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Mobile therapeutic attention for treatment-resistant schizophrenia (m-RESIST): a prospective multicentre feasibility study protocol in patients and their caregivers.

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Abstract

Introduction: Treatment-resistant schizophrenia (TRS) is a severe form of schizophrenia, suffered by approximately 40% in the European Union. Factors such as the persistence of positive symptoms, or higher risk of comorbidities leave clinicians with a complex scenario when treating these patients. Intervention strategies based on mHealth have demonstrated their ability to support and promote self-management-based strategies. m-RESIST, an innovative mHealth solution, has been developed specifically for TRS patients and their caregivers, based on novel technology and offering high modular and flexible functioning. As intervention in TRS is a challenge, it is necessary to perform a feasibility study before the cost-effectiveness testing stage.

Methods and analysis: This manuscript describes the protocol for a prospective multicentre feasibility study in 45 TRS patients and their caregivers who will be attended in the public health system of three localities: Hospital Santa Creu Sant Pau (Barcelona, Spain), Semmelweis University (Budapest, Hungary) and the Gertner Institute & Sheba Medical Center (Tel-Aviv, Israel). The primary aim is to investigate the feasibility and acceptability of the m-RESIST solution, configured by three mHealth tools, app, wearables, and a web-based platform. The solution collect data about acceptability, usability and satisfaction, together with preliminary data on perceived quality of life, symptoms and economic variables. The secondary aim is to collect preliminary data on change in perceived quality of life, symptoms and economic variables.

Ethics and dissemination: This study protocol, funded by the Horizon 2020 Framework Programme of the European Union, has the approval of the Ethical Committees of the participating institutions. Participants will be fully informed of the purpose and procedures of the study and signed written inform consents will be obtained. The results will be published in peer-reviewed journals and presented in scientific conferences to ensure widespread dissemination.

Trial Registration: The trial registered at ClinicalTrials.gov in February 2017 (NCT03064776).

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STRENGTHS AND LIMITATIONS

- To the authors' knowledge, m-RESIST is the first mHealth platform specifically addressed to TRS.

- The m-RESIST solution includes a sophisticated tool to detect early warning signs for preventing symptoms before they occur.

  - This study promotes the involvement of the caregivers in the therapeutic process and a closer monitoring and communication with clinicians.

  - The outcomes of this study will help in future performance of a cost-effectiveness randomised controlled trial.

  - The study focuses on feasibility and acceptability, so any differences found in outcomes should be treated with caution due to the design (small sample size, absence of control group, and short length of intervention and follow-up period).

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1. INTRODUCTION

1.1 Background

In the European Union, between 0.2% and 2.6% of the population suffer from psychotic disorders [1]. The largest group is patients with schizophrenia, and around 40% are patients whose condition does not respond satisfactorily to adequate treatment and clearly have harder-to-treat psychotic symptoms, despite adherence to current optimized treatment [4]. These patients are referred to as treatment-resistant schizophrenia (TRS) patients [2,3]. TRS is a complex phenomenon influenced by variety in schizophrenia subtypes, psychiatric comorbidity, and coexisting medical illnesses. Such patients pose a common, challenging presentation to psychiatric and primary care clinicians, generating a financial burden on society due to frequent emergency visits, hospitalizations and chronic use of polytherapy [5]. Moreover, there is also a huge impact in terms of the humanistic burden, which concerns patients and caregivers, involving several dimensions such as quality of life, treatment side effects, caregiver burden, social impairment, and high mortality [6].

Standard intervention in patients with TRS is challenging due to persistence of positive symptoms, extensive periods of hospitalization and elevated risk of somatic and psychiatric comorbidities. Improvement obtained by current drug therapy, such as clozapine alone or in combination with another antipsychotic/mood stabilizer, is frequently not effective enough to achieve remission in TRS patients [7]. Therefore, development of innovative evidence-based interventions adjunctive to pharmacological and psychosocial treatment is needed.

Studies have shown feasibility, acceptability and also preliminary efficacy of mobile interventions (mHealth) for schizophrenia [8,9]. Intervention strategies based on mHealth have demonstrated their ability to support and promote self-management-based strategies in psychotic disorders.

Mobile interventions may be effective in preventing relapses, increasing treatment adherence, and relieving some of the symptoms, though the effects on social functioning remain unclear [10–14]. Smartphone ownership among people with schizophrenia is relatively high and increasing [15]. Moreover, patients also seem to be willing and able to use smartphones to monitor their symptoms, engage in therapeutic interventions and increase physical exercise [8]. Alvarez-Jimenez and colleagues performed a meta-analysis of 12 studies, where evidence on acceptability, feasibility, safety and benefits of online and mobile-based interventions for psychosis were analysed 16. Results showed that 74–86% of patients used web-based interventions efficiently, 75–92% perceived them as positive and useful, and 70–86% of patients completed or engaged with the interventions during follow-up. On the other hand,

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26% of patients experienced difficulties in using web-based psychoeducation and cognitive behaviour therapy (CBT), where the main causes were lack of motivation, poor engagement and poor understanding [16]. It is noteworthy that no published mHealth studies have focused on patients with TRS, becoming a particular challenge for designing novel interventions. Therefore, attention should be paid to exploring the recruitment of patients, in delivering an mHealth intervention easy enough and interesting to use, and in minimizing the amount of drop-outs in future mHealth studies in TRS. Performing a feasibility study would be helpful to explore acceptability and adequacy of intervention components, to assess recruitment and assessment procedures, and to ensure if changes will be necessary during a subsequent cost-effectiveness RCT.

This study protocol (Version 1. Date: 05 July 2016) is part of a European research project, co-funded by the Horizon 2020 Framework Programme of the European Union (grant agreement nº 643552). This project aims to develop and test the use of m-RESIST, a mobile system based on Information and Communications Technology (ICT), addressed to empower patients suffering from TRS and to involve their caregivers. This platform offers a holistic approach to integrate psychiatric and psychological assistance, offering a better monitoring of patients through a personalised and optimised therapeutic process, promoting acceptance and self-management of the condition, and potentiating a proactive role of patients and caregivers in the therapeutic process.

As stated by Aranda-Jan et al. (17), the main considerations for an effective m-Health project are an appropriate project design (adapted to the local context), availability of technology and resources, involvement of stakeholders and integration to the healthcare system. According to these conditions, a qualitative study about the receptivity of TRS patients, caregivers and clinicians toward possible m-RESIST components was performed during the first stage of the m-RESIST solution development. Hypothetic positive acceptability of the solution in terms of usefulness, increase of patient's empowerment and social contact promotion was shown (9).

The current study protocol corresponds to the second stage of the project, aimed at ensuring that the designed solution satisfies the needs of end-users. To explore this, a feasibility study will be performed and the m-RESIST prototype will be deployed with the target group (patients, caregivers, clinicians) in an environment as close as possible to real life settings.

1.2 Aims and hypothesis

The objectives of this study are:

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- to investigate the attrition of delivering m-RESIST solution as intended in TRS: willingness to enrol, non-usage attrition and drop-out attrition
- to investigate the acceptability of m-RESIST solution in TRS patients, caregivers and clinicians
- to examine participants' satisfaction and m-RESIST solution's usability
- to explore the suitability and availability of proposed clinical, functional and economic outcomes measures

The hypotheses are:

1- The m-RESIST solution will have acceptable rates of willingness to enrol, non-usage and drop-out attrition in TRS patients.

2- The m-RESIST solution will be highly accepted by TRS patients, caregivers and clinicians in terms of acceptability, usability and satisfaction.

3- The proposed clinical, functional and economic outcomes measures will be suitable and available for TRS.

2. METHODS AND ANALYSIS

The following methods adhere to the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guidelines for the reporting of study protocols (18).

2.1. Study design and setting

This is a prospective multicentre feasibility study, without a control group, following an iterative process in patients with TRS and their caregivers. Participants will be recruited from three sites: Gertner Institute & Sheba Medical Centre-Psychiatric Division (Tel Aviv, Israel), Semmelweis University-Department of Psychiatry and Psychotherapy (Budapest, Hungary), and Hospital de la Santa Creu i Sant Pau-Unit of Psychiatry (Barcelona, Spain). These sites provide full-spectrum mental health services to adult people from their catchment area, and have wide experience in participating in large scale clinical trials in patients with schizophrenia.

2.2 Participants

A total of 45 TRS patients (15 per centre), with their caregivers, will be selected for invitation to participate by researchers. The eligibility for participation will be based on the inclusion and exclusion criteria described in table 1. Due to the voluntary nature of participation in clinical trials, participants may leave the study without having to specify their reasons. The investigators could also dismiss a participant from the study whenever they consider it appropriate.

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Reasons for withdrawal include events such as inpatient psychiatric hospitalization. A participant will be withdrawn from the study participation if s/he:

- Refuses to cooperate.
- Wishes to drop-out (in this instance a specific reason must be recorded by the investigator).
- Experiences adverse events sufficiently severe that, in the opinion of the investigator, it would be harmful to continue in the study.
- Has a general medical condition that, in the opinion of the investigator, it would be harmful to continue in the study.
- Does not complete the study as outlined in the study protocol.

2.3 Intervention

In the current study the intervention will involve patients and their caregivers, and the main actors involved in the deployment of the m-RESIST solution will be a psychiatrist, a psychologist and a case manager. The key aim of the intervention delivered by the m-RESIST solution is to engage TRS patients, together with their caregivers, in an active participation in therapeutic processes, and empower them to enable the self-management of their condition. To achieve this objective, the intervention is supported by three mHealth tools: wearable (smartwatch), mobile app and web-based platform (see figure 1). Patient engagement will be measured by the number of days that the m-RESIST was used during the 3 months of intervention. Data for usage will be captured automatically by the m-RESIST software.

The functionality of the smartphone is based on the m-RESIST app. Through this app, patients will have access to educational content about TRS condition and related issues; track their early warning signs, symptoms and biological variables; ask for help by questionnaires or the "alarm bottom"; receive and practice helpful CBT-based coping strategies; and exchange messages with their caregiver or healthcare provider.

The wearable will consist of a smartwatch that will collect data from patients and send it wirelessly to the smartphone. Sensor data will be recorded through automatic passive upload. The variables collected will be level of activity, heart rate, sleep pattern and steps counter.

The web-based platform is the tool that the healthcare providers (case manager, psychiatrist, psychologist) will use to collect assessment data, to monitor patients' state and review data

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collected by sensors, to communicate by texting with patients, caregivers and other professionals, and to consult recommendations (based on guidelines and experts' opinion).

The m-RESIST intervention has been designed in order to meet the following assumptions:

Be focused on key problems: before starting the m-RESIST intervention, the patient's early warning signs (EWS) and current problems will be assessed. There will be two outputs. First, the patient's relapse signature configured by the 3 main EWS presented by the patient before a worsening occurs. Each EWS will be linked with a predefined (based on CBT) or tailored (based on patient's experience) coping strategy. These strategies will be triggered as a recommendation through the app when patients express distress or the system detects risk of worsening. The second output will be the treatment plan which will identify the 3 main problems and corresponding goals in the patient's life, and link these goals with a specific module of intervention. This process will be agreed between patient, caregiver and clinician.

Be modular and tailored to the patient's condition: two categories of interventions have been designed, basal and risk intervention (see definition and characteristics in table 2). They are related with the list of problems mentioned previously, in order to set the most appropriate intervention depending on the patient's situation.

Be capable of detecting worsening: the m-RESIST intervention is capable of changing the system's triggers to patients when worsening is detected by means of the baseline sensor and clinical profiles. During a 15-day period, the patients will use the smartwatch and the smartphone to capture continuously multidimensional sensor data. The baseline sensor profile will be based on the analyses of these data. Furthermore, a complete assessment of clinical variables (e.g. symptoms, risk behaviours, functionality, and adherence) will also be performed in this period. The baseline clinical profile will be based on the analysis of these data. A set of predefined algorithms will detect significant changes in predefined thresholds, and to trigger specific questionnaires, recommendations and notifications. Whenever a moderate or high risk of an oncoming episode of worsening is detected, the clinical team will be alerted and the patient will be offered tailored recommendations or emergency assistance.

Concomitant Therapy: Apart from the intervention associated with the m-RESIST solution, patients will keep receiving their treatment-as-usual (including outpatient case management, linkage to services and medication monitoring). If it is necessary to make changes in the psychiatric treatment, they will be recorded in the patient profile created in the platform.

2.5 Outcomes

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The evaluation framework to understand the factors affecting the user experience and acceptance of the m-RESIST solution among various stakeholders , as well as the main determinants affecting user experience at a feasibility level, will follow the Living Lab approach (19). It is defined as "a user-centric research methodology for sensing, prototyping, validating and refining complex solutions in multiple and evolving real-world contexts". Living Lab research goes beyond mere usability studies and acceptance studies, as it also takes the impact of the context of use into account. A multi-methodological approach, with both qualitative and quantitative methodologies, is chosen so as to be able to capture different aspects of the implemented solution.

The protocol diagram based on SPIRIT guideline (18) provides an overview of the measures used in the trial and their time points (see table 3).

Primary outcomes

The primary outcomes include feasibility and acceptability of using the m-RESIST solution. Qualitative and quantitative feedback will be collected to identify the main determinants of experience and acceptance of the m-RESIST solution.

Feasibility will be examined by composite analysis of the following elements of attrition(20,21)

Willingness to enrol: the proportion of patients approached about the study that will proceed to the consent stage. Operational criteria definition: ≥70% of patients approached will agree to enrol;

- Dropout attrition: the proportion of participants who fail to complete the study protocol, and thus do not complete study assessments. Operational criteria definition: <15% of participants are lost to follow-up or withdraw from study;

- Non-usage attrition: the proportion of participants who do not drop out (e.g., who are still completing the follow-up), but who stop using the m-RESIST tools (smartwatch, app). Operational criteria definition: <15% of participants will stop using devices;

- Compliance: extent to which participants experience the content of the m-RESIST intervention, measured by number of logins, time spent online, number of questionnaires completed, number of messages sent and answered, and number of successful appointments.

Acceptability of the m-RESIST solution will be assessed in terms of acceptability, usability and satisfaction in TRS patients, caregivers and clinicians. Critical measures are the following:

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- A questionnaire, delivered by online data collection (Qualtrics software), which will use a combination of survey questions (4-point Likert scale) and open questions. The survey will explore ease of use, perceived usefulness, attitude/intention and content quality. The score for each variable will be calculated by summing the scores within each variable section and dividing it by the maximum score of the section. The open questions will explore lasting impressions and recommendations.

- An interval question, aimed at better capturing a more constant experience of the participants, will be asked every week on different days and at different times. The question (e.g. what is it like to use the m-RESIST solution?) will remain the same throughout the pilot and will be sent to participants via m-RESIST message system.

- A modified version of the Technology Acceptance Model scale [TAM](22), adapted to TRS patients by the research team. It will measure, at the end of the study, the following dimensions: perceived usefulness, perceived ease of use, intention, compatibility, subjective norm, facilitators and habit.

Finally, satisfaction will be measured by the Client Satisfaction Questionnaire-8 [CSQ-8](23).

Secondary outcomes

A complete clinical and economic evaluation would be premature in this feasibility study, due to the small sample. However, it will be useful to collect necessary parameters for planning a full prospective RCT to test the cost-effectiveness of m-RESIST solution. Completion rates and missing data will be explored. Operational criteria definition for missing data: <10% of each set of secondary outcomes are missed during study data collection.

The proposed clinical, functional and economic outcomes and measures are the following:

Clinical outcomes:

- Socio-demographic and clinical characteristics (e.g. years of evolution, past and current treatment, comorbidities) will be collected by using a semi-structured interview.
- Severity of symptoms will be assessed using the instruments Positive and Negative Syndrome Scale [PANSS](24) and Calgary Depression Scale(CDS)(25).
- Insight will be assessed using the instrument Scale Unawareness Mental disorders (SUMD)(26).
- Adherence will be assessed using the instrument Adherence to Refills and Medications Scale(27).

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Functional outcomes:

- Functionality will be assessed using the instruments Clinical Global Impression-Schizophrenia [CGI-SCH](28), Global Assessment of Functioning [GAF](29) and Social Functioning Scale [SFS](30).

- Perceived quality of life will be assessed using the instrument EuroQol 5 dimensions questionnaire [EQ-5D] (31).

Economic and organizational outcomes:

Questionnaires with open questions ad-hoc form and semi-structured interviews will be used to assess the *use of resources* (e.g. unit cost of personnel of remote or face to face visits, number of emergency admissions and length of stay) and the *impact* of m-RESIST *in organization* (questions regarding effects on the structure, work process and the culture of the organization).

Finally, safety measures will also be collected before and after participating in the study. The presence of serious and non-serious adverse events, defined as any clinical change or illness reported during the study, will be monitored on every clinical visit. The adverse events observed when carrying out the study, either by the clinician or by the patient him/herself and regardless of the causality relationship ascribed, will be recorded in the clinical records and at the patient's dashboard.

2.4 Participant timeline

The study will consist of four periods: recruitment, pre-intervention, intervention and analyses.

1) <u>Recruitment period,</u> aimed at contacting and checking the eligibility of candidates. The outputs of an in-depth report about healthcare routes and clinical pathways in the three participant regions, made within the context of the m-RESIST project, has helped to identify the strengths and weakness of the recruitment capabilities. In order to reach the total sample of participants, two recruitment strategies will be used. Leaflets to promote the study will be distributed to healthcare providers, informing them about the study and inviting them to contact the research staff if potential participants are identified. In addition, research staff at the recruitment sites will approach eligible patients directly to suggest participating in the study. Informed consent signature for TRS patient and caregiver will be obtained if inclusion and exclusion criteria are met, and both patient and caregiver agree to participate in the study.

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2) <u>Pre-Intervention period</u>, aimed at training the participants in using the smartwatch and the app, and collecting clinical and sensor baseline information. At the beginning of the pre-intervention period, patients will be given the study smartwatch and smartphone with m-RESIST app pre-installed, and caregivers will be given permission to install the app in their own smartphone. Both will be trained by the research staff on how to use the functions of the smartwatch and the different features of the app. Research staff will also provide patients and caregivers with a help user guide and an online video tutorial. Patients will be asked to wear the smartwatch for a period of at least 15 days, in order to collect enough sensor data to establish the baseline sensor profile. Furthermore, patients and caregivers will also be encouraged to use and familiarise themselves with the app by consulting the educational content and using the messaging system. Patients will also attend a clinical assessment, where secondary outcomes will be collected (see table 3). At the end of the pre-intervention period, the key elements to deliver a tailored intervention (relapse signature and treatment plan) will be explored.

3) <u>Intervention period</u>, aimed at testing the features and action flows that configure the m-RESIST interventions, and at assessing the experience of participants. At the beginning of the intervention, the treatment plan will be defined and the corresponding basal intervention will be activated. Participants will use the solution over 3-months, and appointments with clinicians will be scheduled every 15 days. This period will be comprised of 4 online visits and 3 onsite visits. In each visit the treatment plan will be reviewed, the CGI scale and measure of patients' perceived health status will be assessed, and changes in the current antipsychotic treatment and potential adverse events will be explored. At the end of this period, a final visit will be held, made up of the full global assessment, to get post-test measures of the variables assessed in the pre-intervention period (see table 3).

4) <u>Analyses period,</u> aimed at the evaluation of the study primary and secondary outcomes.

2.5 Sample size

This protocol study is a non-randomised feasibility study where the primary outcomes are not measures of intervention effects, but factors that could affect successfully completing a RCT. The proposed sample size of 45 patients, with their corresponding caregivers, is consistent with the recommendations for feasibility studies (32,33).

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2.6 Data Analysis

Analysis of primary outcomes:

Descriptive statistics will be used to ascertain *feasibility*. Attrition components will be summarised for participants, overall and in relation to selected baseline characteristics. Differences between followed up patients and those who were lost to follow-up will be examined in terms of baseline characteristics, by a paired sample T-Test (normal distribution) or Wilcoxon signed-rank test (non-normal distribution).

Quantitative and qualitative data for *acceptability* and *usability* will be examined:

- Quantitative data: descriptive statistics for average scores in acceptability and usability variables (perceived ease of use, perceived use, content quality, attitudes/intention and experience), and in satisfaction questionnaire, will be calculated. Group differences will be analyzed by a paired sample T-Test (normal distribution) or Wilcoxon signed-rank test (non-normal distribution). The following assumptions will be tested: perceived usefulness and perceived ease of use will influence attitude, and so the intention to use the solution; a direct influence of perceived usefulness on the intention of use will be found; perceived ease of use will influence the perceived usefulness; perceived quality of content will influence the user satisfaction, and respectively the perceived usefulness and ease of use of the m-RESIST solution.

- Qualitative data: for the analysis of self-reported data collected from Qualtrics open questions and from interval question, qualitative thematic/content analysis will be conducted as proposed by Mayring (34). This method is a technique of summarization, whereby categories are created in an inductive procedure by reducing, paraphrasing and generalizing relevant text passages. Patterns in the text will be found and coded in order to search for themes in the data.

Analysis of secondary outcomes:

Descriptive statistics (means and standard deviations or percentages) will be used to summarise baseline socio-demographic and clinical characteristics of participants.

Descriptive statics will be used to explore availability and utility of data relating to proposed clinical, functional and economic outcomes measures, and a range of summary measures will be presented in the final statistical outputs.

Analysis Statistical analysis

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Analyses will be conducted using STATA 13 . Descriptive statistics will be used to summarise clinical and demographic characteristics of patients. Feasibility of trial procedures will be examined using proportions and 95% confidence intervals for assessments of feasibility and acceptability in terms of recruitment, consent, dropout, follow-up and integrity of double blinding. The variance observed in this sample will be used for sample size calculation for the future RCT. As recommended by Browne [37] and Lancaster and colleagues

2.7 Quality Control

The researcher will ensure the accuracy and integrity of the data and reports required. The data included in the m-RESIST derived from source documents, will be consistent with such documents, otherwise the discrepancies will be justified. The researcher will keep the study documents for at least 5 years after the study is completed.

Data monitoring will be done by the ethics committee of each site. Clinicians will have available all the study-related files, allowing direct access to data or source documents to perform monitoring, audit, review by the ethics committee or any inspection by the competent authorities. All data collected will only be accessible to m-RESIST partners.

3. ETHICS AND DISSEMINATION

Before entering the study, all participants will be legally competent and will provide written informed consent to the clinical team. All the data collected will be treated confidentially and analysed anonymously. The study protocol has already been approved by the local Research Ethics Committee of each site: Gertner Institute (Tel-Aviv, Israel), Semmelweis University (Budapest, Hungary) and Hospital de la Santa Creu i Sant Pau (Barcelona, Spain). Any protocol amendments will be made though the Ethics Committee of each site. The results of this study will be published in international peer-review journals. A wide dissemination of the project results is planned to take place at European and International level. Patients, caregivers, health professionals, institutions and stakeholders will be the main targets of the m-RESIST outcome spread.

4. STUDY STATUS

At the time of the elaboration of this manuscript the m-RESIST solution was in a testing phase by technological and clinical partners belonging to the project's consortium, and potential participants were assessed.

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5. DISCUSSION

This article summarizes the protocol of a multicentre feasibility study aimed at assessing rates of attrition and acceptability of the m-RESIST solution. This information will provide important parameters to consider running a cost-effective RCT, and to identify potential constraints and possible solutions.

TRS is a complex phenomenon usually excluded from RCT. Our research group, integrated by experienced clinicians and researchers in TRS patients follow-up, is interested in understanding the factors that lead to resistance or response in this patient population, and in developing new approaches to treatment.

The m-RESIST project is targeted towards facing the "high end" (in terms of severity) of psychiatric morbidity–TRS, which is characterized by a chronic and continuous prolonged course, low level of adherence, insight and judgement, and is particularly challenging also due to impairments in interpersonal communication. These challenges reduce the possibility of the patients taking full responsibility for their treatment and self-care, and communicating their needs and changes in clinical state. The TRS multi-dimensional presentation, diverse course, and multi-dimensional functioning impairment involves treating TRS patients by a multidimensional approach, including multidisciplinary teamwork and different interventions.

Current trends in treating schizophrenia result from general social trends and recent evolvements in medical care, including implementation of evidence-based medicine tools and novel technological developments in the field of healthcare, specifically regarding data collection using various sensors, data processing and communication. Healthcare systems are also moving towards personalized medicine, combining a large body of personal and disease-related information. The aforementioned view of the heterogeneous complicated needs of TRS patients, their caregivers and treating clinicians, emphasizes the need for a comprehensive system that will allow and encourage different modes of communication between potential users involved in the clinical complexity of the disease.

The m-RESIST solution is an initiative targeted to create a hybrid system aimed at optimization of chronic care by integrating technological solutions, and assisting clinicians in their decision-making process. The developed solution also enhances the involvement of patients in their own treatment process, encouraging active participation in therapeutic processes, self-managing of their condition, thus reinforcing a sense of empowerment and improving quality of life.

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The novel principles include new technology, high modularity and flexibility, and personalized response to heterogenic needs. In order to overcome the disadvantages of the current healthcare system, m-RESIST solution intends to provide continuity of care, immediate attention for prevention of worsening and hospitalizations, automated and personalised interventions and recommendations, as well as easy and efficient communication between the solution users.

This study has limitations in that it is mainly a feasibility study, and lacks randomisation and a control group. It may have a high dropout rate, so in order to establish predictors of discontinuation the characteristics of compliant patients will be compared with those who have not completed all outcomes measures at the two time points or were lost to follow-up. Furthermore, studies in mHealth require a minimum range of skills to use the tools. In this regard, TRS patients can present limitations in using the devices due to some degree of cognitive impairment, and caregivers could show a poorer knowledge of the Internet and computer use devices due to their age range.

However, and despite of the aforementioned limitations, the findings and outputs from the proposed study will take us closer to designing a future cost-effectiveness trial in treatment-resistant patients.

References

1.   Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2011 Sep;21(9):655–79.

2.   Elkis H, Buckley PF. Treatment-Resistant Schizophrenia. The Psychiatric clinics of North America. United States; 2016 Jun;39(2):239–65.

3.   Conley RR, Kelly DL. Management of treatment resistance in schizophrenia. Biological psychiatry. United States; 2001 Dec;50(11):898–911.

4.   Kennedy JL, Altar CA, Taylor DL, Degtiar I, Hornberger JC. The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. International clinical psychopharmacology. 2014 Mar;29(2):63–76.

5.   de Silva J, Hanwella R, de Silva VA. Direct and indirect cost of schizophrenia in outpatients treated in a tertiary care psychiatry unit. The Ceylon medical journal. Sri Lanka; 2012 Mar;57(1):14–8.

6.   A. Millier, U. Schmidt b, M.C. Angermeyer c D, E DC, E VM, F MT, G NC-S. Humanistic burden in schizophrenia: A literature review. Journal of Psychiatric Research [Internet]. Pergamon; 2014 Jul 1 [cited 2017 Sep 14];54:85–93. Available from: https://xpv.uab.cat/science/article/pii/,DanaInfo=.awxyCwholvloou4sr9Qu76+S002239 5614001034?via%253Dihub

7.   Samara MT, Dold M, Gianatsi M, Nikolakopoulou A, Helfer B, Salanti G, et al. Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia: A Network Meta-analysis. JAMA psychiatry. United States; 2016 Mar;73(3):199–210.

8.   Firth J, Torous J. Smartphone Apps for Schizophrenia: A Systematic Review. JMIR

16

mHealth and uHealth. Canada; 2015 Nov;3(4):e102.

9. Huerta-Ramos E, Escobar-Villegas MS, Rubinstein K, Unoka ZS, Grasa E, Hospedales M, et al. Measuring Users' Receptivity Toward an Integral Intervention Model Based on mHealth Solutions for Patients With Treatment-Resistant Schizophrenia (m-RESIST): A Qualitative Study. JMIR mHealth and uHealth. Canada; 2016 Sep;4(3):e112.

10. Spaniel F, Vohlidka P, Kozeny J, Novak T, Hrdlicka J, Motlova L, et al. The Information Technology Aided Relapse Prevention Programme in Schizophrenia: an extension of a mirror-design follow-up. International journal of clinical practice. England; 2008 Dec;62(12):1943–6.

11. Granholm E, Ben-Zeev D, Link PC, Bradshaw KR, Holden JL. Mobile Assessment and Treatment for Schizophrenia (MATS): a pilot trial of an interactive text-messaging intervention for medication adherence, socialization, and auditory hallucinations. Schizophrenia bulletin. United States; 2012 May;38(3):414–25.

12. Ben-Zeev D, Brenner CJ, Begale M, Duffecy J, Mohr DC, Mueser KT. Feasibility, acceptability, and preliminary efficacy of a smartphone intervention for schizophrenia. Schizophrenia bulletin. United States; 2014 Nov;40(6):1244–53.

13. Kimhy D, Vakhrusheva J, Bartels MN, Armstrong HF, Ballon JS, Khan S, et al. Aerobic fitness and body mass index in individuals with schizophrenia: Implications for neurocognition and daily functioning. Psychiatry research. Ireland; 2014 Dec;220(3):784–91.

14. Ben-Zeev D, Wang R, Abdullah S, Brian R, Scherer EA, Mistler LA, et al. Mobile Behavioral Sensing for Outpatients and Inpatients With Schizophrenia. Psychiatric services (Washington, DC). United States; 2016 May;67(5):558–61.

15. Firth J, Cotter J, Torous J, Bucci S, Firth JA, Yung AR. Mobile Phone Ownership and Endorsement of "mHealth" Among People With Psychosis: A Meta-analysis of Cross-sectional Studies. Schizophrenia bulletin. United States; 2016 Mar;42(2):448–55.

16. Alvarez-Jimenez M, Alcazar-Corcoles MA, Gonzalez-Blanch C, Bendall S, McGorry PD, Gleeson JF. Online, social media and mobile technologies for psychosis treatment: a systematic review on novel user-led interventions. Schizophrenia research. Netherlands; 2014 Jun;156(1):96–106.

17. Aranda-Jan CB, Mohutsiwa-Dibe N, Loukanova S. Systematic review on what works, what does not work and why of implementation of mobile health (mHealth) projects in Africa. BMC public health. England; 2014 Feb;14:188.

18. Chan A-W, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ (Clinical research ed). England; 2013 Jan;346:e7586.

19. Eriksson M, Niitamo V, Oyj N, Kulkki S. State-of-the-art in utilizing Living Labs approach to user- centric ICT innovation - a European approach . Technology [Internet]. 2005;1(13):1–13. Available from: http://openlivinglabs.i2cat.cat/documents/SOA_LivingLabs.pdf

20. Eysenbach G. The law of attrition. Journal of medical Internet research. Canada; 2005 Mar;7(1):e11.

21. Eldridge SM, Lancaster GA, Campbell MJ, Thabane L, Hopewell S, Coleman CL, et al. Defining Feasibility and Pilot Studies in Preparation for Randomised Controlled Trials: Development of a Conceptual Framework. PloS one. United States; 2016;11(3):e0150205.

22. Davis FD. A technology acceptance model for empirically testing new end-user information systems: Theory and results. Massachusetts Institute of Technology; 1985.

23. Attkisson C. Client Satisfaction Questionnaire. Attkisson & Pascoe. 2008;1–3.

24. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia bulletin. United States; 1987;13(2):261–76.

25. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics.

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Schizophrenia research. Netherlands; 1990;3(4):247–51.

26. Amador XF, Strauss DH, Yale SA, Flaum MM, Endicott J, Gorman JM. Assessment of insight in psychosis. The American journal of psychiatry. United States; 1993 Jun;150(6):873–9.

27. Kripalani S, Risser J, Gatti ME, Jacobson TA. Development and evaluation of the Adherence to Refills and Medications Scale (ARMS) among low-literacy patients with chronic disease. Value in Health. Elsevier; 2009;12(1):118–23.

28. Haro JM, Kamath SA, Ochoa S, Novick D, Rele K, Fargas A, et al. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. Acta psychiatrica Scandinavica Supplementum. Denmark; 2003;(416):16–23.

29. Endicott J, RL S, JL F, Cohen J. The global assessment scale: A procedure for measuring overall severity of psychiatric disturbance. Archives of General Psychiatry [Internet]. 1976 Jun 1;33(6):766–71. Available from: http://dx.doi.org/10.1001/archpsyc.1976.01770060086012

30. Birchwood M, Smith J, Cochrane R, Wetton S, Copestake S. The Social Functioning Scale. The development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. The British Journal of Psychiatry [Internet]. 1990 Dec 1;157(6):853 LP-859. Available from: http://bjp.rcpsych.org/content/157/6/853.abstract

31. Brooks R. EuroQol: the current state of play. Health policy (Amsterdam, Netherlands) [Internet]. 1996;37(1):53–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10158943

32. Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. BMC medical research methodology. England; 2010 Jul;10:67.

33. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC medical research methodology. England; 2010 Jan;10:1.

34. Mayring P. Qualitative content analysis: theoretical foundation, basic procedures and software solution. 143 [Internet]. 2014;(JANUARY 2014):143. Available from: http://www.ssoar.info/ssoar/handle/document/39517

35. Andreasen NC, Carpenter WTJ, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. The American journal of psychiatry. United States; 2005 Mar;162(3):441–9.

36. Suzuki T, Remington G, Mulsant BH, Uchida H, Rajji TK, Graff-Guerrero A, et al. Defining treatment-resistant schizophrenia and response to antipsychotics: a review and recommendation. Psychiatry research. Ireland; 2012 May;197(1–2):1–6.

37. Elkis H, Meltzer HY. [Refractory schizophrenia]. Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999). Brazil; 2007 Oct;29 Suppl 2:S41-7.

38. Atkinson C, Greenfield TK. The client satisfaction questionnaire (CSQ) scales and the service satisfaction scale-30 (SSS-30). Outcomes Assessment in Clinical Practice Williams & Wilkins. 1995;120–7.

39. EuroQol--a new facility for the measurement of health-related quality of life. Health policy (Amsterdam, Netherlands). Ireland; 1990 Dec;16(3):199–208.

Author's contribution

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Authors AA and KR wrote the first draft of this study protocol. Authors EG and IC conceived the idea of the study and participated in the design of the solution. Author EJ, MI and AS served as advisors in this project and provided their expertise in studies in schizophrenia. VV and JC provided their expertise in quality and health assessments. AC, ZU and KF collaborated in the development of the intervention. SV, MS and TC collaborated in the definition and creation of the technological solution. EH and SM collaborated to the writing of the manuscript. Authors JB and MH served as a coordinators of the study. All authors contributed to the revising of the manuscript and writing of the final version of the manuscript, and gave their approval for the submission.

Competing Interests

The authors declare that they have no competing interests

Table 1- Inclusion and exclusion criteria for the study

Inclusion Criteria	Exclusion Criteria
1. Patients with age between 18 - 45 years old with a diagnosis of Schizophrenia according to DSM-V criteria. 2. Duration of disease less than 15 years. 3. Meet criteria for TRS (*see operational definition below). 4. Used to ICT tools and physical capability to use them. 5. Presence (and willingness to participate) of a caregiver or informal carer.	1. Meet criteria for remission according to the Remission of Schizophrenia Working Group [17]. 2. Presence of delusions mainly related with their therapists or with new technologies. 3. To have hearing, vision or motor impairment that makes impossible to operate a smartphone. 4. The caregiver or informal carer is not used to ICT tools or has physical incapability to use them. 5. Presence of intellectual developmental disability.
*Operational definition of treatment-resistant schizophrenia, modified from Suzuki and colleagues [18]: 1) Patients having at least two failed adequate trials with different antipsychotics (at chlorpromazine-equivalent doses of ≥600mg/day for ≥6 consecutive weeks) as well as scores of ≥4 on the Clinical Global Impression-Severity (CGI-SCH) and ≤50 on the Global Assessment of Functioning (GAF) scales; OR 2) Patients with clozapine ongoing treatment due to meeting treatment-resistant criteria as well as scores of ≥4 on the CGI-SCH and ≤50 on the GAF scale. Some patients may be considered pseudo-resistant to treatment [19]. In this case, presence of active symptoms may be influenced by psychiatric and medical conditions such as social isolation, consumption of toxic substances, presence of nutritional and medical problems, inappropriate health habits which may substantially contribute to poor responses or insufficient effects of medication. Data regarding these conditions will be collected.	

Table 2- m-RESIST modules of intervention

	Basal intervention	Risk intervention
Aim	oriented to develop abilities to deal with symptoms and early warning signs, to reinforce the involvement in the treatment plan, and to solve problems influenced by an unhealthy lifestyle	oriented to deal with possible situations of worsening (e.g. detection of risk behaviours)
Modules	Integrated by three modules: symptoms management, treatment adherence and healthy lifestyle	Integrated by one module: risk
Core elements	Relapse signature identification, coping strategies selection	Risk scale
Activation Triggers	External trigger: any of the modules can be activated by clinicians through the web-based platform (m-RESIST dashboard)	Internal trigger: when the system itself detect risk situations such as significant changes in threshold of specific sensor data External trigger: patients or caregivers ask for help by the app's alarm bottom
Actions involved	Delivery of a basic set of questions by the app, to measure patients' clinical status and appropriate follow	Delivery of appropriate questions, to check patient's current condition and to send specific recommendations

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	up questions or recommendations depending on the patients' answers; use of reminders and psychoeducational content to help patients	messages or notifications depending on the patients' answers (by the app)

Table 3- Schedule of study protocol periods and assessments

	STUDY PERIOD									
	Recruitment	Pre-Intervention	Intervention							Final visit
TIMEPOINT		*V0*	*V1*	*V2*	*V3*	*V4*	*V5*	*V6*	*V7*
RECRUITMENT:									
Eligibility screen	X								
Informed consent	X								
Training devices	X								
PRE-INTERVENTION		X							
INTERVENTION									
ASSESSMENTS:									
Demographic Data		X							
Psychiatric and Medical Background		X							
Attrition	X	X	X	X	X	X	X	X	X
Qualtrics survey (Experience user questionnaire)			X		X		X		X
TAM(22)									X
CSQ-8 (38)									X
PANSS (24)		X							X
CDS(25)		X							X
SUMD (26)		X							X
ARMS (27)		X							X
CGI-SCH(28)		X	X	X	X	X	X	X	X
GAF(29)		X							X
SFS(30)		X							X
EQ-5D(39)		X							X
Economic Outcomes		X							X

Figure Legends

Figure 1. mHealth tools of the m-RESIST solution

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118x41mm (150 x 150 DPI)

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	5
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,18
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

1

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6,7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	NA
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA

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3   Data management   19   Plans for data entry, coding, security, and storage, including any related processes to promote data quality   14
4   (eg, double data entry; range checks for data values). Reference to where details of data management
5   procedures can be found, if not in the protocol
6
7   Statistical methods 20a   Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the   13
8   statistical analysis plan can be found, if not in the protocol
9
10   20b   Methods for any additional analyses (eg, subgroup and adjusted analyses)   13
11
12   20c   Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any
13   statistical methods to handle missing data (eg, multiple imputation)   NA
14
15   **Methods: Monitoring**
16
17   Data monitoring   21a   Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of   14
18   whether it is independent from the sponsor and competing interests; and reference to where further details
19   about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not
20   needed
21
22   21b   Description of any interim analyses and stopping guidelines, including who will have access to these interim   NA
23   results and make the final decision to terminate the trial
24
25   Harms   22   Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse   11
26   events and other unintended effects of trial interventions or trial conduct
27
28   Auditing   23   Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent   NA
29   from investigators and the sponsor
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32   **Ethics and dissemination**
33
34   Research ethics   24   Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   14
35   approval
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37   Protocol   25   Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes,   14
38   amendments   analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals,
39   regulators)
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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12, 14	
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20	
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14	
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2	
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA	

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.
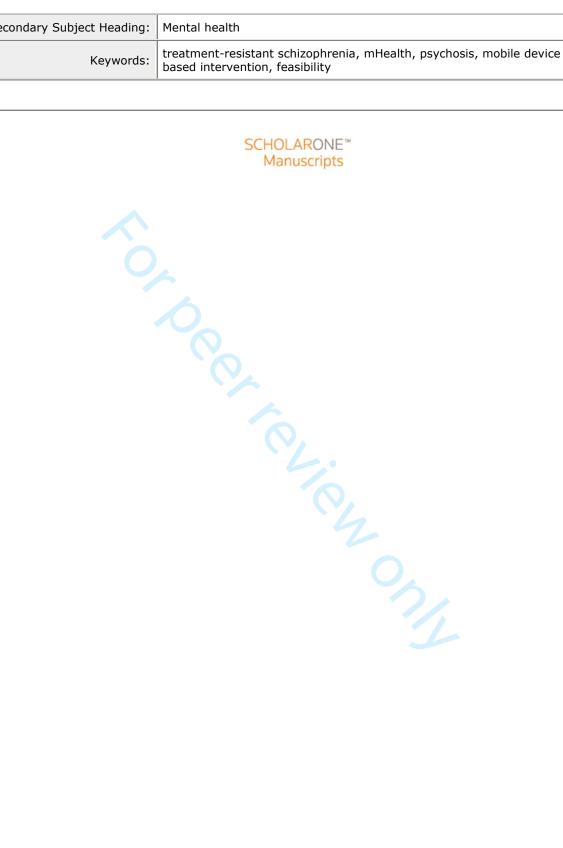
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BMJ Open

Mobile therapeutic attention for treatment-resistant schizophrenia (m-RESIST): a prospective multicentre feasibility study protocol in patients and their caregivers.

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Primary Subject Heading:	Mental health

Secondary Subject Heading:	Mental health
Keywords:	treatment-resistant schizophrenia, mHealth, psychosis, mobile device based intervention, feasibility

SCHOLARONE™
Manuscripts

Mobile therapeutic attention for treatment-resistant schizophrenia (m-RESIST): a prospective multicentre feasibility study protocol in patients and their caregivers.

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1

Abstract

Introduction: Treatment-resistant schizophrenia (TRS) is a severe form of schizophrenia. In the European Union, TRS is suffered by approximately 40% of people with schizophrenia. Factors such as the persistence of positive symptoms or higher risk of comorbidities leave clinicians with a complex scenario when treating these patients. Intervention strategies based on mHealth have demonstrated their ability to support and promote self-management-based strategies. . m-RESIST, an innovative mHealth solution based on novel technology and offering high modular and flexible functioning, has been developed specifically for TRS patients and their caregivers. As intervention in TRS is a challenge, it is necessary to perform a feasibility study before the cost-effectiveness testing stage.

Methods and analysis: This manuscript describes the protocol for a prospective multicentre feasibility study in 45 TRS patients and their caregivers, who will be attended in the public health system of three localities: Hospital Santa Creu Sant Pau (Spain), Semmelweis University (Hungary) and Gertner Institute & Sheba Medical Center (Israel). The primary aim is to investigate the feasibility and acceptability of the m-RESIST solution, configured by three mHealth tools, an app, wearable, and a web-based platform. The solution collects data about acceptability, usability and satisfaction, together with preliminary data on perceived quality of life, symptoms and economic variables. The secondary aim is to collect preliminary data on perceived quality of life, symptoms and economic variables.

Ethics and dissemination: This study protocol, funded by the Horizon 2020 Programme of the European Union, has the approval of the Ethics Committees of the participating institutions. Participants will be fully informed of the purpose and procedures of the study, and signed inform consents will be obtained. The results will be published in peer-reviewed journals and presented in scientific conferences to ensure widespread dissemination.

Trial Registration: Trial registered at ClinicalTrials.gov in February 2017 (NCT03064776).

Keywords: treatment-resistant schizophrenia, mHealth, psychosis, mobile device based intervention, feasibility.

STRENGTHS AND LIMITATIONS

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- To the authors' knowledge, m-RESIST is the first mHealth platform specifically addressed to TRS.

- The m-RESIST solution includes a sophisticated tool to detect early warning signs for preventing symptoms before they occur.

- This study promotes the involvement of the caregivers in the therapeutic process and a closer monitoring and communication with clinicians.

- The outcomes of this study will help in future performance of a cost-effectiveness randomised controlled trial.

- The study focuses on feasibility and acceptability, so any differences found in outcomes should be treated with caution due to the design (small sample size, absence of control group, and short length of intervention and follow-up period).

3

1. INTRODUCTION

1.1 Background

In the European Union, between 0.2% and 2.6% of the population suffer from psychotic disorders(1). The largest group is patients with schizophrenia, and around 20-30% are patients whose condition does not respond satisfactorily to adequate treatment and clearly have harder-to-treat psychotic symptoms, despite adherence to current optimized treatment(2). These patients are referred to as treatment-resistant schizophrenia (TRS) patients(3,4). TRS is a complex phenomenon influenced by a great variety schizophrenia subtypes, psychiatric comorbidity, and coexisting medical illnesses. Such patients pose a challenge to psychiatric and primary care clinicians, generating a financial burden on society due to frequent emergency visits, hospitalizations and chronic use of polypharmacy (5). Moreover, there is also a huge impact in human terms with regard to patients and caregivers, involving several dimensions such as quality of life, treatment side effects, caregiver burden, social impairment, and high mortality(6).

Standard intervention in patients with TRS is challenging due to the persistence of positive symptoms, extensive periods of hospitalization and elevated risk of somatic and psychiatric comorbidities. Improvement obtained by current drug therapy, such as clozapine alone or in combination with another antipsychotic/mood stabilizer, is frequently not effective enough to achieve remission in TRS patients (7). Therefore, the development of innovative evidence-based interventions adjunctive to pharmacological and psychosocial treatment is needed.

Previous studies have shown feasibility, acceptability and also preliminary efficacy of mobile interventions (mHealth) for schizophrenia (8–14). Over 80% of participants indicated that they would recommend the interventions and that they were easy to use and useful, reporting also high levels of satisfaction. Intervention strategies based on mHealth have demonstrated their ability to support and promote self-management-based strategies in psychotic disorders.

Mobile interventions may be effective in preventing relapses, increasing treatment adherence, and relieving some of the symptoms, though the effects on social functioning remain unclear (11,13,15,16). Smartphone ownership among people with schizophrenia is relatively high and increasing (17). Moreover, patients also seem to be willing and able to use smartphones to monitor their symptoms, engage in therapeutic interventions and increase physical exercise (9). Alvarez-Jimenez et al. performed a meta-analysis of 12 studies, where evidence on acceptability, feasibility, safety and benefits of online and mobile-based interventions for psychosis were analysed (18). Results showed that 74–86% of patients used web-based interventions efficiently, 75–92% perceived them as positive and useful, and 70–86% of

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patients completed or engaged with the interventions during follow-up. On the other hand, 26% of patients experienced difficulties in using web-based psychoeducation and cognitive behaviour therapy (CBT), the main causes being lack of motivation, poor engagement and poor understanding (18). It should be noted that the lack of published mHealth studies focusing on patients with TRS makes it more difficult to design novel interventions. Therefore, future mHealth studies in TRS should pay attention to some essential aspects: the recruitment process, the design and delivery of patient-centred and easy-to-use mHealth programmes, and strategies to maximize retention rates. Performing a feasibility study would be helpful to explore the acceptability and adequacy of intervention components, evaluate recruitment and assessment procedures, and to ensure if changes will be necessary during a subsequent cost-effectiveness RCT.

This study protocol (Version 1. Date: 05 July 2016) is part of a European research project, co-funded by the Horizon 2020 Framework Programme of the European Union (grant agreement nº 643552). This project aims to develop and test the use of m-RESIST, a mobile system based on Information and Communications Technology (ICT), addressed to empower patients suffering from TRS and to involve their caregivers. This platform offers a holistic approach to integrate psychiatric and psychological assistance, offering a better monitoring of patients through a personalised and optimised therapeutic process, promoting acceptance and self-management of the condition, and potentiating a proactive role of patients and caregivers in the therapeutic process.

As stated by Aranda-Jan et al. (19), the main considerations for an effective mHealth project are an appropriate project design (adapted to the local context), the availability of technology and resources, the involvement of stakeholders, and the implementation process in healthcare systems. According to these conditions, a qualitative study about the receptivity of TRS patients, caregivers and clinicians toward possible m-RESIST components was performed during the first stage of the m-RESIST solution development. The hypothetic positive acceptability of the solution in terms of usefulness, increase of patient's empowerment and social contact promotion was shown (10).

The current study protocol corresponds to the second stage of the project, aimed at ensuring that the designed solution satisfies the needs of end-users. To explore this, a feasibility study will be performed in an environment as close as possible to real life settings, where the m-RESIST prototype will be tested in the target group (patients, caregivers, clinicians).

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1.2 Aims and hypothesis

The objectives of this study are:

- to investigate rates of willingness to enrol, attrition (non-usage and drop-out attrition) and compliance with the study,
- to investigate the acceptability of the m-RESIST solution in TRS patients, caregivers and clinicians
- to examine participants' satisfaction and the usability of the m-RESIST solution
- to explore the suitability and availability of proposed clinical, functional and economic outcomes measures

The hypotheses are:

1- The m-RESIST solution will have acceptable rates of willingness to enrol (≥70%) , non-usage and drop-out attrition (both <15%) in TRS patients.

2- The m-RESIST solution will be highly accepted by TRS patients, and reflected in high scores in acceptability, usability and satisfaction reported by more than 80% of patients.

3- The proposed clinical, functional and economic outcomes measures will be suitable and available for TRS.

2. METHODS AND ANALYSIS

The following methods adhere to the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guidelines for the reporting of study protocols (20).

2.1. Study design and setting

This is a prospective multicentre feasibility study, without a control group, following an iterative process in patients with TRS and their caregivers. Participants will be recruited from three sites: Gertner Institute & Sheba Medical Centre-Psychiatric Division (Tel Aviv, Israel), Semmelweis University-Department of Psychiatry and Psychotherapy (Budapest, Hungary), and Hospital de la Santa Creu i Sant Pau-Unit of Psychiatry (Barcelona, Spain). These sites provide full-spectrum mental health services to adult people from their catchment area, and have wide experience in participating in large-scale clinical trials in patients with schizophrenia.

2.2 Participants

A total of 45 TRS patients (15 per centre), with their caregivers, will be selected for invitation to participate by researchers. The eligibility for participation will be based on the following inclusion and exclusion criteria (also described in table 1). *Inclusion*

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criteria: 1. Patients with age between 18 - 45 years old with a diagnosis of Schizophrenia according to DSM-V criteria; 2. Duration of disease less than 15 years; 3. Meet criteria for TRS (21,22); 4. Used to ICT tools and physical capability to use them; 5. Presence (and willingness to participate) of a caregiver or informal carer. The following exclusion criteria will be applied: 1. Meet criteria for remission according to the Remission of Schizophrenia Working Group (23); 2. Presence of delusions mainly related with their therapists or with new technologies; 3. To have vision, hearing, or motor impairment, that makes impossible to operate a smartphone; 4. The caregiver or informal carer is not used to ICT tools or has physical incapability to use them; 5. Presence of intellectual developmental disability.

Due to the voluntary nature of participation in clinical trials, participants may leave the study without having to specify their reasons. The investigators could also dismiss a participant from the study whenever they consider it appropriate.

Reasons for withdrawal include events such as inpatient psychiatric hospitalization. A participant will be withdrawn from the study participation if s/he:

- Refuses to cooperate.
- Wishes to drop out (in this instance a specific reason must be recorded by the investigator).
- Experiences adverse events sufficiently severe that, in the opinion of the investigator, it would be harmful to continue in the study.
- Has a general medical condition that, in the opinion of the investigator, would make it harmful to continue in the study.
- Does not complete the study as outlined in the study protocol.

2.3 Intervention

In the current study the intervention will involve patients and their caregivers, and the main actors involved in the deployment of the m-RESIST solution will be a psychiatrist, a psychologist and a case manager. The key aim of the intervention delivered by the m-RESIST solution is to engage TRS patients, together with their caregivers, in an active participation in therapeutic processes, and empower them to enable the self-management of their condition. To achieve this objective, the intervention is supported by three mHealth tools: a wearable (smartwatch), a mobile app and a web-based platform (see figure 1). Patient compliance will

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be measured by the number of days that the m-RESIST was used during the 3 months of intervention. Data for usage will be captured automatically by the m-RESIST software.

The functionality of the smartphone is based on the m-RESIST app. Through this app, patients will have access to educational content about TRS condition and related issues; track their early warning signs, symptoms and biological variables; ask for help by questionnaires or the "alarm bottom"; receive and practice helpful CBT-based coping strategies; and exchange messages with their caregiver or healthcare provider.

The wearable is a smartwatch that will collect data from patients and send it wirelessly to the smartphone. Sensor data will be recorded through automatic passive upload. The variables collected will be level of activity, heart rate, sleeping pattern and steps counter.

The web-based platform is the tool that the healthcare providers (case manager, psychiatrist, psychologist) will use to collect assessment data, to monitor patients' state and review data collected by sensors, to communicate by texting with patients, caregivers and other professionals, and to consult recommendations (based on guidelines and experts' opinion).

The m-RESIST intervention has been designed in order to meet the following assumptions:

It focuses on key problems: before starting the m-RESIST intervention, the patient's early warning signs (EWS) and current problems will be assessed. There will be two outputs. First, the patient's relapse signature configured by the 3 main EWS presented by the patient before a worsening occurs. Each EWS will be linked with a predefined (based on CBT) or tailored (based on patient's experience) coping strategy. These strategies will be triggered as a recommendation through the app when patients express distress or the system detects risk of worsening. The second output will be the treatment plan, which will identify the 3 main problems and corresponding goals in the patient's life, and link these goals with a specific module of intervention. This process will be agreed between patient, caregiver and clinician.

It is modular and tailored to the patient's condition: two categories of interventions have been designed, basal and risk intervention (see definition and characteristics in table 2). They are related with the list of problems mentioned previously, in order to set the most appropriate intervention depending on the patient's situation.

It is capable of detecting worsening: the m-RESIST intervention is capable of changing the system's triggers to patients when worsening is detected by means of the baseline sensor and clinical profiles. During a 15-day period, the patients will use the smartwatch and the smartphone to capture continuously multidimensional sensor data. The baseline sensor profile

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will be based on the analyses of these data. Furthermore, a complete assessment of clinical variables (e.g. symptoms, risk behaviours, functionality, and adherence) will also be performed in this period. The baseline clinical profile will be based on the analysis of these data. A set of predefined algorithms will detect significant changes in predefined thresholds, and trigger specific questionnaires, recommendations and notifications. Whenever a moderate or high risk of an oncoming episode of worsening is detected, the clinical team will be alerted and the patient will be offered tailored recommendations or emergency assistance.

Concomitant Therapy: Apart from the intervention associated with the m-RESIST solution, patients will keep receiving their treatment-as-usual (including outpatient case management, linkage to services and medication monitoring). If it is necessary to make changes in the psychiatric treatment, they will be recorded in the patient profile created in the platform.

2.5 Outcomes

The evaluation framework to understand the factors affecting the user experience and acceptance of the m-RESIST solution among various stakeholders, as well as the main determinants affecting user experience at a feasibility level, will follow the Living Lab approach (24). It is defined as "a user-centric research methodology for sensing, prototyping, validating and refining complex solutions in multiple and evolving real-world contexts". Living Lab research goes beyond mere usability studies and acceptance studies, as it also takes the impact of the context of use into account. A multi-methodological approach, with both qualitative and quantitative methodologies, is chosen so as to be able to capture different aspects of the implemented solution.

The protocol diagram based on SPIRIT guideline (20) provides an overview of the measures used in the trial and their time points (see table 3). In addition to outcomes described in Table 3 and below, socio-demographic and clinical characteristics (e.g. years of evolution, past and current treatment, comorbidities) will be collected by using a semi-structured interview.

The primary and secondary outcomes (see table 4) of the study protocol are the following:

<u>Primary outcomes</u>

The primary outcomes include feasibility and acceptability of using the m-RESIST solution. Qualitative and quantitative feedback will be collected to identify the main determinants of experience and acceptance of the m-RESIST solution.

Feasibility will be examined by analysing willingness to enrol, attrition and compliance. The measures and operational criteria are as follows:

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- Willingness to enrol: the proportion of patients approached about the study that proceed to the consent stage. Operational criteria definition: ≥70% of patients approached will agree to enrol;

- Attrition (25,26): two measures will be collected, drop-out and non-usage attrition.

  o Dropout attrition: proportion of participants who fail to complete the study protocol, and thus do not complete the study assessments. Operational criteria definition: <15% of participants will be lost to follow-up or withdraw from the study.

  o Non-usage attrition: proportion of participants who do not drop out (e.g., who are still completing the follow-up), but who stop using the m-RESIST tools (smartwatch, app). Operational criteria definition: <15% of participants will stop using devices

- Compliance: extent to which participants experience the content of the m-RESIST intervention, measured by number of logins, time spent online, number of questionnaires completed, number of messages sent and answered, and number of successful appointments.

Acceptability of the m-RESIST solution will be assessed in terms of acceptability, usability and satisfaction in TRS patients, caregivers and clinicians. Critical measures are the following:

- Acceptability: a modified version of the Technology Acceptance Model scale [TAM] (27), adapted to TRS patients by the research team, will be used. The following variables will be evaluated: perceived usefulness, perceived ease of use, intention, compatibility, subjective norm, facilitators and habit. Each variable is composed of a series of Likert-type items (7 levels, from "totally disagree" to "totally agree"). Data will be collected at the end of the intervention (V7).

- Usability: two instruments will be used, User experience questionnaire and Interval question. The User experience questionnaire will be delivered by online data collection (Qualtrics software), and is composed of a combination of survey questions (4-point Likert-type scale) and open questions. The survey will explore perceived ease of use, perceived usefulness, attitude and perceived quality of content. The open questions will explore lasting impressions and recommendations. The participants will be asked to complete the questionnaire on three occasions during the three-month intervention: at the start (V0), in the middle (V3), and at the end of the intervention (V7).

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The Interval question, aimed at better capturing a more constant experience of the participants, will ask always the same question: *What is it like to use the m-RESIST solution?*. It will be sent to participants via m-RESIST message system once a week, but on different days and at different times.

- Satisfaction: this variable will be assessed using the Client Satisfaction Questionnaire-8 [CSQ-8](28). This instrument will be completed at the end of the intervention (V7).

Secondary outcomes

A complete clinical and economic evaluation would be premature in this feasibility study, due to the small sample. However, it will be useful to collect necessary parameters for planning a full prospective RCT to test the cost-effectiveness of m-RESIST solution.

Completion rates and missing data will be explored. Operational criteria definition for missing data: <10% of each set of secondary outcomes is missed during study data collection.

The measures for clinical, functional, quality of life and economic outcomes are the following:

Clinical outcomes:

- Severity of symptoms will be assessed using the instruments Positive and Negative Syndrome Scale [PANSS](29), Calgary Depression Scale [CDS](30) and Clinical Global Impression-Schizophrenia [CGI-SCH](31). PANNS and CDS will be completed on two occasions, at the start (V0) and at the end (V7) of the intervention. CGI-SCH will be rated in all protocol visits (V0-V7).

  - Insight will be assessed using the instrument Scale Unawareness Mental Disorders [SUMD](32). This scale will be administered on two occasions, at V0 and at V7.

  - Adherence will be assessed using the Adherence to Refills and Medications Scale [ARMS] (33). This instrument will be administered on two occasions, at V0 and at V7.

Functional and perceived quality of life outcomes:

  - Functionality will be assessed using the instruments Global Assessment of Functioning [GAF](34) and Social Functioning Scale [SFS](35). GAF and SFS will be administered on two occasions, at V0 and at V7.

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- Perceived quality of life will be assessed using the EuroQol 5 dimensions 5 levels questionnaire [EQ-5D-5L] (36). This instrument will be administered on two occasions, at V0 and at V7.

Economic and organizational outcomes:

Questionnaires with open ad-hoc questions and semi-structured interviews will be used to assess the *use of resources* (e.g. unit cost of personnel of remote or face to face visits, number of emergency admissions and length of stay) and the *impact* of m-RESIST *in organization* (questions regarding effects on the structure, work process and the culture of the organization). This information will be gathered at V0 and V7.

Safety measures:

Finally, *safety measures* will also be collected throughout the study. The presence of serious and non-serious adverse events, defined as any clinical change or illness reported during the study, will be monitored in every clinical visit. The adverse events observed when carrying out the study, either by the clinician or by the patient him/herself and regardless of the causality relationship ascribed, will be recorded in the clinical records and at the patient's dashboard.

2.4 Participant timeline

The study will consist of four periods: recruitment, pre-intervention, intervention and follow-up.

1) <u>Recruitment period,</u> aimed at contacting and checking the eligibility of candidates. The outputs of an in-depth report about healthcare routes and clinical pathways in the three participant regions, made within the context of the m-RESIST project, have helped to identify the strengths and weakness of the recruitment capabilities. In order to reach the total sample of participants, two recruitment strategies will be used. Leaflets to promote the study will be distributed to healthcare providers, informing them about the study and inviting them to contact the research staff if potential participants are identified. In addition, research staff at the recruitment sites will approach eligible patients directly to suggest participating in the study. Informed consent signature for TRS patient and caregiver will be obtained if inclusion and exclusion criteria are met, and both patient and caregiver agree to participate in the study.

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2) <u>Pre-Intervention period (V0)</u>, aimed at training the participants in using the smartwatch and the app, and collecting clinical and sensor baseline information. At the beginning of the pre-intervention period, patients will be given the study smartwatch and smartphone, with m-RESIST app pre-installed. Caregivers will be given permission to install the app in their own smartphone. Both will be trained by the research staff in how to use the functions of the smartwatch and the different features of the app. Research staff will also provide patients and caregivers with training material (user guide and online video tutorial). Patients will be asked to wear the smartwatch for a period of at least 15 days, in order to collect enough sensor data to establish the baseline sensor profile. Furthermore, patients and caregivers will also be encouraged to use and familiarise themselves with the app by consulting the educational content and using the messaging system. Patients will also attend a clinical assessment, where secondary outcomes will be collected (see table 3). At the end of the pre-intervention period, the key elements (relapse signature and treatment plan) to deliver a tailored intervention will be explored.

3) <u>Intervention period (V1-V7)</u>, aimed at testing the features and action flows that configure the m-RESIST interventions, and at assessing the experience of participants. At the beginning of the intervention, the treatment plan will be defined and the corresponding basal intervention will be activated. Participants will use the solution over 3 months, and appointments with clinicians will be scheduled every 15 days. This period will be comprised of 4 online visits and 3 onsite visits. In each visit the treatment plan will be reviewed, the CGI scale and measure of patients' perceived health status will be assessed, and changes in the current antipsychotic treatment and potential adverse events will be explored. At the end of this period, a final visit will be held, made up of the full global assessment, to get post-test measures of the variables assessed in the pre-intervention period (see table 3).

4) <u>Follow-up period,</u> aimed at evaluating the primary and secondary outcomes of the study.

2.5 Sample size

This protocol study is a non-randomised feasibility study where the primary outcomes are not measures of intervention effects, but factors that could affect the successful execution of RCT. The proposed sample size of 45 patients, with their corresponding caregivers, is consistent with the recommendations for feasibility studies (37,38).

2.6 Data Analysis

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Descriptive statistics (means and standard deviations or percentages) will be used to summarise baseline socio-demographic and clinical characteristics of participants.

Analysis of primary outcomes:

Descriptive statistics will be used to ascertain *feasibility*. Willingness to enrol and attrition components will be summarised for participants, overall and in relation to selected baseline characteristics. Differences between followed up patients and those who were lost to follow-up will be examined in terms of baseline characteristics, by a paired sample T-Test (normal distribution) or Wilcoxon signed-rank test (non-normal distribution).

Quantitative and qualitative data for *acceptability* and *usability* will be examined:

Quantitative data: each variable measured in acceptability and usability configured a Likert scale. The composite score (mean) of each variable will be calculated and treated as an interval/ratio scale. Pearson correlations between the constructs will be calculated to explore the following hypotheses: perceived usefulness and perceived ease of use is positively and significantly correlated to attitude; perceived ease of use is positively and significantly correlated to perceived usefulness; perceived quality of content will influence perceived usefulness and ease of use. Repeated measures of the user experience questionnaire will be tested by repeated measures ANOVA method.

Qualitative data: for the analysis of self-reported data collected from user experience questionnaire and from Interval question, qualitative thematic/content analysis will be conducted as proposed by Mayring (39). This method is a technique of summarization, whereby themes are created in an inductive procedure by reducing, paraphrasing and generalizing relevant text passages. Patterns in the text will be found and coded in order to search for themes in the data. The data will be subjected to thematic content analysis with the help of Atlas-ti software.

Finally, descriptive statistics will be used to regarding assess satisfaction with m-RESIST intervention .

Analysis of secondary outcomes:

Descriptive statics will be used to explore the availability and utility of data relating to proposed clinical, functional and economic outcomes measures, and a range of summary measures will be presented in the final statistical outputs.

Statistical analysis

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Analyses will be conducted using STATA 13. Descriptive statistics will be used to summarise clinical and demographic characteristics of patients. Feasibility of trial procedures will be examined using proportions and 95% confidence intervals for assessments of feasibility and acceptability in terms of recruitment, consent, dropout, follow-up and integrity of double blinding. The variance observed in this sample will be used for sample size calculation for the future RCT, as recommended by Lancaster and colleagues (40).

2.7 Quality Control

The researcher will ensure the accuracy and integrity of the data and reports required. The data included in the m-RESIST derived from source documents will be consistent with such documents; otherwise the discrepancies will be justified. The researcher will keep the study documents for at least 5 years after the study is completed.

Data monitoring will be done by the ethics committee of each site. Clinicians will have all the study-related files available, allowing direct access to data or source documents to perform monitoring, audit, review by the ethics committee or any inspection by the competent authorities. All data collected will only be accessible to m-RESIST partners.

3. ETHICS AND DISSEMINATION

Before entering the study, all participants will be legally competent and will provide written informed consent to the clinical team. All the data collected will be treated confidentially and analysed anonymously. The study protocol has already been approved by the local Research Ethics Committee of each site: Gertner Institute (Tel-Aviv, Israel), Semmelweis University (Budapest, Hungary) and Hospital de la Santa Creu i Sant Pau (Barcelona, Spain). Any protocol amendments will be made through the Ethics Committee of each site. The results of this study will be published in international peer-review journals. A wide dissemination of the project results is planned to take place at European and International level. Patients, caregivers, health professionals, institutions and stakeholders will be targeted as the main recipients of the m-RESIST outcomes.

4. STUDY STATUS

At the time of writing, the m-RESIST solution was still being tested by technological and clinical partners belonging to the project's consortium, and potential participants were being assessed.

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5. DISCUSSION

This article summarizes the protocol of a multicentre feasibility study aimed at assessing rates of attrition and acceptability of the m-RESIST solution. This information will provide important parameters to consider running a cost-effective RCT, and to identify potential constraints and possible solutions.

TRS is a complex phenomenon usually excluded from RCT. Our research group, made up of experienced clinicians and researchers in TRS patient follow-up, is interested in understanding the factors that lead to resistance or response in this patient population, and in developing new approaches to treatment.

The m-RESIST project targets the "high end" (in terms of severity) of psychiatric morbidity–TRS, which is characterized by a chronic and continuous prolonged course, low level of adherence, insight and judgement, and is particularly challenging also due to impairments in interpersonal communication. These challenges reduce the possibility of the patients taking full responsibility for their treatment and self-care, and communicating their needs and changes in clinical state. The TRS multi-dimensional presentation, diverse course, and multi-dimensional functioning impairment involves treating TRS patients by a multidimensional approach, including multidisciplinary teamwork and different interventions.

Current trends in treating schizophrenia result from general social trends and recent developments in medical care, including implementation of evidence-based medicine tools and novel technological developments in the field of healthcare, specifically regarding data collection using various sensors, data processing and communication. Healthcare systems are also moving towards personalized medicine, combining a large body of personal and disease-related information. The aforementioned view of the heterogeneous complicated needs of TRS patients, their caregivers and treating clinicians, emphasizes the need for a comprehensive system that will allow and encourage different modes of communication between potential users involved in the clinical complexity of the disease.

The m-RESIST solution is an initiative targeted to create a hybrid system aimed at optimization of chronic care by integrating technological solutions, and assisting clinicians in their decision-making process. The developed solution also enhances the involvement of patients in their own treatment process, encouraging active participation in therapeutic processes, self-managing of their condition, thus reinforcing a sense of empowerment and improving quality of life.

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The novel principles include new technology, high modularity and flexibility, and personalized response to heterogenic needs. In order to overcome the disadvantages of the current healthcare system, the m-RESIST solution intends to provide continuity of care, immediate attention for prevention of worsening and hospitalizations, automated and personalised interventions and recommendations, as well as easy and efficient communication between the solution users.

The main limitations of the study are those characteristic of feasibility studies, the lack of randomisation and a control group. It may have a high dropout rate, so predictors of discontinuation should be assessed comparing characteristics of compliant patients with those who were lost to follow-up. Furthermore, studies in mHealth require a minimum range of skills to use the tools. In this regard, TRS patients can present limitations in using the devices due to some degree of cognitive impairment, and caregivers might have a poor knowledge of the Internet, computer and other devices due to their age range.

However, and despite the aforementioned limitations, the findings and outputs from the proposed study will take us closer to designing a future cost-effectiveness trial in treatment-resistant patients.

Refrences

1. Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2011 Sep;21(9):655–79.

2. Elkis H, Buckley PF. Treatment-Resistant Schizophrenia. The Psychiatric clinics of North America. United States; 2016 Jun;39(2):239–65.

3. Conley RR, Kelly DL. Management of treatment resistance in schizophrenia. Biological psychiatry. United States; 2001 Dec;50(11):898–911.

4. Kennedy JL, Altar CA, Taylor DL, Degtiar I, Hornberger JC. The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. International clinical psychopharmacology. 2014 Mar;29(2):63–76.

5. de Silva J, Hanwella R, de Silva VA. Direct and indirect cost of schizophrenia in outpatients treated in a tertiary care psychiatry unit. The Ceylon medical journal. Sri Lanka; 2012 Mar;57(1):14–8.

6. A. Millier, U. Schmidt b, M.C. Angermeyer c D, E DC, E VM, F MT, G NC-S. Humanistic burden in schizophrenia: A literature review. Journal of Psychiatric Research [Internet]. Pergamon; 2014 Jul 1 [cited 2017 Sep 14];54:85–93. Available from: https://xpv.uab.cat/science/article/pii/,DanaInfo=.awxyCwholvloou4sr9Qu76+S002239 5614001034?via%253Dihub

7. Samara MT, Dold M, Gianatsi M, Nikolakopoulou A, Helfer B, Salanti G, et al. Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia: A Network Meta-analysis. JAMA psychiatry. United States; 2016 Mar;73(3):199–210.

8. Bonet L, Izquierdo C, Escarti MJ, Sancho JV, Arce D, Blanquer I, et al. Use of mobile technologies in patients with psychosis: A systematic review. Revista de psiquiatria y

17

salud mental. Spain; 2017 Jul;10(3):168–78.

9. Firth J, Torous J. Smartphone Apps for Schizophrenia: A Systematic Review. JMIR mHealth and uHealth. Canada; 2015 Nov;3(4):e102.

10. Huerta-Ramos E, Escobar-Villegas MS, Rubinstein K, Unoka ZS, Grasa E, Hospedales M, et al. Measuring Users' Receptivity Toward an Integral Intervention Model Based on mHealth Solutions for Patients With Treatment-Resistant Schizophrenia (m-RESIST): A Qualitative Study. JMIR mHealth and uHealth. Canada; 2016 Sep;4(3):e112.

11. Ben-Zeev D, Brenner CJ, Begale M, Duffecy J, Mohr DC, Mueser KT. Feasibility, acceptability, and preliminary efficacy of a smartphone intervention for schizophrenia. Schizophrenia bulletin. United States; 2014 Nov;40(6):1244–53.

12. Ben-Zeev D, Kaiser SM, Krzos I. Remote "hovering" with individuals with psychotic disorders and substance use: feasibility, engagement, and therapeutic alliance with a text-messaging mobile interventionist. Journal of dual diagnosis. United States; 2014;10(4):197–203.

13. Ben-Zeev D, Wang R, Abdullah S, Brian R, Scherer EA, Mistler LA, et al. Mobile Behavioral Sensing for Outpatients and Inpatients With Schizophrenia. Psychiatric services (Washington, DC). United States; 2016 May;67(5):558–61.

14. Bogart K, Wong SK, Lewis C, Akenzua A, Hayes D, Prountzos A, et al. Mobile phone text message reminders of antipsychotic medication: is it time and who should receive them? A cross-sectional trust-wide survey of psychiatric inpatients. BMC psychiatry. England; 2014 Jan;14:15.

15. Spaniel F, Vohlidka P, Kozeny J, Novak T, Hrdlicka J, Motlova L, et al. The Information Technology Aided Relapse Prevention Programme in Schizophrenia: an extension of a mirror-design follow-up. International journal of clinical practice. England; 2008 Dec;62(12):1943–6.

16. Granholm E, Ben-Zeev D, Link PC, Bradshaw KR, Holden JL. Mobile Assessment and Treatment for Schizophrenia (MATS): a pilot trial of an interactive text-messaging intervention for medication adherence, socialization, and auditory hallucinations. Schizophrenia bulletin. United States; 2012 May;38(3):414–25.

17. Firth J, Cotter J, Torous J, Bucci S, Firth JA, Yung AR. Mobile Phone Ownership and Endorsement of "mHealth" Among People With Psychosis: A Meta-analysis of Cross-sectional Studies. Schizophrenia bulletin. United States; 2016 Mar;42(2):448–55.

18. Alvarez-Jimenez M, Alcazar-Corcoles MA, Gonzalez-Blanch C, Bendall S, McGorry PD, Gleeson JF. Online, social media and mobile technologies for psychosis treatment: a systematic review on novel user-led interventions. Schizophrenia research. Netherlands; 2014 Jun;156(1):96–106.

19. Aranda-Jan CB, Mohutsiwa-Dibe N, Loukanova S. Systematic review on what works, what does not work and why of implementation of mobile health (mHealth) projects in Africa. BMC public health. England; 2014 Feb;14:188.

20. Chan A-W, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ (Clinical research ed). England; 2013 Jan;346:e7586.

21. Suzuki T, Remington G, Mulsant BH, Uchida H, Rajji TK, Graff-Guerrero A, et al. Defining treatment-resistant schizophrenia and response to antipsychotics: a review and recommendation. Psychiatry research. Ireland; 2012 May;197(1–2):1–6.

22. Elkis H, Meltzer HY. [Refractory schizophrenia]. Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999). Brazil; 2007 Oct;29 Suppl 2:S41-7.

23. Andreasen NC, Carpenter WTJ, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. The American journal of psychiatry. United States; 2005 Mar;162(3):441–9.

24. Eriksson M, Niitamo V, Oyj N, Kulkki S. State-of-the-art in utilizing Living Labs approach to user- centric ICT innovation - a European approach . Technology [Internet].

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2005;1(13):1–13. Available from:
http://openlivinglabs.i2cat.cat/documents/SOA_LivingLabs.pdf

25. Eysenbach G. The law of attrition. Journal of medical Internet research. Canada; 2005 Mar;7(1):e11.

26. Eldridge SM, Lancaster GA, Campbell MJ, Thabane L, Hopewell S, Coleman CL, et al. Defining Feasibility and Pilot Studies in Preparation for Randomised Controlled Trials: Development of a Conceptual Framework. PloS one. United States; 2016;11(3):e0150205.

27. Gagnon MP, Orruno E, Asua J, Abdeljelil A Ben, Emparanza J. Using a modified technology acceptance model to evaluate healthcare professionals' adoption of a new telemonitoring system. Telemedicine journal and e-health : the official journal of the American Telemedicine Association. United States; 2012;18(1):54–9.

28. Atkinson C, Greenfield TK. The client satisfaction questionnaire (CSQ) scales and the service satisfaction scale-30 (SSS-30). Outcomes Assessment in Clinical Practice Williams & Wilkins. 1995;120–7.

29. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia bulletin. United States; 1987;13(2):261–76.

30. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. Schizophrenia research. Netherlands; 1990;3(4):247–51.

31. Haro JM, Kamath SA, Ochoa S, Novick D, Rele K, Fargas A, et al. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. Acta psychiatrica Scandinavica Supplementum. Denmark; 2003;(416):16–23.

32. Amador XF, Strauss DH, Yale SA, Flaum MM, Endicott J, Gorman JM. Assessment of insight in psychosis. The American journal of psychiatry. United States; 1993 Jun;150(6):873–9.

33. Kripalani S, Risser J, Gatti ME, Jacobson TA. Development and evaluation of the Adherence to Refills and Medications Scale (ARMS) among low-literacy patients with chronic disease. Value in Health. Elsevier; 2009;12(1):118–23.

34. Endicott J, RL S, JL F, Cohen J. The global assessment scale: A procedure for measuring overall severity of psychiatric disturbance. Archives of General Psychiatry [Internet]. 1976 Jun 1;33(6):766–71. Available from:
http://dx.doi.org/10.1001/archpsyc.1976.01770060086012

35. Birchwood M, Smith J, Cochrane R, Wetton S, Copestake S. The Social Functioning Scale. The development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. The British Journal of Psychiatry [Internet]. 1990 Dec 1;157(6):853 LP-859. Available from:
http://bjp.rcpsych.org/content/157/6/853.abstract

36. Brooks R. EuroQol: the current state of play. Health policy (Amsterdam, Netherlands) [Internet]. 1996;37(1):53–72. Available from:
http://www.ncbi.nlm.nih.gov/pubmed/10158943

37. Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. BMC medical research methodology. England; 2010 Jul;10:67.

38. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC medical research methodology. England; 2010 Jan;10:1.

39. Mayring P. Qualitative content analysis: theoretical foundation, basic procedures and software solution. 143 [Internet]. 2014;(JANUARY 2014):143. Available from:
http://www.ssoar.info/ssoar/handle/document/39517

40. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. Journal of evaluation in clinical practice. England; 2004 May;10(2):307–12.

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Author's contribution

Authors AA and KR wrote the first draft of this study protocol. Authors EG and IC conceived the idea of the study and participated in the design of the solution. Author EJ, MI and AS served as advisors in this project and provided their expertise in studies in schizophrenia. VV and JC provided their expertise in quality and health assessments. AC, ZU and KF collaborated in the development of the intervention. SV, MS and TC collaborated in the definition and creation of the technological solution. EH and SM collaborated to the writing of the manuscript. Authors JB and MH served as a coordinators of the study. m-RESIST group contributed to revising the manuscript. All authors contributed to the revising of the manuscript and writing of the final version of the manuscript, and gave their approval for the submission.

Competing Interests

The authors declare that they have no competing interests

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Valentina Simonetti, Matthias Stevens, Vittorio Tauro, Anna Triantafillou, Zsolt Szabolcs Unoka, Judith Usall, Vincenzo Vella, David Vermeir, Ilaria de Vita.

Table 1- Inclusion and exclusion criteria for the study

Inclusion Criteria	Exclusion Criteria
1. Patients with age between 18 - 45 years old with a diagnosis of Schizophrenia according to DSM-V criteria. 2. Duration of disease less than 15 years. 3. Meet criteria for TRS (*see operational definition below). 4. Used to ICT tools and physical capability to use them. 5. Presence (and willingness to participate) of a caregiver or informal carer.	1. Meet criteria for remission according to the Remission of Schizophrenia Working Group (23). 2. Presence of delusions mainly related with their therapists or with new technologies. 3. To have hearing, vision or motor impairment that makes impossible to operate a smartphone. 4. The caregiver or informal carer is not

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	used to ICT tools or has physical incapability to use them. 5. Presence of intellectual developmental disability.

*Operational definition of treatment-resistant schizophrenia, modified from Suzuki and colleagues (21)]:

1) Patients having at least two failed adequate trials with different antipsychotics (at chlorpromazine-equivalent doses of ≥600mg/day for ≥6 consecutive weeks) as well as scores of ≥4 on the Clinical Global Impression-Severity (CGI-SCH) and ≤50 on the Global Assessment of Functioning (GAF) scales; OR

2) Patients with clozapine ongoing treatment due to meeting treatment-resistant criteria as well as scores of ≥4 on the CGI-SCH and ≤50 on the GAF scale.

Some patients may be considered pseudo-resistant to treatment (22)]. In this case, presence of active symptoms may be influenced by psychiatric and medical conditions such as social isolation, consumption of toxic substances, presence of nutritional and medical problems, inappropriate health habits which may substantially contribute to poor responses or insufficient effects of medication. Data regarding these conditions will be collected.

Table 2- m-RESIST modules of intervention

	Basal intervention	Risk intervention
Aim	oriented to develop abilities to deal with symptoms and early warning signs, to reinforce the involvement in the treatment plan, and to solve problems influenced by an unhealthy lifestyle	oriented to deal with possible situations of worsening (e.g. detection of risk behaviours)
Modules	Integrated by three modules: symptoms management, treatment adherence and healthy lifestyle	Integrated by one module: risk
Core elements	Relapse signature identification, coping strategies selection	Risk scale
Activation Triggers	External trigger: any of the modules can be activated by clinicians through the web-based platform (m-RESIST dashboard)	Internal trigger: when the system itself detect risk situations such as significant changes in threshold of specific sensor data External trigger: patients or caregivers ask for help by the app's alarm bottom
Actions involved	Delivery of a basic set of questions by the app, to measure patients' clinical status and appropriate follow up questions or recommendations depending on the patients' answers; use of reminders and psychoeducational content to help patients	Delivery of appropriate questions, to check patient's current condition and to send specific recommendations messages or notifications depending on the patients' answers (by the app)

Table 3- Schedule of study protocol periods and assessments

	STUDY PERIODS and VISITS			
	Recruitment	Pre-Intervention	Intervention		Follow-

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Activity/Assessment		V0	V1	V2	V3	V4	V5	V6	up V7
Eligibility screen	X								
Informed consent	X								
Delivery and training of devices	X								
Sociodemographic data		X							
Clinical characteristics		X							
Relapse signature and treatment plan		X							
Willingness to enrol	X								
Attrition		X	X	X	X	X	X	X	X
TAM(27)									X
Experience user questionnaire			X		X		X		X
Interval question			X	X	X	X	X	X	X
CSQ-8 (28)									X
PANSS (29)		X							X
CDS(30)		X							X
SUMD (32)		X							X
ARMS (33)		X							X
CGI-SCH(31)		X	X	X	X	X	X	X	X
GAF(34)		X							X
SFS(35)		X							X
EQ-5D(36)		X							X
Economic and organizational outcomes		X							X
Safety measures		X	X	X	X	X	X	X	X

Table 4. Baseline assessent and outcome measures

Measure	Definition	Data source
Baseline assessment		
Sociodemographic and clinical characteristics	Variables such as years of evolution, past and current treatment and comorbidities will be collected	Patient interview at baseline
Primary outcomes		
Willingness to enrol	The proportion of patients approached about the study that proceed to the consent stage	Protocol database
Dropout attrition	The proportion of participants that fail to complete the study.	Protocol database
Non-usage attrition	The proportion of participants who do not drop out (e.g., who are still completing the follow-up), but who stop using the m-RESIST tools (smartwatch, app).	Protocol database
Compliance	Variables such as logins, time online and questionnaires completed will be collected	Protocol database
Acceptability	TAM	Patient/Caregiver interview at the end of

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		study
Usability	User experience questionnaire Interval question	Patient/Caregiver/Clinician interview throughout the study
Satisfaction	CSQ-8	Patient/Caregiver interview at the end of study
Secondary outcomes		
Severity of symptoms	PANSS, CDS	Patient interview at baseline and at the end of study
	CGI-SCH	Patient interview throughout the duration of the study
Insight	SUMD	Patient interview at baseline and at the end of study
Adherence	ARMS	
Functionality	GAF, SFS	
Perceived quality of life	EQ-5D-5L	
Economic and organizational outcomes	Questionnaires with open ad-hoc questions form and semi-structured interviews	Central hospital database queried at 3 months before recruitment and at the end of the study
Safety	The presence of serious and non-serious adverse events, defined as any clinical change or illness reported during the study, will be monitored in every clinical visit.	Patient interview throughout the duration of the study

Figure Legends

Figure 1. mHealth tools of the m-RESIST solution

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	5
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,18
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

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Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6,7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	NA
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA

Ethics and dissemination

| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 14 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 14 |

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12, 14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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