC in the national languages relevant to participant recruitment. The investigator will provide each participant with the lay summary at the end of the study and ensure that participants are informed about its availability in the patient information document.

Potential conflicts of interest, including financial, intellectual, and proprietary considerations, will be disclosed in study publications. The study maintains independence from external influences, with data integrity and analysis remaining the responsibility of the research team. Additional contractual agreements related to publication and data sharing are outlined in separate study documents where applicable.

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Appendix 1: Schedule of assessments

Time (hour, day, week)	**≥-7 day**	**0**	**+6 months**	**+12 months**
Visit	Information	Screening and baseline assessment	1st Follow-up assessment	2nd Follow-up assessment
Oral and written patient information	+			
Written consent		+		
Inclusion-/ exclusion criteria		+		
Blood draw		+	+	+
Clinical assessment		+	+	+
Questionnaires		+	+	+
Wearing of device		+	+	+
Intervention (lasting 6 months)		+		
Debriefing (following assessment)				+