**Statistical Analysis Plan for the PRODIGITAL -D individually randomised controlled trial**

**Administrative information**

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| **Title** | Statistical analysis plan (SAP) for the PRODIGITAL-D: A digital psychosocial intervention for depression among older adults in socioeconomically deprived areas in Brazil (individually randomised trial). |
| **Trial registration** | Registro Brasileiro de Ensaios Clínicos (ReBEC), RBR-4c94dtn |
| **SAP version** | Version: 1.0. |
| **Protocol version** | This document has been written based on information contained in the study protocol version, dated 16 March 2022. |
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1. **Introduction**

This statistical analysis plan corresponds to the PRODIGITAL-D study, a parallel two-arm superiority individually randomised controlled trial with a 1:1 allocation ratio. It was designed to assess the effectiveness of treating older adults with depression by a 6-week digital psychosocial intervention (Viva Vida) delivered by WhatsApp messages. PRODIGITAL-D is taking place in poor neighbourhoods in Guarulhos, Brazil and participants were recruited based on lists of 24 primary care clinics, known as Unidades Básicas de Saúde (UBS). The main component of the intervention is a 6-week psychosocial digital programme, named Viva Vida, which will be delivered via WhatsApp to participants allocated to the intervention arm. Viva Vida sends psychoeducational and behavioural activation audio and visual messages to participants allocated to the intervention arm four days a week for six weeks. The control group receive a single audio message. Primary and secondary outcomes are assessed at three and five months after randomisation becomes effective.

Inclusion criteria:

1. Adults aged 60 or over and with a PHQ-9 score equal or higher to 10
2. Individuals able to read and listen to WhatsApp messages

Exclusion criteria:

1. Individuals with communication issues (non-Portuguese speaking, cognitively impaired or other problem hindering communication to engage in trial assessments or intervention, such as vision or hearing problems)
2. Individuals unable to engage in the study for the total period of five months (terminal illness or partner with terminal illness, other)
3. Individuals presenting acute suicidal risk (i.e. reported suicidal attempt in the two weeks prior to the screening assessment, as assessed by the 9th item of the PHQ-9 and the Immediate Suicide Risk Protocol)
4. Individuals living in the same household as another participant in the study
5. Individuals who participated in the PROACTIVE trial

The contents of the Viva Vida programme are based on the PROACTIVE intervention [5] and will include psychoeducation about depression and health promotion guidelines, simple ways to solve day-to-day problems related to depressive symptoms, and behaviour activation. Such an approach is anchored in recommendations by the WHO in guides containing step-by-step orientation for digital interventions targeting depression [12]. The proposed intervention is also based on concepts of interactive applications of health communication [13, 14]. Participants will receive approximately 48 audio and visual messages, delivered four days a week in the morning and afternoon over a 6-week period. The duration of six weeks was chosen as an appropriate timeframe to ensure sustained participation throughout the whole period.

The audio messages last on average three minutes and employ the technique of storytelling, which is a powerful communication tool when used to share and create bonds with other individuals. This technique can involve, convince, remind, and motivate. It can also improve the attention and retention of important information by the target audience. By creating empathy and interest in a story, we can encourage new behaviours and reflections on personal problems.

Once a week, participants will be invited to share their opinions about the programme by responding to a question through the WhatsApp ‘quick reply’ tool, with an up to three-answer option (e.g. yes, more or less, no). After answering the question, participants will also be invited to record and send audio messages to share their experience with the programme. Messages sent by the participants will be answered by automated reply only, as this programme was not designed to reply to individual demands. However, during the intervention, participants will receive messages advising them that they can visit health professionals to receive further advice and care for depression if they feel they need additional support.

Our sample size was based on estimates from the PROACTIVE RCT [5] and PROACTIVE pilot study in São Paulo [26]. A sample size of 330-374 individuals will detect a 15-percentage point difference (25% versus 40%) in recovery between the control and intervention groups after three months, with 80-85% power and two-sided 5% significance level. Such a difference in recovery rate is considered clinically meaningful [21-25]. We anticipate 25% attrition, which is readily achievable according to the experience we had collecting follow-up data by phone in our previous RCT in Guarulhos, yielding a corrected total sample size of 440-500.

We expect that on average 10% of the individuals registered with each UBS will be aged 60 years or older. On average, there are approximately 1,600 individuals in the eligible age range registered with each UBS. Based on the PROACTIVE data, we would be able to reach 440 individuals by phone and 60% of them (250 individuals) would have a mobile phone and would use the WhatsApp application. With a proportion of depressive symptomatology (PHQ-9≥10) of around 20% [26, 27], there would be about 50 individuals potentially eligible in each UBS, though this is likely to reduce to 35 once other entry criteria are applied.

We will work with 24 UBSs, and we plan to complete recruitment in six months. We will need to screen approximately 25,000 individuals to achieve a sample of 500 participants. Of these 25,000 individuals, we expect that we will be able to contact 6,800. Among the individuals we can contact, 3,800 will use WhatsApp. We expect that at least 20% will have depressive symptomatology (n=760), and 530 will consent to participate in the study – that is, at the upper end of the above range from our sample size calculation.

1. **Primary and secondary quantitative outcomes**

The primary outcome will be the proportion of participants recovered (PHQ-9 total scores < 10) three months after receiving the first message if allocated to the intervention arm, or the single message if in the control arm. These messages were planned to be sent out no later than 10 days after randomisation.

We have several secondary outcomes measured at 3- and 5-month follow-ups:

1. Proportion of participants recovered (PHQ-9 total scores < 10), five months after receiving the first message;
2. Proportion of the participants with at least a 50% reduction in PHQ-9 scores between baseline at both three- and five-month assessments;
3. Continuous PHQ-9 scores measured at three and five months;
4. Anxiety symptomatology assessed using the Generalised Anxiety Disorder-7 (GAD-7) measured at both three and five months. [17]
5. Loneliness assessed using the 3-time University of California, Los Angeles (UCLA) loneliness scale (3-item UCLA). [18].
6. Assessment of quality of life with the European Quality of Life five-dimensional questionnaire, five-level version (EQ-5D-5L) [19] at three and five months;
7. Capability wellbeing assessed with the ICEpop CAPability measure for Older people (ICECAP-O) [20] at three and five months.
8. **Objectives**

The main objective is to estimate the effectiveness of the Viva Vida programme as applied in the PRODIGITAL-D trial, namely a 6-week psychosocial intervention delivered by WhatsApp messages, compared with a single message in improving depression recovery rates among older adults in poor neighbourhoods in Guarulhos, Brazil.

Further objectives from the original protocol were to:

c.1. verify whether the randomisation was effective in the trial;

c.2. investigate the impact of missing outcome data through multiple imputation and sensitivity analyses using either the selection model approach or pattern mixture models;

c.3. conduct unbiased analyses comparing the effects on the outcome of actually receiving different amounts of the intended interventions;

c.4. perform pre-specified subgroup analyses to investigate potential differential intervention effects according to gender, age, educational level, co-morbid physical illness, and baseline PHQ-9.

**Statistical analyses**

The analysis and presentation of data will be in accordance with CONSORT guidelines for individually randomised trials (including the standard participant flow chart), with the primary comparative analysis being conducted on the basis of treatment as allocated (including only those individuals with known primary outcome and emphasis placed on confidence intervals for between-group comparisons). Descriptive statistics of demographic and clinical measures will be used to ascertain any marked imbalance between the treatment arms at baseline, and comprehensive descriptive statistics will be derived and presented for all of the measures involved in the comparative analyses.

**Primary outcome**

The primary comparative analysis will employ logistic regression to obtain an odds ratio of recovery (PHQ-9 total scores < 10) between the (as randomised) groups at three months after adjusting for baseline PHQ-9 scores and stratification. Stratification will be based on the PHQ-9 groups (scores of 10-14, 15-19 and 20+), gender (male and female) and age groups (60-69, 70-79 and 80+ years).

**Secondary outcomes**

Continuous secondary outcomes (PHQ-9, GAD-7, 3-item UCLA, EQ-5D-5L and ICECAP-O) will be evaluated using linear regression models that adjust for stratification, and the baseline assessment of the corresponding outcome. Coefficients and associated 95% confidence intervals for these outcomes represent differences in means between the intervention and control arms. Logistic regression models will be used to evaluate for the binary secondary outcomes (recovery from depression at five months, and reduction of PHQ-9 scores by at least 50% between baseline at three months and five months). Odds ratios with 95% confidence intervals will be used to estimate recovery from depression at three and five months. Sensitivity analyses will be conducted to investigate any potential clustering at the USB level, for instance by introducing a random effect for USB or fitting appropriate multi-level models.

**Additional analyses**

Any baseline variables that are substantially imbalanced between treatment arms (assessed using descriptive statistics) will be adjusted in a secondary analysis for the primary outcome and if such an adjustment has any noticeable effect, then we will conduct such analyses for the secondary outcomes as well. Likewise we will perform sensitivity analysis for the primary outcome adjusting for the time between randomisation and the (primary) follow-up, and similarly for the secondary outcomes where possible and this analysis for the primary outcome indicates a potential impact of any such differences.

Complier Average Causal Effect (CACE) analyses using instrumental variables regression techniques will investigate the effect of number of messages listened to on recovery from depression at both three and five months. A threshold value (listening to more than half of the messages received) will be used for the CACE analysis with PHQ-9 scores at both time points. We will use this threshold as it was hypothesised to be the minimum number of messages participants need to engage with in order to have a therapeutic effect. A sensitivity analysis will be conducting using these additional thresholds: (1) listening to half the messages or less; and (2) listening all of the messages.

Subgroup analyses will be used to estimate whether the following pre-specified characteristics of the participants modified the effect of the intervention: baseline PHQ-9; gender; age; education level; presence of co-morbid physical illnesses. To test for such effect-modification, an interaction term will be introduced between the pre-specified variable and the treatment arm. We will conduct these analyses through Wald tests using the *testparm* command in Stata, presenting estimates and their 95% confidence intervals (and using margins to consider specific odds ratios where there is any evidence of an interaction). Results of these analyses will, however, need to be interpreted with caution due to the limited power to detect such interactions as well as the paucity of evidence on the theoretical basis for these hypotheses.

Our analysis will include an economic evaluation examining the cost-effectiveness of the intervention at improving patient recovery rates and quality adjusted life years (QALYs). These analyses will be described in a separate Health Economics Analysis Plan (HEAP).

Patterns and the proportion of missing data for the primary and secondary outcomes will be investigated. If there are any marked differences in missing data between treatment arms, or if greater than 10% of the data are missing, multiple imputation using chained equations (MICE models) under the assumption that data are missing at random (MAR) will be used. Data will be imputed separately for the different treatment arms and MICE models will include any variables that predict missingness. Sensitivity analyses testing for modest departures against the MAR assumption will be conducted using the Selection Model Approach.

**Trial status**

The recruitment started in September 2021 and ended in April 2022. A total of 603 participants were randomised to the intervention (n=298) and control (n=305) arms. Data collection is expected to be completed by October 2022.