Application No.:

 PI1 Name:

**Research Program**

**Scientific background**

Schizophrenia is a neuropsychiatric disorder characterized by positive symptoms (delusions, hallucinations, abnormal flow of thoughts), negative symptoms (withdrawal, apathy, anhedonia), and cognitive deficits.1 It affects approximately 1% of the worldwide population and presents substantial domestic and global burden due to the presence of comorbidities, risk of relapse, and excess early mortality.2-3 Schizophrenia is likely to be a product of interacting genetic and environmental influences, and despite the dramatic research advances in its underlying molecular genetics, its pathogenesis, presentation and course remain poorly understood. Clinical management of schizophrenia often requires antipsychotic medication which can provide symptomatic remission. Nevertheless, even with appropriate medication, up to 40% of patients may still relapse within 1 year.4 Relapse can have devastating consequences and is associated with poorer prognosis, high risk of injury, decreased quality of life, and decreased cognitive ability.5 Predicting relapse is challenging given the complexity of schizophrenia. A reliable prediction of risk for relapse would enable early intervention and reduce its devastating repercussions. The present study aims to address this issue by suggesting an integrative model including biological and psychological risk factors predicting relapse using digital phenotyping as behavioral measurement mediating this prediction. In an era aspiring for personalized medicine, providing multifactorial predictive model would aid in identifying people at varying risk of relapse, and could allow customized risk management of relapse.

*Stress-Vulnerability model for onset and relapse in schizophrenia.* In the context of stress-vulnerability framework, combination of neurobiological and psychosocial factors is responsible for the onset and course of schizophrenia. Relapse in schizophrenia is recognized as the reemergence or worsening of psychotic symptoms. About half of the patients are non-adherent to treatment.6 The non-adherence may be due to various factors depicted in a stress-vulnerability model. Stress is thought to emerge from exposure to single or ongoing life events. In the last two decades, researchers focused on the objective levels of stress exposure as well as on the subjective level, naming the perceived stress in response to events.7 Vulnerability is assumed to arise from a combination of biological and psychological factors. Among the psychological factors, depression, anxiety, and lack of motivation have been identified as factors that may drive relapse.6 Vulnerability for relapse address biological antecedents including various body systems involved in the neuroimmunology of relapse.

*Neuroimmune factors for relapse in schizophrenia.* Biological factors that predict relapse in schizophrenia have been studied extensively in the past decade and include immune, neural, metabolic, and endocrine systems.8 There is evidence for immune system abnormalities, including inflammatory, in schizophrenia patients.9 The autonomic nervous system (ANS) regulates the immune system through the sympathetic (SNS) and parasympathetic (PNS) networks. Dysfunction of the ANS may contribute to the inflammatory profile reported in schizophrenia.10 Schizophrenia patients tend to have autonomic imbalance with low heart rate variability (HRV) suggesting a reduced parasympathetic and increased sympathetic tone.11 Stress has been associated with ANS dysfunction (including increased outputs of the SNS, such as increases in catecholamine levels) and with the PNS/vagal withdrawal.12  Stress has been also associated with alterations in HPA (hypothalamus-pituitary-adrenal) axis function, including higher levels of circulating cortisol (a glucocorticoid; the main end product of the HPA axis in humans), which in turn cause focal or general inflammation.13 Accumulative evidence of the HPA axis abnormalities in the risk for psychosis suggesting a tonic (chronic) HPA hyperactivation and phasic (acute) HPA blunting.7

Research in the last two decades expanded our understanding as for the linkage between stressors, the HPA axis and ANS, and the risk for schizophrenia, and demonstrated the role of the microbiota-gut-brain (MGB) axis signaling on brain function and neurochemistry.14 MGB axis communicates with the brain through the vagus nerve, immune system, enteric nervous system, and enteroendocrine signaling15. The microbiome comprises a dynamic ecological communities of commensal microorganisms that consist of bacteria, viruses, fungi, and protozoa which are diverse and personalized and influenced by lifestyle factors including stress.14,16 Studies showed schizophrenia is related with the dysfunction of the MGB17, and improving the gut microbiota could possibly produce beneficial effects.18 These effects are explained through the MGB axis signaling on various systems involved in the pathogenesis of schizophrenia. Gut microbiota perform a central function in the development of the neuroimmune system. Immune system alterations are key factors in the etiology of schizophrenia, with studies showing infections increase the risk of schizophrenia.19 Recent studies with schizophrenia participants receiving probiotic supplements (e.g, Lactobacilli, Bifidobaterium breve) provided preliminary evidence that probiotic supplementation has anti-inflammatory effects20,21 through transforming growth factor-*β* signaling.13 Also, the MGB axis affect development and regulation of the HPA axis. Animal studies showed significant changes in HPA axis with elevated ACTH and cortisol levels in germ-free stressed mice.22 However, there is a scarcity in human studies addressing the crosstalk between HPA and MGB axes in schizophrenia. In a recent review, Seeman examined the role of gut microbiota in treatment resistance among schizophrenia patients.23 He postulated that there is a drug refractory form of psychosis for which the composition of gut bacteria is responsible.

There are well-documented findings showing sex differences regarding to disease risk, course, and outcome of schizophrenia. There are sex differences in the age-at-onset of schizophrenia with men reaching peak onset at the ages 18-24 years, whereas for women it occurs up to 4 years later.24 Furthermore, in females there is another peak age-at-onset at 45-50 years.25 Also, women present less severe course of illness, a more favorable antipsychotic treatment response, and improved outcome and quality of life compared to men.26-28 In light of these described sex differences, it has been hypothesized that sex hormones may play a role in explaining individual differences in the development of schizophrenia. Sex hormones, including androgens, estrogens, and progestins are chemical messengers secreted by the gonads (ovaries in women and testes in men) and by the adrenal glands through the HPG (hypothalamus-pituitary-gonads) axis.29 Among women, variations in estrogen and progesterone secretions create differences between women across different phases of the menstrual cycle, and among pre-, peri-, and postmenopausal women.30 Further, it has been proposed that differences in the ANS may be due to differences in several potential functions of the nervous system such as differences in afferent stimulation, central reflex transmission, and post-synaptic signaling.30 Recently, Barel and colleagues demonstrated that sex hormones modulated the HPA axis and the SNS reactivity to psychosocial stress, emphasizing the need to include sex hormone fluctuations when examining stress effects in typical, as well as clinical samples.31

The underlying mechanism for these sex differences in schizophrenia involves complex interplay between various factors. Among the biological factors identified, sex hormones have been suggested as important factor. The leading explanation is the estrogen hypothesis, which postulates that estrogen plays a protective role against schizophrenia.32 Studies demonstrated increase symptom severity, greater relapse rates, and higher symptoms scores during times of low circulating estrogen.33 Apart from the role of estrogen in schizophrenia, the role of androgens was studied as well. For example, few studies showed that lower total and free testosterone levels were associated with sever negative symptoms in men with schizophrenia.34 Recent meta-analysis concluded that blunted testosterone response to acute stress is associated with relapse of schizophrenia.35 The authors have suggested to further investigate the alterations in testosterone in patients with schizophrenia together with indices of the HPA axis and other biological mechanisms involved in psychotic disorders. Indeed, previous studies have investigated the involvement of the MGB in the association between sex hormones and the development of diseases. They found a bidirectional relationship between estrogen and gut microbiota in the influence on brain function, cardiovascular disease, and cancer.36 Furthermore, Testosterone has found to enrich gut microbiota with specific bacteria, which in turn reduced inflammation.37 In their recent review regarding the etiology of depression Markis and colleagues showed that the interconnection between the gut microbiota and the brain is affected by several factors such as inflammation, sex hormones, and stress. This communication is facilitated through the activation of the HPA-axis following stress, which stimulate the immune system that causes gut dysbiosis, which in turn arises hypoestrogenic conditions including depression.38

*Digital Phenotyping: 24/7 behavioral monitoring platforms*. Smartphone technology, and in particular advances in smartphone sensors, can also offer a new approach to the study of Mental health in general and to Schizophrenia in particular.39 Smartphone technology now allows researchers to passively collect data about human behavior using the embedded mobile sensors and system logs that are already embedded in the devices (e.g., GPS, accelerometer, gyroscope, application use statistics, battery states and charges, network activity, rotation, magnetometer, log of outgoing and incoming calls and text messages and more) compounded with patients` real time self-reporting capabilities .40,41 Over the past few years, smartphones and other digital platforms have become promising sources through which to learn and investigate various psychological factors. The fields of psychological as well as medical science could benefit from analyzing digital footprints left on various digital sources.42 Digital phenotyping refers to the act of collecting and using data from smartphones and other personal digital devices and subsequently connecting that data to behavioral and personality data. Studies examining the adverse health effects of smartphone use found that problematic smartphone use was associated with negative health symptoms43 and weakened immunity.44 These methodologies have been applied to the fields of psychology and psychiatry; for example, it has been shown that phone call data extracted from smartphones were associated with extraversion, agreeableness, and conscientiousness.45,46 Another study demonstrated a link between longer use of a social media application and lower levels of conscientiousness.47 Further, studies examining the relationship between smartphone use and psychopathological symptomatology found a link between smartphone use and depression (lower depression severity predicted increased smartphone use),48,49 as well as anxiety severity (anxiety severity was negatively associated with frequency of phone screen unlocking).49

*Digital Phenotyping of Schizophrenia.* Digital phenotyping research approaches using the intensive data collection capabilities of modern smartphone, are just beginning to be utilized in the study of Schizophrenia. None smartphone-based early digital phenotyping studies showed schizophrenic patients exhibited reduced motor activity, which was correlated with high interview-based apathy levels.50,51 Studies aimed at using technology to augment relapse prediction demonstrated that detecting early relapse signs via simple SMS weekly communication and reporting of relapse symptoms (and increasing medication during the warning state), is an effective intervention during the early stages of relapse.52,53 Another study tested for changes in mobility patterns and social behavior over time as measured through smartphone use, to identify anomalies in patient behavior in the days prior to relapse.54 The study found that the rate of behavioral anomalies detected in the 2 weeks prior to relapse was 71% higher than the rate of anomalies during other time periods. Autonomic dysfunctions in people with schizophrenia were also measured with Mobile Health (mHealth) methods using wearable technology.55 Compared to controls, people with schizophrenia showed lower levels of HRV, movement and functioning. In people with schizophrenia illness severity, particularly positive symptoms, was associated with parasympathetic deregulation proving that autonomic abnormalities can be detected using wearable technology from people's everyday life and that this method may be developed as a monitoring system or well-being and relapse prevention.

In conclusion, there is ample of evidence to suggest that relapse is associated with biological factors involving immune, neural, metabolic, and endocrine systems, as well as psychosocial risk factors as depression and anxiety, alongside with exposure to stress and perceived stress. Furthermore, with many smartphone and wearable sensors now able to detect psychological as well as physiological data from subjects, digital phenotyping for relapse prediction would enable to generate a comprehensive predictive model for relapse prediction. To that end, the proposed objectives of the current research are outlined below.

**Research objectives and expected significance**

Our research will examine the stress-vulnerability model for relapse including biological, psychological, stress and perceived stress through behavioral mechanisms (measured by digital footprints). Based on previous findings, the specific aims of the current study are as follows:

1. To examine the association between biological markers (i.e., gut microbiota, ANS, HPA axis, HPG axis) and their interrelation and relapse in schizophrenia.
2. To examine the associations between psychological variables (i.e., depression, anxiety) and relapse in schizophrenia.
3. To examine the role of the interconnectivity among the HPG axis, the ANS and the HPA axis in relapse prediction. Previous studies have demonstrated the associations among the HPG axis, the ANS and the HPA axis. Furthermore, the role of each system in predicting relapse was explored independently. However, to the best of our knowledge, the interconnectivity among these systems, both in general and specifically in psychopathological context, has not yet been investigated.
4. To examine the associations between smartphone Digital Phenotyping sensors data and novel biosensors/biomarkers, as well as to generate predictive clusters combining bio+digital data for SD relapse prediction.
5. To examine the behavioral mechanisms associated with relapse using digital footprints from smartphones (i.e., digital phenotyping) that predict relapse.

With the use of unprecedented monitoring and data collection abilities modern smartphone devices allow, we expect our findings to shed light on the mediating role of behavioral mechanisms in the association between individuals’ psychological/biological states and relapse. Uncovering such associations and relationships among the variables may serve to validate the use of digital footprints (collected from smartphones) to predict relapse which may, in turn, promote the use of this technology to create preventive programs. Importantly, studies measuring behavioral mechanisms through digital footprints in schizophrenia had only recently emerged and are limited to very small sample sizes. Nevertheless, they provide promising preliminary results that indicate the feasibility in predicting relapse. Findings of the current research are also expected to contribute to a better understanding of the predicting role of the joint modulation of the ANS with the HPG axis. Our findings will thus have implications for personalized medicine, as it could allow for customized interventions for relapse in patients that are gender-specific and specific to patients’ sex hormone profiles.

**Detailed description of the proposed research**

**Our working hypotheses**

Individualized patient profiles that consider behavioral expressions of psychological factors (measured by smartphone sensors, digital diaries, and self-report questionnaires), as well as biological expressions (measured through saliva sample levels of cortisol, alpha-amylase, testosterone, estrogen, progesterone; epithelial samples for gut microbiota; ANS activity through wearable device) will constitute predictable risk factors for relapse (measured using XXXX). The following are our specific hypotheses (see section on Digital phenotyping measurements of smartphone data below precise definition of smartphones-related sensor and measurement terms):

1. Patients experiencing relapse will exhibit higher levels of anxiety and depression than patients without relapse within 1-7 days prior to the relapse.
2. Patients experiencing relapse will exhibit higher levels of stress and perceived stress than patients without relapse within 1-7 days prior to the relapse.
3. Patients experiencing relapse will exhibit higher levels of stress biomarkers (i.e., cortisol, alpha-amylase), autonomic abnormalities, gut-microbiota anomalies, and lower levels of estrogen than patients without relapse within 1-7 days prior to the relapse.
4. The interaction of the HPG axis, the ANS, and the HPA axis will mediate the association between psychological factors and stress levels among patients experiencing relapse.
5. Biomarkers of the ANS and HPG axis will be associated with patients’ behavioral measures (measured through digital phenotyping) and will act as the mediator in the association between a given psychological/biological factors and relapse.
6. Patients experiencing relapse will have longer periods of “active screen state”, will exhibit higher rates of “compulsive" smartphone use and non-use, will receive higher numbers of incoming calls and will place higher numbers of outgoing calls, and will receive higher numbers of incoming calls and will place higher numbers of outgoing calls within a 24-hour period (see research tools section below) than patients without relapse.
7. Patients’ behavioral measures (measured through digital phenotyping) will act as the mediator in the association between a given psychological/biological factors and relapse.

**Methodology**

**Participants**. The 200 participants in the study (age range 18-45, both genders) would include patients with schizophrenia diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V)x. All participants will be interviewed using All participants will be interviewed using the Structured Clinical Interview for DSM-5 (SCID). Patients will be recruited from Maale HaCarmel Mental Health Center (and other Centers) from November 2021 toXXX. All patients will receive a stable dose of antipsychotic medication for at least 30 days before entry. They will be judged clinically stable by the principal investigator in the XXX. Exclusion criteria will include another DSM-V Axis I diagnosis, and Axis II diagnosis of borderline personality or antisocial personality disorder, substance dependence or abuse, medical illness…. XXXXX  inability to participate in an interview or to take an online questionnaire, an inability to operate a digital diary smartphone app, and having underwent total abdominal hysterectomy with bilateral ovariectomies (women). Enrollment would be set to begin in XXX.

**Research procedure**

The current study design is a between-subject (patients experiencing relapse vs. patients without relapse). The study will begin following the approval from the XXX Helsinki Committee. All patients will be asked to provide their informed consent prior to starting the study. Standard data privacy and security practices will be followed, in accordance with the General Data Protection Regulation (GDPR).62,63

At entry into the study, assessments of baseline psychological characteristics and biological markers will be collected. To obtain other biomarker data (cortisol, alpha-amylase, testosterone, estrogen, progesterone), patients will be asked to provide saliva samples at several assessment points – at baseline and at multiple follow-up timepoints, up to X months. Epithelia….Patients will also be provided with a digital diary and will receive a detailed explanation about how to use the e-diary. The digital diary smartphone app will also include a digital phenotyping sensor that will monitor accelerometer data, smartphone power states, number of incoming/outgoing calls, etc.). Relapse will be assessed through the Brief Psychiatric Rating Scale (BPRS).xx

**Data analyses and statistical plan**

Digital footprints from smartphone data (digital phenotyping), biological markers, and self-report questionnaires representing psychological states will be associated with XXXX in order to detect potential behavioral predictors of relapse.

Data collection: Smartphone sensor and logs data collection software (open source Aware digital phenotyping framework) will be customized for our research goals (Android and OS environment). Data preparation: Various R and Python packages for data prep. Data analysis software for machine learning and other AI modeling: Machine learning packages for Python and RapidMiner server installation on AWS. Statistical analysis using: Jamovi open-source R statistical package for R, R software, and SPSS software version 25, will be used to conduct statistical data analyses. The statistical significance level will be set to an alpha of 0.05, such that the null hypothesis would be rejected if p < .05. Pearson's correlation analyses will be performed between endocrine parameters and ANS parameters. Patients who experienced relapse during the XX-month follow-up period will be part of the experimental group (relapse patients), whereas patients without relapse will be part of the control group. Hypotheses regarding differences in psychological variables, biomarkers, allostatic overload (AO), and digital footprints between relapse patients and control patients will be tested using XXXXX. Hierarchical logistic regressions will be used to test the moderation hypotheses regarding the role of the interaction between the HPG axis and the ANS and the MGB in the associations among psychological variables, AO, and relapse. Logistic regression and linear regression analyses will be used to test the mediation hypotheses regarding the role of digital phenotyping in explaining the association between psychological and biological variables and relapse.

**Research tools**

We intend to utilize several research tools, which fall under four broad categories, to measure indicators that we deem to be potentially relevant to important psychological and biological risk factors of relapse. In addition, a general demographic questionnaire will be administered, which will include questions about participants’ age and gender, as well as contact information for follow-up questionnaires and email addresses to obtain participants’ consent to take part in the study.

**Measuring behavioral indicators that are potentially related to psychological and biological risk factors of relapse**

**Biological factors:**

**1) ANS function –** ANS function will be assessed through a wearable device worn on participant's wrist recording electrodermal activity (will assess sympathetic nervous system arousal); blood volume pulse (from this measure it is possible to extract inter-beat intervals (IBIs), and in turn, from IBIs it is possible to extract HRV. 2) **Biological markers for stress and HPG** – Saliva samples will be collected to test for cortisol, alpha-amylase, testosterone, estrogen, and progesterone. Saliva samples will be analyzed in the endocrine laboratory of the Rambam health care campus. 3) gut microbiota

**Psychological factors:**

**1) Stress and perceived stress** – Measures of stress and perceived stress will be based on the concept of allostatic overload (AO). AO occurs when one’s cumulative life events and chronic stressors exceed one’s resources.67,68 To experience AO two criteria must be met. First, it requires the presence of an identifiable stressor that is perceived as exceeding or taxing the individual's coping skills. The presence of a stressor, and one’s perceived inability to effectively cope with the situation, will be measured using the self-report psychosocial index, specifically the stress subscales.69 The second criteria is that the stressor must be associated with at least one of the following: psychiatric symptoms, psychosomatic symptoms, impaired functioning, or compromised well-being. The presence of AO will be determined if the participant’s self-report satisfies both criteria.70 **2) Depressive symptoms –** The Beck Depression Inventory (BDI) will be used to assess depressive symptomatology. This measure contains 21 self-report items, each of which are rated on 0 to 3 scale. 71 **3) Anxiety** – Anxiety will be assessed using the state anxiety subscale of the State Trait Anxiety Inventory (STAI). The subscale consists of 20 items, each of which are rated on a 4-point Likert scale ranging from 1 (not at all) to 4 (very much so).72 **4) Sleep quality XXX 5) Psychosis XXXX 6) Warning symptom scale XX 7)** Treatment adherence XXX

**Digital phenotyping measurements of smartphone data: Behavioral data:**

Maintaining a reliable data collection platform that uses smartphone sensors is a major challenge. We will use the open source Aware-light platform, a platform with which we have already gained experience in the past year in two different studies. The Aware research platform is part of the broader Aware framework and was developed by the Academy of Finland and by the University of Melbourne, Australia.13 AWARE captures hardware, software, and human-based data from smartphones. Aware is fully complied with GDPR standards. By design, AWARE does not collect any personal identifiers in its data and stores data locally on the users’ phones. Integrating the mobile client with an AWARE Server allows replication of the data to a secure remote database. AWARE offers data encryption and obfuscation by default, crucial to safeguard the transition between local-only data and shared data. During a study deployment, a user can withdraw and remove the collected data from the server and the mobile phone at any time, directly from his phone. As the data is primarily stored on the users’ device, it will be backed to a secured AWS RDS MySQL database using an SQLite client.79 The app collects phone sensor data (e.g., using a GPS, accelerometer, magnetometer smartphone sensors) and phone usage data (e.g., communication logs and screen activity). The Aware app also allows for administrating an e-Diary (Experience Sampling module) which is a method to measure behavior, thoughts, and feelings of study participants throughout their daily lives. Data is collected through self-reports completed by the study participants. We plan to use the Experience Sampling module as well for short daily and weekly questionnaire. Below are the parameters we plan to use:23,67,80–83 Note: The data will be collected under three broad temporal sections: Daytime = 06:00-18:00; Evening = 18:00-24:00; Nighttime = 24:00-06:00. Of the many sensor and log data to be collected, we summarize by example the main four groups:

**Example of Experience Sampling online popup daily questionnaire (e-Diary) categories:** Depression, Sleep quality, Psychosis, Warning symptoms scale, Taking medication, Anxiety

**Example of Mobility indicators from smartphone**: % of Time spent at home per 24 hours, Distance traveled, Radius of gyration, Maximum travel diameter, Maximum distance from home, Number of signiﬁcant locations, Fraction of the day spent stationary, Signiﬁcant location entropy, Minutes of GPS data missing, Physical circadian rhythm, Physical circadian rhythm stratiﬁed.

**Example** **smartphone indictors of Sociability**: Hours spent on social media applications, Number of outgoing texts, Total outgoing text length, texting out-degree, Number of incoming texts, Total incoming text length, Texting in-degree, Texting reciprocity, Texting responsiveness, Number of outgoing calls, Total outgoing call duration, Call out-degree, Number of incoming calls, Total incoming call durations,

**Examples of smartphone indictors of agitated & irritable & compulsive behavior:** Total duration of “active screen state” per hour/day, Sum of each press of the power button per hour/day, Total event of short "screen on” per hour/day, Total “Compulsive” phone checkout per hour/day, Battery charging events per day, Frequency of checking/refreshing Social Media applications

**Available resources**

**Intellectual capital and experience**

The proposed research represents an interdisciplinary collaboration of experts in the fields of Psychiatry, Psychology, Psychobiology, and computer and data science.

Prof. Michael Poyurovsky, psychiatric specialist, heads the Department of First Admissions and the Research Unit at a state psychiatric hospital, an Associate Professor of Psychiatry at the Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, and a visiting Prof. at Stanford University. Prof. Poyurovsky is an eminent psychiatric specialist, well - known in Israel and abroad for his expertise as a diagnostician and in administration of psychopharmacological therapy especially for obsessive-compulsive disorder, schizophrenia and complex conditions of the co-occurrence of the two disorders. His book on Schizo-Obsessive Disorder was published in Cambridge University Press (2013). Prof. Yonathan Mizrachi, (Harvard PhD, Anthropology), former head of the departments of Information Systems and Anthropology and Sociology and YVC Academic college; ICT4D and BPR information systems specialist + former CTO of several startups; affiliated Research Scientist (focused on Digital Phenotyping research) at Lambda: Laboratory for AI, Machine Learning, Business + Data Analytics, Tel Aviv University. Dr. Efrat Barel received her PhD in Psychology from Haifa University, is currently a faculty member in the Department of Behavioral Sciences at Emek Yezreel Academic College, and a member of the Psychobiology Laboratory at Emek Yezreel Academic College. Dr. Barel has an extensive background in stress research and its relation to physiological stress and reproductive systems. Further, she is well-experienced in the performance and interpretation of biochemical tests. Dr. Noa Cohen, completed PhD in computer science and computational biology from the Hebrew University. Dr. Cohen is currently a researcher and senior lecturer (Israeli equivalent to assistant professor), at the department of software engineering at the Azrieli College of Engineering Jerusalem. Experienced in machine learning, deep learning, and data science research. Project advisor - Dr. Fruchter served in many leading positions in the field of mental health in the Israeli Defense Force (IDF). In his last position, with the rank of Colonel, he headed the mental health department in the IDF Medical Corps. During his military service, Dr. Fruchter also earned a M.H.A. from Ben Gurion University of the Negev. Dr. Fruchter recently returned from a year at USC in Los Angeles, where he was studying treatment and prevention of PTSD (Post Traumatic Stress Disorder). He joined the in- patient psychiatric ward in Rambam and subsequently became the director of the division. Dr. Fruchter is a leading clinician and researcher in the fields of suicide prevention and PTSD. He participates in conferences, and collaborative research with many professionals in the US and Europe. Dr. Fruchter has published over 40 articles in leading professional journals, with many more in Hebrew, and two chapters in professional books – on the topics of suicide prevention and aviation psychology.

**Physical, facilities and other resources**

The Maale Carmel Mental Health Center (MCMHC), which is branched to the Faculty of Medicine at the Technion, provides treatment to a variety of mental disorders among teenagers, adults and the elderly, aimed at improving the mental health and functioning of patients, in consideration of ad with the help of their families. The treatment is provided with a sense of purpose and a desire for constant improvement. The center serves a population of half a million people, living in Haifa and its suburbs, the Krayot, at the north, Kiryat Tivon and an Nesher in the East, Carmel City, Tirat Carmel, to down to Atlit and the Carmel beach towns in the south. For Biomarkers, the laboratory staff of the \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Medical Center will carry out the measurement of biomarkers levels in the saliva samples. Stable Digital Phenotyping and data science platform. An accumulated 3 years of experience with the open-source Digital Phenotyping platforms over AWS system for Android smartphone data collection. The system includes an initial smartphone sensors data pipeline (Android based) for Machine learning data cleansing. (to be expanded to IOS systems).

**Expected results, potential pitfalls, and alternative research plans**

Given the precision of our expected measurements for both the dependent and the independent variables, we believe that the current study offers a unique opportunity to examine the multifaceted associations between psychological/biological factors and the risks of relapse in schizophrenia. We do not foresee major pitfalls, but we do however secure alternative data collection alternative. For the predicting variables, given that we have several complementary measures, we do not see any problems in collecting or recollecting data as need. The main engineering challenges that will need to be resolved are as follows:

1) Maintaining a reliable smartphone data collection platform (which is currently performing better on Android smartphones). We plan to use the open source Aware digital phenotyping and run its backend on the reliable Amazon AWS infrastructure. 2) Developing a reliable data cleaning and preparation process that links between the data collected through mobile sensors and participants’ smartphones. We plan to utilize relevant R and Python packages to overcome this challenge. 3) Modeling a prediction framework that utilizes the above features. We may utilize R, Python and/or non-open-sourced commercial tools, such as RapidMiner and SparkBeyond, to overcome this challenge.

Additionally, we anticipate a sample size challenge. We plan to recruit a large number of participants to offset the expected study potential dropout rates. However, the initial recruitment may still be insufficient and the potential high dropout rates may require the recruitment of additional participants, which may extend the time needed for completing data collection. A relatively high compensation will be offered to participants together with some softer measures (personal connection with medical staff and research assistants) to incentives participants.

Despite the challenges, the current study has several strengths, including: the prospective study design, which includes a XX follow-up; the use of validated psychological measures; the inclusion of various biomarkers; and the innovative application of digital phenotyping to behavioral mechanisms that play a role in schizophrenia. Additionally, our study will have high external validity as the population will include those patients who experienced first psychotic episode.

**Figure**

**Figure 1:**

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